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A convenient synthesis of functionalized isoxazolines and related 5-hydroxyisoxazolidine-4-carboxylates

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ABSTRACT

The effectiveness of $Sc(OTf)_3$ as a Lewis acid catalyst for the 1,4-addition reaction of carbamates to appropriate 2-acetyl-2-pentenoic esters is herein reported. In particular, *N*-benzyl-(*tert*-butyldimethylsilyloxy)carbamate added efficiently to the title substrates to afford a new class of polyfunctionalized isoxazolidines and isoxazolines.

1. Introduction

In the field of organic and medicinal chemistry, the preparation of small heterocyclic rings by means of simple and efficient routes is receiving ever-increasing attention. In this context, substituted isoxazolidines constitute versatile synthetic intermediates as a result of the easy cleavage of the N–O bond under reducing conditions.[1] Indeed, various isoxazolidines are extensively used as 1,3-amino alcohol equivalents,[2]as masked amino acids[3] or as amino-sugar mimetics.[4] Furthermore, substituted isoxazolidines, isoxazolines, and isoxazoles are important substrates for mechanistic studies of biologically interesting processes. For example, isoxazolines have been incorporated as conformational constraint element in $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrin antagonists,[5] as well as in several transcriptional activators.[6] In a similar way, combretastatin analogues containing the isoxazoline or isoxazole ring have been reported,[7] and several AMPA (*S*-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)-propionic acid) receptor agonists have been synthesized and tested.[8] Finally, the use of chiral isoxazolidines as auxiliaries in asymmetric synthesis has been also reported.[9] On the other hand, the synthesis of unnatural nucleoside analogs[3a,10] containing the isoxazolidinic and isoxazolinic ring is currently of significant interest since it has been reported that the presence of an isoxazoline ring increases the antibacterial activity of carbapenem derivatives.[11] Although 1,3-dipolar cycloaddition[1,12] is the simplest method for the preparation of isoxazolidines, conjugate addition of nitrogen containing nucleophiles to unsaturated carbonyl compounds represents a useful alternative approach.[13] In this regard, we have been active in the field of aza-Michael addition, especially by means of metal catalyzed 1,4-addition of hydroxylamine derivatives to appropriate electrophilic acceptors.[14] This protocol has been applied to the synthesis of several biologically active compounds.

Recently, we developed a practical and selective synthesis of 4-carboxylated-5-hydroxyisoxazolidines.[15] In this paper we report a new approach to this class of compounds, using *N*-benzyl-(*tert*-butyldimethylsilyloxy)carbamate[16] as nucleophile and highly reactive alkylidene acetoacetates as suitable acceptors. This procedure directly furnished *N*-Cbz-protected-5-hydroxyisoxazolidines that can be easily transformed into the corresponding dehydrated isoxazolines, which are useful precursors of aromatic oxazoles.

The electrophilic substrates were prepared according to the previously reported procedure,[17] by condensation of ethyl acetoacetate with aliphatic and aromatic aldehydes. Thus, compounds **1a–e** were obtained in 70% yield, as ca. 4:1 mixtures of Z/*E* isomers, which were easily separable by flash chromatography. With these ketoesters in hand, we carried out the critical carbamate addition under Lewis acid-catalyzed conditions (Scheme 1).

2. Results and discussion

2.1. Addition of *N*-benzyl-(*tert*-butyldimethylsilyloxy)-carbamate to alkylidene acetoacetates 1a–e

Lewis acids have attracted much attention in organic synthesis because of their strong influence on the rate, the regio-, and the stereochemistry of numerous reactions.[18] In this context, carbamates have only recently been the subject of investigation as nucleophilic reagents for conjugate addition.[19] The low

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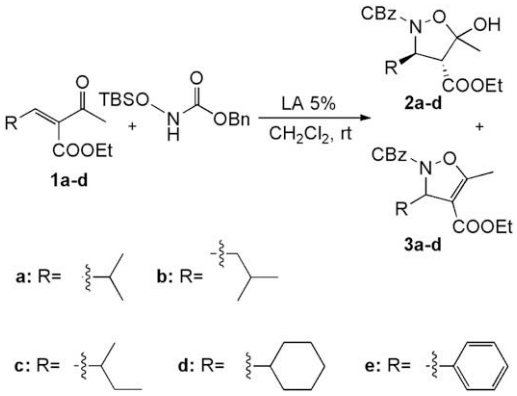


Scheme 1. Conjugate addition of *N*-benzyl-(*tert*-butyldimethylsilyloxy)carbamate to **1a**–**e**.

nucleophilicity of most carbamates compared with the precursor aromatic and aliphatic amines dictates the use of a suitable catalyst able to activate acceptor olefins via the lowering in energy of LUMO orbitals to match the HOMO of the carbamate.

A survey of metal salts that have been used for the successful addition of carbamates to α,β-unsaturated ketones has been recently reported by Kobayashi and co-workers.[20] Furthermore, enhanced reaction rates and improved yields can also be achieved by simply changing the nature of the nucleophile; in particular, use of the more reactive benzyl-(*tert*-butyldimethylsilyloxy)carbamate, recently introduced by MacMillan and co-workers,[16] has led to excellent results. Indeed, *N*-protected hydroxylamines react with unsaturated aldehydes to give hydroxyisoxazolidines, in good yields. Apparently, the intramolecular hemiacetal formation is an important driving force of the reaction.[21]

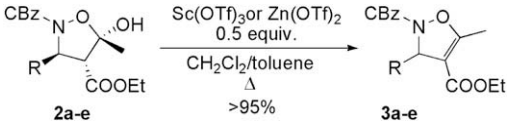
To our knowledge, functionalized alkylidene acetoacetates **1a**–**e** have not been ever investigated in this kind of reaction. In our hands, **1a**–**e** were treated with benzyl-(*tert*-butyldimethylsilyloxy)-carbamate in the presence of various Lewis acids in CH_2Cl_2 solvent, to afford isoxazolidine hemiketals **2** and the corresponding dehydrated isoxazoline **3** in ratios that depend on the reaction conditions (Table 1).[17] It should be noted that the TBS protecting group was removed during the usual work-up procedure.

From Table 1 it can be appreciated that the reaction with (*Z*)-**1a** $Zn(OTf)_2$ as catalyst, at 0 °C or at room temperature (entries 1 and 2) proceeded with unsatisfactory yields. Similarly, when the reaction was run in the presence of $Cu(OTf)_2$ at 0 °C, the starting material was recovered even after long reaction times (entry 3). On the other hand, the reaction proceeded very slowly at room temperature, so it was gently warmed to 40 °C, affording the complete conversion of the starting material to a mixture of *trans*-**2a** ($J_{3,4}$=6.6 Hz) and **3a** (entries 4 and 5 in Table 1). The cyclization to **2a** led to the formation of a single epimer. Compounds **2a** and **3a** were easily isolated by flash chromatography on silica gel, eluting with cyclohexane/ethyl acetate 80:20 as eluant. Similar results were observed using $Yb(OTf)_3$ as catalyst (entries 6–8 in Table 1). Scandium triflate showed an excellent efficiency for the activation of the desired reaction. Indeed, at ambient temperature and in the presence of $Sc(OTf)_3$, complete conversion of the starting material was observed in 5 h. A single epimer of the *trans*-isoxazolidine **2a** was obtained, accompanied by the corresponding product of dehydration **3a** in 60:40 ratio (entry 10 in Table 1). Warming the reaction to 40 °C afforded an increased amount of **3a** (Entry 11). On the other hand, in a unique experiment carried out at room temperature, a 46% conversion of (*Z*)-**1a** into *trans*-**2a** could be observed after 1.5 h, while only traces of dehydrated **3a** were detected in the crude ^{1}H NMR. After 3 h of reaction, the conversion reached

Table 1
1,4-Addition of benzyl-(*tert*-butyldimethylsilyloxy)carbamate to **1a**–**e**[a]

Entry	**1** S.M.	L.A. (5%)	*T* (°C)	*t* (h)	Conversion[b] **2**+**3** (%)	*trans*-**2**/**3**
1	**1a**	$Zn(OTf)_2$	0	40	—	—
2	**1a**	$Zn(OTf)_2$	40	16	23	>99:1
3	**1a**	$Cu(OTf)_2$	0	40	—	60:40
4	**1a**	$Cu(OTf)_2$	rt	20	>95	58:42
5	**1a**	$Cu(OTf)_2$	40	5	>95	50:50
6	**1a**	$Yb(OTf)_3$	0	40	—	—
7	**1a**	$Yb(OTf)_3$	rt	20	44	>99:1
8	**1a**	$Yb(OTf)_3$	40	5	>95	63:37
9	**1a**	$Sc(OTf)_3$	10	5	70	80:20
10	**1a**	$Sc(OTf)_3$	rt	5	>95	60:40
11	**1a**	$Sc(OTf)_3$	40	5	>95	30:70
12	**1b**	$Sc(OTf)_3$	rt	5	94	62:38
13	**1c**	$Sc(OTf)_3$	rt	5	95	60:40
14	**1d**	$Sc(OTf)_3$	rt	5	93	60:40
15	**1e**	$Sc(OTf)_3$	rt	5	95	58:42

[a] The reaction was performed in the presence of 1 equiv of nucleophile in CH_2Cl_2. A 5% amount of catalyst was used in all reactions.
[b] The rest being unreacted starting material. The conversion was established on the basis of ^{1}H NMR peak integration.



Scheme 2. Lewis acid-induced dehydration of **2a**–**c**.

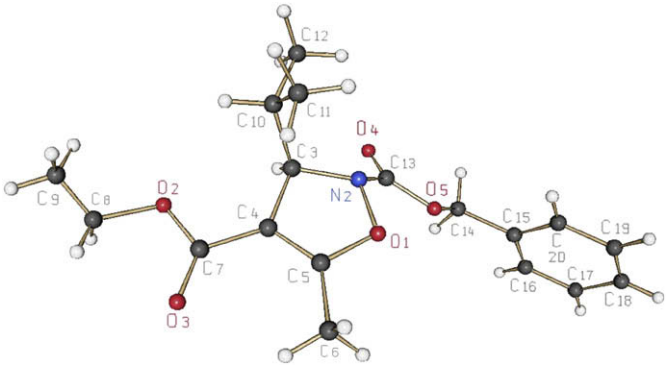
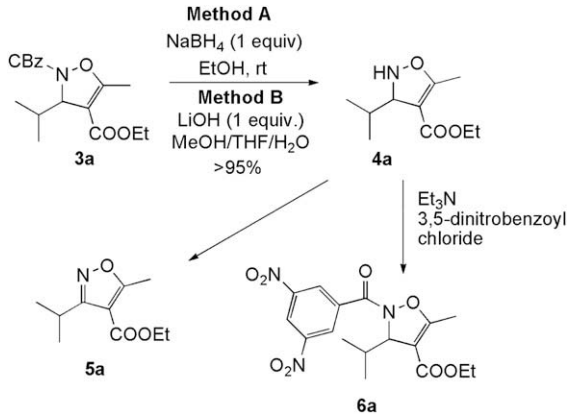
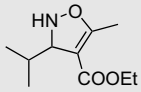
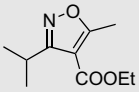
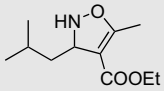
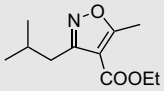
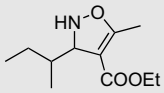
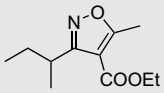
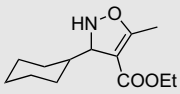
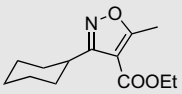
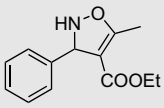
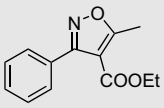


Figure 1. ORTEP representation of **3a** as obtained from X-ray crystallography.



Scheme 3. Reactivity of isoxazolidine **3a**.

Table 2
Transformation of isoxazolidines **3a–e** into isoxazoline **4a–e** and oxazoles **5a–e**

Entry	S.M.	Product **4**	Yield (%)	Product **5**	Yield (%)
1	**3a**		>95		>95
2	**3b**		>95		>95
3	**3c**		>95		>95
4	**3d**		>95		>95
5	**3e**		>95		>95

90%, and *trans*-**2a** was present together with the corresponding dehydrated product **3a**, in 60:40 ratio.

The experimental conditions selected for **1a** were then explored with substrates **1b–e**. Thus, treatment of **1b–e** with carbamate at room temperature overnight in the presence of scandium catalyst, afforded essentially quantitative conversion of the starting materials to 60:40 mixtures of **2b–e** and **3b–e** (entries 12–15 in Table 1).

Complete conversion of **2a–e** to **3a–e** was achieved upon addition of an additional half equivalent of $Sc(OTf)_2$ or $Zn(OTf)_2$ in toluene to the reaction mixture, while simultaneously heating to reflux for 3 h (Scheme 2).

The structures of compounds **2a** and **3a** were established by NMR techniques (DEPT, HETCOR, and COSY). The formation of a single epimer of isoxazolidine **2a** was supported by the presence of a single set of signals in the ^{1}H NMR spectrum. The relative stereochemistry of **2a** was established by means of NOE experiments that exhibited a strong enhancement (8%) of the isopropylic side chain upon irradiation of the C(4) hydrogen. By contrast, a weaker NOE effect (2%) was observed on the trans hydrogen at C(3). Furthermore, a medium NOE effect on the anomeric methyl substituent indicated a cis relationship between this group and the hydrogen at C(4). X-ray analysis of **3a** secured the configuration assigned to this heterocycle (Fig. 1).[22]

2.2. Reactivity of isozaxoline-4-carboxylates. Synthesis of oxazoles

In order to remove the CBz protecting group, **3a** was stirred at room temperature with an equimolar amount of $NaBH_4$ in ethanol under argon (method A) or LiOH in MeOH/H_2O/THF (method B), until the reaction was found to be complete by TLC. Following these protocols, isoxazoline **4a** was isolated in almost quantitative yield. Isoxazoline **4a** was characterized by spectroscopic analysis as well. This compound was unstable and spontaneously converted to the corresponding aromatic oxazole **5a**, even under inert atmosphere (Scheme 3).[23] Therefore, as soon as formed **4a** was treated with the 3,5-dinitrobenzoyl chloride to afford derivative **6a** in quantitative yield.

Similar deprotection was carried out on **3b–e**, affording **4b–e** in quantitative yield. Rapid oxidation of isoxazolines **4b–e** took place upon exposure to air, affording **5b–e** in quantitative yield (Table 2). Compound **4e** resulted particularly unstable, being detected only in the ^{1}H NMR spectra of the crude product.

3. Conclusion

In summary, the reactivity of carbamates as nucleophiles in the conjugate addition to alkylidene acetoacetates has been investigated. Excellent results were also obtained with *N*-benzyl-(*tert*-butyldimethylsilyloxy)carbamate as nucleophilic reagent. The procedure described here affords new classes of polyfunctionalized isoxazolidines and isoxazolines. The structure of these heterocycles was established on the basis of NMR spectra, and further supported by X-ray analysis of the dehydrated derivative.

4. Experimental

4.1. General

All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in sure seal bottles over molecular sieves and used without further drying. Flash chromatography was performed on silica gel (230–400 mesh). NMR Spectra were recorded with Varian spectrometers Gemini 200 MHz, Inova 300 MHz or Mercury 600 MHz. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at δ=7.27 (^{1}H NMR) or δ=77.0 (^{13}C NMR). Infrared spectra were recorded with an FT-IR Nicolet 205 spectrometer. MS analyses were performed on a liquid chromatograph coupled with an electrospray ionization-mass spectrometer (LC–ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 *m*/*z*, fragmentor 70 V). Elemental CHN analyses were performed with a Fisons EA1108—Eager 200 instrument, using *K* factor calculation method. General procedure for the preparation of acetoacetate **1** and complete characterization for **1a–d** has been already reported.[14,17]

4.2. General procedure for the 1,4-addition of benzyl-(*tert*-butyldimethylsilyloxy)carbamate to 1a–e

To a stirred solution of **1a–e** (0.5 mmol) and Lewis acid (0.05 equiv, 0.025 mmol), in dry CH_2Cl_2 (5 mL) at the selected

temperature under nitrogen atmosphere, the carbamate (1 equiv, 0.5 mmol, 140 mg) was added in one portion. The reaction was followed by TLC and quenched with water. The residue was then diluted with CH_2Cl_2 (10 mL) and washed twice with water (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **2a–e** and **3a–e** were purified by flash chromatography on silica gel (eluant cyclohexane/EtOAc, 85:15).

*4.2.1. Compound **2a***

Colorless oil; [Found: C, 61.58; H, 7.14; N, 4.01. $C_{18}H_{25}NO_6$ requires: C, 61.52; H, 7.17; N, 3.99]; R_f (30% EtOAc/cyclohexane) 0.51; IR ν_{max} (film) 3332, 2963, 2925, 1709, 1465, 1393, 1242, 1020 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ_H 7.27–7.34 (5H, m, *Ph*), 5.18 (1H, d, *J*=12.6 Hz, O*CH*$_2$Ph), 5.10 (1H, d, *J*=12.6 Hz, O*CH*$_2$Ph), 4.60 (1H, t, *J*=6.6 Hz, NC*H*), 4.23 (2H, q, *J*=7.2 Hz, O*CH*$_2$CH$_3$), 2.90 (1H, d, *J*=6.6 Hz, CH$_3$CC*H*), 1.81 (1H, m, CH$_3$C*H*CH$_3$), 1.70 (3H, s, OCC*H*$_3$), 1.22 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 0.89 (3H, d, *J*=6.9 Hz, C*H*$_3$CHCH$_3$), 0.86 (3H, d, *J*=6.6 Hz, C*H*$_3$CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ_C 14.0, 18.1, 18.7, 22.9, 32.7, 59.3, 61.3, 67.0, 68.0, 106.3, 127.9, 128.0, 128.4, 135.8, 159.9, 168.2. LC–ESI-MS: rt 9.6 min, *m*/*z* 352 (M+1), 725 (2M+Na).

*4.2.2. Compound **2b***

Pale yellow oil; [Found: C, 62.41; H, 7.47; N, 3.84. $C_{19}H_{27}NO_6$ requires: C, 62.45; H, 7.45; N, 3.83]; R_f (30% EtOAc/cyclohexane) 0.49; IR ν_{max} (film) 3299, 2969, 1961, 1734, 1476 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.30–7.39 (5H, m, *Ph*), 5.15–5.24 (2H, m, O*CH*$_2$Ph), 4.87 (1H, dd, *J*=6.2, 7.8 Hz, NC*H*), 4.17–4.28 (2H, m, O*CH*$_2$CH$_3$), 2.82 (1H, d, *J*=6.2 Hz, OCC*H*), 1.75 (3H, s, OCC*H*$_3$), 1.64 (1H, m, CH$_3$C*H*CH$_3$), 1.23 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.07–1.44 (2H, m, CHC*H*$_2$), 0.80 (6H, d, *J*=6.6 Hz, C*H*$_3$CHC*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 14.0, 21.9, 22.8, 23.0, 25.2, 26.9, 60.6, 61.4, 62.5, 68.0, 106.1, 127.8, 128.2, 128.5, 135.6, 159.8, 168.1. LC–ESI-MS: rt 10.3 min, *m*/*z* 366 (M+1).

*4.2.3. Compound **2c***

Pale yellow oil; [Found: C, 62.48; H, 7.42; N, 3.86. $C_{19}H_{27}NO_6$ requires: C, 62.45; H, 7.45; N, 3.83.]; R_f (30% EtOAc/cyclohexane) 0.45; IR ν_{max} (film) 3385, 2952, 2921, 2850, 1712, 1644, 1463, 1267 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.32–7.35 (5H, m, *Ph*), 5.15–5.24 (2H, m, O*CH*$_2$Ph), 4.74 (1H, q, *J*=7.2 Hz, NC*H*), 4.18–4.24 (2H, m, O*CH*$_2$CH$_3$), 3.97 (1H, br s, O*H*), 2.97 (1H, d, *J*=6.3 Hz, OCC*H*), 1.74 (3H, s, OCC*H*$_3$), 1.46–1.54 (1H, m, CH$_3$C*H*CH$_2$CH$_3$), 1.28 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.02–1.15 (2H, m, CH$_3$CHC*H*$_2$CH$_3$), 0.86–0.91 (6H, m, C*H*$_3$CHCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.4, 14.1, 14.8, 23.0, 25.7, 39.2, 58.7, 61.4, 66.2, 68.0, 106.5, 127.9, 128.4, 135.8, 159.9, 168.3. LC–ESI-MS: rt 10.0 min, *m*/*z* 366 (M+1).

*4.2.4. Compound **2d***

Pale yellow oil; [Found: C, 64.40; H, 7.51; N, 3.56. $C_{21}H_{29}NO_6$ requires: C, 64.43; H, 7.47; N, 3.58]; R_f (30% EtOAc/cyclohexane) 0.55; IR ν_{max} (film) 3381, 3035, 2914, 2857, 1734, 1456, 1124; ^1H NMR ($CDCl_3$, 200 MHz) δ_H 7.32–7.35 (5H, m, *Ph*), 5.25 (1H, d, *J*=18.2 Hz, O*CH*$_2$Ph), 5.15 (1H, d, *J*=18.2 Hz, O*CH*$_2$Ph), 4.62 (t, 1H, *J*=6.8 Hz, NC*H*), 4.16–4.27 (2H, m, O*CH*$_2$CH$_3$), 3.81 (1H, br s, O*H*), 2.99 (1H, d, *J*=6.6 Hz, CH$_3$CC*H*), 1.74 (3H, s, OCC*H*$_3$), 1.44–1.82 (6H, m, cyclohexyl), 1.29 (3H, t, *J*=7.0 Hz, OCH$_2$C*H*$_3$), 0.98–1.32 (5H, m, cyclohexyl); ^{13}C NMR ($CDCl_3$, 50 MHz) δ_C 14.1, 23.1, 25.8, 26.2, 28.8, 29.3, 29.7, 42.5, 59.5, 61.4, 66.5, 68.0, 106.3, 127.9, 128.1, 128.4, 135.9, 160.0, 168.3. LC–ESI-MS: rt 11.2 min, *m*/*z* 414 (M+Na), 805 (2M+Na).

*4.2.5. Compound **2e***

Yellow oil; [Found: C, 65.43; H, 5.99; N, 3.66. $C_{21}H_{23}NO_6$ requires: C, 65.44; H, 6.02; N, 3.63]; R_f (30% EtOAc/cyclohexane) 0.56; IR ν_{max} (film) 3374, 3089, 2983, 2554, 2254, 1955, 1714, 1604, 1496, 1243, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.28–7.46 (10H, m, *Ph*), 5.89 (1H, d, *J*=7.8 Hz, NC*H*), 5.22 (2H, s, O*CH*$_2$Ph), 4.42 (1H, br s, O*H*), 4.23–4.31 (2H, m, O*CH*$_2$CH$_3$), 3.27 (1H, d, *J*=7.8 Hz, CH$_3$CC*H*), 1.88 (3H, s, OCC*H*$_3$), 1.32 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 14.0, 22.6, 61.5, 64.7, 65.2, 68.0, 105.9, 126.1, 127.6, 127.7, 128.1, 128.4, 128.7, 135.7, 140.6, 158.9, 167.3. LC–ESI-MS: rt 9.8 min, *m*/*z* 408 (M+Na), 793 (2M+Na).

*4.2.6. Compound **3a***

White solid; [Found: C, 64.84; H, 6.94; N, 4.23. $C_{18}H_{23}NO_5$ requires: C, 64.85; H, 6.95; N, 4.20]; R_f (30% EtOAc/cyclohexane) 0.80; IR ν_{max} (film) 2961, 2926, 2851, 1728, 1667, 1457, 1264 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.26–7.30 (5H, m, *Ph*), 5.12 (2H, s, O*CH*$_2$Ph), 4.98 (1H, br d, *J*=2.4 Hz, NC*H*), 4.04–4.13 (2H, m, O*CH*$_2$CH$_3$), 2.18 (3H, s, OCC*H*$_3$), 1.97–2.17 (1H, m, CH$_3$C*H*CH$_3$), 1.17 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 0.88 (3H, d, *J*=6.6 Hz, C*H*$_3$CHCH$_3$), 0.71 (3H, d, *J*=6.6 Hz, C*H*$_3$CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.5, 14.2, 15.3, 19.5, 31.3, 60.0, 68.5, 70.3, 103.0, 128.1, 128.3, 128.5, 135.2, 158.5, 163.4, 163.7. LC–ESI-MS: rt 11.7 min, *m*/*z* 334 (M+1), 689 (2M+Na).

*4.2.7. Compound **3b***

Sticky yellow oil; [Found: C, 65.70; H, 7.22; N, 4.01. $C_{19}H_{25}NO_5$ requires: C, 65.69; H, 7.25; N, 4.03]; R_f (30% EtOAc/cyclohexane) 0.77; IR ν_{max} (film) 2955, 2925, 2857, 1712, 1444, 1260, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.30–7.37 (5H, m, *Ph*), 5.15–5.24 (2H, m, O*CH*$_2$Ph), 4.87 (1H, dd, *J*=6.2, 7.8 Hz, NC*H*), 4.19 (2H, m, O*CH*$_2$CH$_3$), 2.28 (3H, s, OCC*H*$_3$), 1.77 (2H, m, CHC*H*$_2$+CH$_3$C*H*CH$_3$), 1.56 (1H, m, CHC*H*$_2$), 1.29 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 0.95 (3H, d, *J*=6.6 Hz, CH$_3$CHC*H*$_3$), 0.91 (3H, d, *J*=6.6 Hz, C*H*$_3$CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.7, 14.2, 21.3, 23.6, 24.6, 43.8, 60.0, 64.1, 68.5, 105.1, 128.2, 128.3, 128.5, 135.3, 158.1, 163.3, 163.5. LC–ESI-MS: rt 12.3 min, *m*/*z* 348 (M+1).

*4.2.8. Compound **3c***

Pale yellow oil; [Found: C, 65.71; H, 7.28; N, 4.07. $C_{19}H_{25}NO_5$ requires: C, 65.69; H, 7.25; N, 4.03]; R_f (30% EtOAc/cyclohexane) 0.78; IR ν_{max} (film) 2965, 1642, 1464, 1253, 1114 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.34–7.40 (5H, m, *Ph*), 5.22 (1H, d, *J*=12.3 Hz, O*CH*$_2$Ph), 5.26 (1H, d, *J*=12.3 Hz, O*CH*$_2$Ph), 5.12 (1H, br d, *J*=2.7 Hz, NC*H*), 4.16–4.22 (2H, m, O*CH*$_2$CH$_3$), 2.30 (3H, s, OCC*H*$_3$), 1.75–1.81 (1H, m, CH$_3$C*H*CH$_2$CH$_3$), 1.42–1.50 (2H, m, CH$_3$CHC*H*$_2$CH$_3$), 1.29 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 0.88 (3H, t, *J*=7.2 Hz, CHCH$_2$C*H*$_3$), 0.80 (3H, d, *J*=6.9 Hz, C*H*$_3$CHCH$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.8, 12.7, 14.2, 16.0, 22.6, 38.5, 60.0, 68.5, 69.7, 103.1, 128.3, 128.5, 129.3, 135.2, 158.3, 163.7, 164.0. LC–ESI-MS: rt 12.18 min, *m*/*z* 348 (M+1).

*4.2.9. Compound **3d***

Colorless clear oil; [Found: C, 67.56; H, 7.32; N, 3.75. $C_{21}H_{27}NO_5$ requires: C, 67.54; H, 7.29; N, 3.75]; R_f (30% EtOAc/cyclohexane) 0.80; IR ν_{max} (film) 2922, 2854, 1724, 1656, 1446, 1264, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 7.35–7.38 (5H, m, *Ph*), 5.23 (2H, s, *J*=2 Hz, O*CH*$_2$Ph), 5.05 (1H, br d, *J*=1.2 Hz, NC*H*), 4.16–4.24 (2H, m, O*CH*$_2$CH$_3$), 2.28 (3H, s, OCC*H*$_3$), 1.55–1.78 (6H, m, cyclohexyl), 1.28 (3H, t, *J*=7.2 Hz, OCH$_2$C*H*$_3$), 1.01–1.27 (5H, m, cyclohexyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.4, 14.1, 25.4, 25.9, 26.1, 26.2, 30.1, 41.0, 60.0, 68.4, 69.9, 102.5, 128.1, 128.3, 128.4, 135.2, 158.4, 163.8, 163.9. LC–ESI-MS: rt 13.6 min, *m*/*z* 396 (M+Na).

*4.2.10. Compound **3e***

Pale yellow oil; [Found: C, 68.62; H, 5.77; N, 3.84. $C_{21}H_{21}NO_5$ requires: C, 68.65; H, 5.76; N, 3.81]; R_f (30% EtOAc/cyclohexane) 0.82; IR ν_{max} (film) 3350, 2961, 2915, 2851, 1717, 1667, 1453, 1268, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.19–7.30 (10H, m, *Ph*), 6.00 (1H, br s, NC*H*), 5.18 (1H, d, *J*=12.6 Hz, O*CH*$_2$Ph), 5.10 (1H, d,

J=12.6 Hz, OCH_2Ph), 3.93–4.05 (2H, m, OCH_2CH$_3$), 2.32 (3H, s, OCCH_3), 1.05 (3H, t, J=7.0 Hz, OCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 300 MHz) δ_C 11.6, 14.0, 60.0, 68.0, 68.5, 105.0, 127.2, 128.2, 128.3, 128.4, 128.5, 135.1, 139.9, 155.9, 162.5, 163.0. LC–ESI-MS: rt 11.2 min, m/z 390 (M+Na), 757 (2M+Na).

4.3. General procedure for the conversion of 2a–e into 3a–e

To the crude reaction mixture containing **2** and **3**, toluene (5 mL) and Sc(OTf)$_3$ or Zn(OTf)$_2$ (0.5 equiv) were added and the solution was heated to reflux for 3 h. The reaction was followed by TLC and quenched, after disappearance of compound **2**, with water. The residue was then diluted with CH_2Cl_2 (10 mL) and washed twice with water (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **3a–e** were purified by flash chromatography on silica gel (eluant cyclohexane/EtOAc, 85:15).

4.4. General procedure for the conversion of 3a–e into 4a–e

Method A. To a stirred solution of **3a–e** (0.5 mmol) in ethanol (5 mL) at 0 °C under nitrogen atmosphere, $NaBH_4$ (1 equiv, 0.5 mmol, 18 mg) was added in one portion. The reaction was stirred at room temperature and followed by TLC. After quenching with water, the residue was diluted with EtOAc (10 mL) and washed twice with water (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **4a–e** were purified by flash chromatography on silica gel (eluant cyclohexane/EtOAc, 75:25).

Method B. To a stirred solution of **3a–e** (0.5 mmol) in THF/methanol/water (4:1:1, 6 mL) at room temperature, LiOH (3 equiv, 1.5 mmol, 36 mg) was added in one portion. The reaction was followed by TLC and quenched with water, the residue was diluted with EtOAc (10 mL) and washed twice with water (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **4a–e** were purified by flash chromatography on silica gel (eluant cyclohexane/EtOAc, 75:25).

4.4.1. Compound ***4a***

Pale yellow oil; [Found: C, 60.30; H, 8.62; N, 7.06. $C_{21}H_{27}NO_5$ requires: C, 60.28; H, 8.60; N, 7.03]; R_f (30% EtOAc/cyclohexane) 0.73; IR ν_{max} (film) 3395, 2932, 2877, 1721, 1654, 1432, 1198 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 6.60–6.80 (1H, br s, NH), 4.31 (1H, br s, NCH), 4.20 (2H, m, OCH_2CH$_3$), 2.24 (3H, s, OCCH_3), 1.99 (1H, m, CH$_3$CHCH$_3$), 1.30 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.97 (3H, d, J=7.0 Hz, CH_3CHCH$_3$), 0.87 (3H, d, J=7.0 Hz, CH_3CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.8, 14.3, 15.4, 19.7, 30.9, 59.6, 68.6, 103.9, 164.8, 167.2. LC–ESI-MS: rt 9.3 min, m/z 200 (M+1), 222 (M+Na).

4.4.2. Compound ***4b***

Yellow oil; [Found: C, 61.99; H, 9.00; N, 6.52. $C_{11}H_{19}NO_3$ requires: C, 61.95; H, 8.98; N, 6.57]; R_f (30% EtOAc/cyclohexane) 0.74; IR ν_{max} (film) 3390, 2918, 2873, 1738, 1662, 1444, 1187 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.40–6.70 (1H, br s, NH), 4.37 (1H, br s, NCH), 4.20 (2H, m, OCH_2CH$_3$), 2.22 (3H, s, OCCH_3), 1.73 (1H, m, CHCH_2), 1.31 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.19–1.33 (2H, m, CHCH_2+CH$_3$CHCH$_3$), 0.95 (3H, d, J=6.6 Hz, CH$_3$CHCH_3), 0.93 (3H, d, J=6.6 Hz, CH_3CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.9, 14.2, 21.5, 23.6, 25.2, 43.6, 60.0, 62.2, 106.2, 164.5, 167.0. LC–ESI-MS: rt 6.8 min, m/z 214 (M+1).

4.4.3. Compound ***4c***

Colorless oil; [Found: C, 61.98; H, 8.95; N, 6.58. $C_{11}H_{19}NO_3$ requires: C, 61.95; H, 8.98; N, 6.57]; R_f (30% EtOAc/cyclohexane) 0.74; IR ν_{max} (film) 3388, 2924, 2855, 1715, 1658, 1442, 1898 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 6.70–6.80 (1H, br s, NH), 4.42 (1H, br s, NCH), 4.24 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 2.21 (3H, s, OCCH_3), 1.74 (1H, m, CH$_3$CHCH$_2$CH$_3$), 1.24 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.20–1.31 (2H, m, CH$_3$CHCH_2CH$_3$), 0.92 (3H, t, J=7.2 Hz, CHCH$_2$CH_3), 0.81 (3H, d, J=6.9 Hz, CH_3CHCH$_2$CH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.9, 12.4, 14.3, 16.0, 22.7, 38.3, 59.3, 68.5, 103.7, 164.7, 167.5. LC–ESI-MS: rt 9.7 min, m/z 214 (M+1).

4.4.4. Compound ***4d***

Colorless oil; [Found: C, 65.23; H, 8.87; N, 5.82. $C_{13}H_{21}NO_3$ requires: C, 65.25; H, 8.84; N, 5.85]; R_f (30% EtOAc/cyclohexane) 0.76; IR ν_{max} (film) 3401, 2955, 2843, 1710, 1653, 1418, 1167 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 6.60–6.80 (1H, br s, NH), 5.05 (1H, br s, NCH), 4.21 (2H, q, J=7.0 Hz, OCH_2CH$_3$), 2.22 (3H, s, OCCH_3), 1.45–1.80 (6H, m, cyclohexyl), 1.30 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.10–1.39 (5H, m, cyclohexyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.6, 14.2, 26.1, 26.3, 26.5, 41.0, 59.6, 68.2, 102.6, 164.7, 167.1. LC–ESI-MS: rt 9.8 min, m/z 240 (M+1).

4.4.5. Compound ***4e***

Pale yellow oil; R_f (30% EtOAc/cyclohexane) 0.78; IR ν_{max} (film) 3401, 3028, 2950, 2837, 1719, 1668, 1432, 1119 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.20–7.45 (10H, m, Ph), 5.46 (1H, br s, NCH), 4.07 (2H, m, OCH_2CH$_3$), 2.34 (3H, s, OCCH_3), 1.12 (3H, t, J=7.0 Hz, OCH$_2$CH_3); LC–ESI-MS: rt 7.6 min, m/z 234 (M+1).

4.4.6. Compound ***5a***

Yellow oil; [Found: C, 60.92; H, 7.69; N, 7.06. $C_{10}H_{15}NO_3$ requires: C, 60.90; H, 7.67; N, 7.10]; R_f (30% EtOAc/cyclohexane) 0.78; IR ν_{max} (film) 2954, 2919, 2847, 1720, 1660, 1460, 1264, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 4.30 (2H, m, OCH_2CH$_3$), 3.44 (1H, m, CH$_3$CHCH$_3$), 2.64 (3H, s, OCCH_3), 1.39 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 0.96 (3H, d, J=7.0 Hz, CH_3CHCH$_3$), 0.85 (3H, d, J=7.0 Hz, CH_3CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 14.2, 17.6, 18.2, 20.9, 26.8, 60.5, 107.7, 162.0, 168.1, 173.3. LC–ESI-MS: rt 3.2 min, m/z 198 (M+1), 417 (2M+Na).

4.4.7. Compound ***5b***

Pale yellow oil; [Found: C, 62.58; H, 8.09; N, 6.67. $C_{11}H_{17}NO_3$ requires: C, 62.54; H, 8.11; N, 6.63]; R_f (30% EtOAc/cyclohexane) 0.75; IR ν_{max} (film) 2960, 2919, 2848, 1721, 1455, 1380, 1260, 1091, 1028 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.30 (2H, m, OCH_2CH$_3$), 2.65 (3H, s, OCCH_3), 2.05 (1H, m, CHCH_2), 1.37 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.18–1.40 (2H, m, CHCH_2+CH$_3$CHCH$_3$), 0.96 (6H, d, J=6.6 Hz, CH_3CHCH$_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 13.4, 14.2, 22.9, 27.3, 34.5, 60.5, 108.4, 162.4, 162.5, 175.2. LC–ESI-MS: rt 10.6 min, m/z 212 (M+1), 445 (2M+Na).

4.4.8. Compound ***5c***

Clear colorless oil; [Found: C, 62.51; H, 8.11; N, 6.58. $C_{11}H_{17}NO_3$ requires: C, 62.54; H, 8.11; N, 6.63]; R_f (30% EtOAc/cyclohexane) 0.76; IR ν_{max} (film) 2960, 2925, 2860, 1724, 1459, 1391, 1266, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 4.32 (2H, q, J=7.2 Hz, OCH_2CH$_3$), 3.27 (1H, m, CH$_3$CHCH$_2$CH$_3$), 2.65 (3H, s, OCCH_3), 1.83 (1H, m, CH$_3$CHCH_2CH$_3$), 1.57 (1H, m, CH$_3$CHCH_2CH$_3$), 1.37 (3H, t, J=7.2 Hz, OCH$_2$CH_3), 1.30 (3H, d, J=7.2 Hz, CH_3CHCH$_2$CH$_3$), 0.93 (3H, t, J=7.5 Hz, CH$_3$CHCH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.7, 13.5, 14.2, 18.2, 28.1, 33.0, 60.5, 108.0, 162.4, 167.3, 175.1. LC–ESI-MS: rt 10.1 min, m/z 212 (M+1).

4.4.9. Compound ***5d***

Pale yellow oil; [Found: C, 65.83; H, 8.04; N, 5.96. $C_{13}H_{19}NO_3$ requires: C, 65.80; H, 8.07; N, 5.90]; R_f (30% EtOAc/cyclohexane) 0.77; IR ν_{max} (film) 2930, 2850, 1728, 1612, 1452, 1314, 1103 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ_H 4.32 (2H, q, J=7.0 Hz, OCH_2CH$_3$) 3.12 (1H, tt, J=3.2, 11.4 Hz, CHC), 2.64 (3H, s, OCCH_3), 1.38 (3H, t, J=7.0 Hz, OCH$_2$CH_3), 1.22–2.05 (10H, m, cyclohexyl); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 13.3, 14.1, 25.9, 26.3, 31.2, 36.1, 60.4, 107.6, 162.3, 167.3, 175.0. LC–ESI-MS: rt 11.3 min, m/z 238 (M+1).

*4.4.10. Compound **5e***

Yellow oil; [Found: C, 67.55; H, 6.11; N, 6.07. $C_{13}H_{13}NO_3$ requires: C, 67.52; H, 5.67; N, 6.06]; R_f (30% EtOAc/cyclohexane) 0.79; IR ν_{max} (film) 2959, 2850, 1958, 1728, 1310, 1261, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.63 (3H, m, *Ph*), 7.46 (3H, m, *Ph*), 4.25 (2H, q, J=7.2 Hz, OCH_2CH_3), 2.75 (3H, s, OCCH_3), 1.23 (3H, t, J=7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 13.6, 13.9, 60.7, 108.5, 127.9, 128.2, 128.6, 129.6, 162.0, 162.6, 175.8. LC–ESI-MS: rt 9.2 min, m/z 232 (M+1).

4.5. Preparation of 6a starting from 4a

3,5-Dinitrobenzoyl chloride (1.2 equiv, 0.6 mmol, 138 mg) was added in one portion to a stirred solution of **4a** (0.5 mmol, 110 mg) and Et_3N (1.2 equiv, 84 μl) in CH_2Cl_2 (5 mL) at 0 °C. The reaction was stirred at rt for 2 h and then quenched with water. The residue was then diluted with CH_2Cl_2 (10 mL) and washed twice with water (2×10 mL). The organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compound **6a** was purified by flash chromatography on silica gel (eluant cyclohexane/EtOAc, 98:2).

*4.5.1. Compound **6a***

Yellow solid; [Found: C, 51.90; H, 4.89; N, 10.71. $C_{17}H_{19}N_3O_8$ requires: C, 51.91; H, 4.87; N, 10.68]; R_f (30% EtOAc/cyclohexane) 0.84; IR ν_{max} (film) 2972, 2911, 2847, 1723, 1658, 1618, 1424, 1255, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ_H 9.10–9.17 (2H, m, Ph), 8.89 (1H, m, Ph), 5.64 (1H, br s, CHN), 4.24 (2H, m, OCH_2CH_3), 2.31 (1H, m, CH_3CHCH_3), 2.24 (3H, s, OCCH_3), 1.34 (3H, t, J=7.2 Hz, OCH_2CH_3), 1.08 (3H, d, J=7.0 Hz, CH_3CHCH_3), 0.96 (3H, d, J=7.0 Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 11.5, 14.2, 15.9, 19.8, 31.7, 56.9, 60.5, 104.5, 121.3, 128.8 (2), 136.0, 148.2 (2), 162.6, 168.9, 182.9. LC–ESI-MS: rt 11.1 min, m/z 394 (M+1).

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.071.

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