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Tandem enantioselective conjugate addition–Mannich reactions: efficient multicomponent assembly of dialkylzincs, cyclic enones and chiral *N*-sulfinimines

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Dedicated to Professor Elias J. Corey on occasion of his 80th birthday

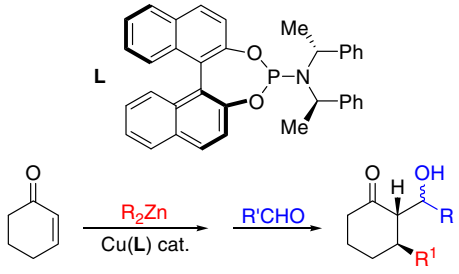
Abstract

A convenient access to enantiopure β-amino ketones through a multicomponent reaction of dialkyl zinc reagents, cyclic enones and chiral *N*-*tert*-butanesulfinimines is disclosed. Four diastereoisomers can be selectively obtained by the appropriate choice of the chiral ligand (L or *ent*-L) and the chiral *N*-sulfinimine (R_S or S_S). The protocol is particularly efficient when enolisable *N*-sulfinimines are used.

Keywords: Conjugate addition; Multicomponent reaction; Chiral sulfinimines; β-Amino ketones; Dialkyl zincs

Chiral β-amino ketones are important building blocks for the asymmetric synthesis of biologically active molecules.[1] For example, these compounds have been used in the stereoselective synthesis of 1,3-aminoalcohols,[2] homoallylic amines,[3] piperidines,[4] indolizidines[5] and other alkaloids.[6] However, to the best of our knowledge, the only asymmetric synthesis of α-substituted β-amino ketones is the diastereoselective addition of lithium enolates to chiral *N*-sulfinyl imines (sulfinimines) that was recently developed by Davis.[7] Chiral sulfinimines have been widely studied—in particular—by Davis, who proposed the use of *N*-*p*-tolylsulfinimines,[8] and by Ellman, who developed *N*-*tert*-butyl derivatives.[9] Indeed, one of the most direct and reliable methods for the asymmetric synthesis of amine derivatives is the addition of an organometallic reagent to the C=N bond of enantiopure sulfinimines.[10] In this context, we envisaged that trapping enolates, generated in the conjugate addition of organometallic reagents to enones, with chiral sulfinimines would provide a convenient route to chiral β-amino ketones.[11]

The use of the phosphoramidite ligand **L** developed by Feringa enables the generation of chiral enolates (ee >98%) through the copper-catalyzed addition of dialkyl zinc reagents to cyclic enones.[12] It is also known that these chiral enolates react stereoselectively with different electrophiles to give predominately trans substitution, and when prostereogenic aldehydes are used, the newly generated stereogenic centre β to the carbonyl group is usually formed in a stereorandom manner (Scheme 1).[13] Herein,



Scheme 1.

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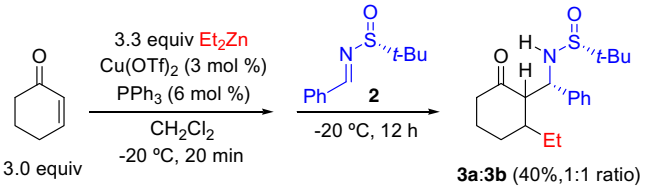
we outline our initial findings on the reactivity of homochiral zinc/copper[14] enolates with chiral sulfinimines.

N-tert-Butanesulfinimines (*t*-BS imines) are known to be less reactive with lithium enolates than other chiral sulfinimines.[15] However, we initially explored their reactivity due to the ready availability of both antipodes[16] and the high stereoinduction of the *tert*-butyl group.[17] In a preliminary experiment, an excess of the enolate, generated by copper-catalyzed conjugate addition of diethylzinc to cyclohexenone, using PPh_3 as a ligand, was quenched with chiral sulfinimine **2**. Under the experimental conditions used, we obtained a 40% yield of the expected products **3a**,**b** as a 1:1 mixture of diastereoisomers (Scheme 2).[18] Two important questions were answered with this experiment: (a) The resulting enolate (Zn or Cu) is reactive enough to add to *t*-BS imines; (b) significant kinetic resolution of the racemic enolate did not take place with chiral *t*-BS imines.[19]

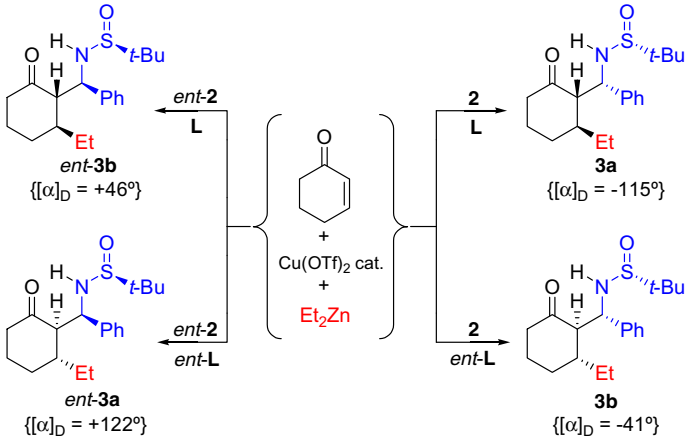


Scheme 2. Reaction of a racemic Zn/Cu enolate with a chiral *N-tert*-butanesulfinimine.

We assumed that chiral *t*-BS imines overcome the directing effect of a chiral enolate at the Mannich stereocentre.[20] With this in mind, we anticipated that this tandem enantioselective conjugate addition–Mannich reaction could provide a selective route to four diastereomeric β-amino ketones. The initial screening is summarized in Table 1.

We were pleased to find that on using the chiral phosphoramidite **L** in the test reaction, the expected compound **3a** was obtained in good yield as a single diastereoisomer (Table 1, entry 1). Importantly, similar results were obtained when Et_2Zn was added either before or after the sulfinimine,[21] indicating that enolate formation is possible in the presence of the electrophile and a truly multicomponent reaction is taking place.[22,23] As illustrated in entries 2–4 of Table 1, 3.5 mol % of copper, 4 equiv of Et_2Zn and 3 equiv of enone were required for a good conversion of the *t*-BS imines. The use of the *S*-sulfinimine (*ent*-**2**) and the enantiomer of ligand **L** (*ent*-**L**), under these optimized conditions, afforded compound *ent*-**3a** in enantiomerically pure form (entry 5). When the pairs *ent*-**L** ligand/*R*-sulfinimine (**2**) or **L** ligand/*S*-sulfinimine (*ent*-**2**) were used, compounds **3b** and *ent*-**3b** were, respectively, the major products (entries 6 and 7). The worst stereoselectivity observed in these cases (about 9:1 dr) would seem to point to a mismatch effect between the corresponding homochiral enolate and the chiral sulfinimine. Interestingly, we observed that this possible mismatch effect could be overcome by using a larger excess of Et_2Zn (entry 8).

Table 1
Screening and optimization of the reaction conditions[a]



Entry	Ligand	Imine	Equiv of Et_2Zn/enone	CuL_2 (mol %)	Yield[b] (product) (%)	dr[b]
1	**L**	**2**	3.3:3	3.5	75 (**3a**)	>98:2
2	**L**	**2**	3.3:3	1.7	42 (**3a**)	>98:2
3	**L**	**2**	4:3	3.5	83 (**3a**)	>98:2
4	**L**	**2**	4:2	3.5	66 (**3a**)	>98:2
5	*ent*-**L**	*ent*-**2**	4:3	3.5	75 (*ent*-**3a**)	>98:2
6	*ent*-**L**	**2**	4:3	3.5	70 (**3b**)	89:11
7	**L**	*ent*-**2**	4:3	3.5	70 (*ent*-**3b**)	91:9
8	**L**	*ent*-**2**	5:3	3.5	75 (*ent*-**3b**)	>98:2

[a] A mixture of $Cu(OTf)_2$, ligand, enone and sulfinimine was stirred over 30 min at room temperature in CH_2Cl_2. The reaction mixture was cooled down to −40 °C before Et_2Zn was added and stirred overnight at −20 °C.
[b] Determined by ^1H NMR and chiral HPLC analysis of the crude reaction mixture.

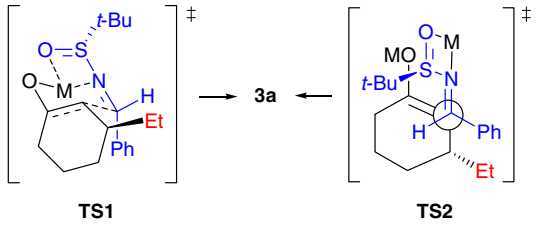


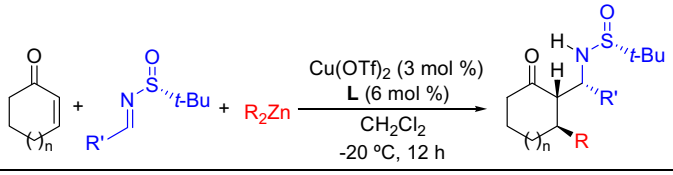
Fig. 1.

In order to assign the absolute configuration at the carbon bonded to the nitrogen, we assume that the reaction could proceed through a six-membered chair-like transition state, in a similar fashion to that proposed by Ellman (TS1, Fig. 1).[24] However, the fact that the reactivity is dependent on both the load of copper and the amount of dialkylzinc suggests that an acyclic transition state (TS2) could be involved.[25]

In order to evaluate the scope of this reaction, we used different *t*-BS imines, cyclic enones and dialkyl zinc reagents (Table 2). Under the previously optimized conditions, we observed that cycloheptenone behaved in a similar way to cyclohexenone (entries 1 and 2). The presence of a chloro-substituent in the aromatic ring of the sulfinimine was well tolerated (entry 3). However, the reaction did not proceed on using the *t*-BS imine obtained from *p*-methoxybenzaldehyde (entry 4). For aliphatic imines, the reactivity was even better (entries 5–9). Compounds **3e–k** were obtained in enantiomerically pure form in excellent yields on using only 1.5 equiv of the enone. Similar efficiency and asymmetric induction were observed when Bu_2Zn was used (entry 9) and even with the less reactive Me_2Zn (entry 8). Importantly, the *tert*-butanesulfinyl group minimizes the competitive α-deprotonation of the imines, allowing the otherwise problematic use of enolisable imines. The mild conditions were also compatible with an ester functionality, providing access to the highly functionalized compounds **3j** (entry 10) and **3k** (entry 11) in high yields and with excellent stereocontrol.[26]

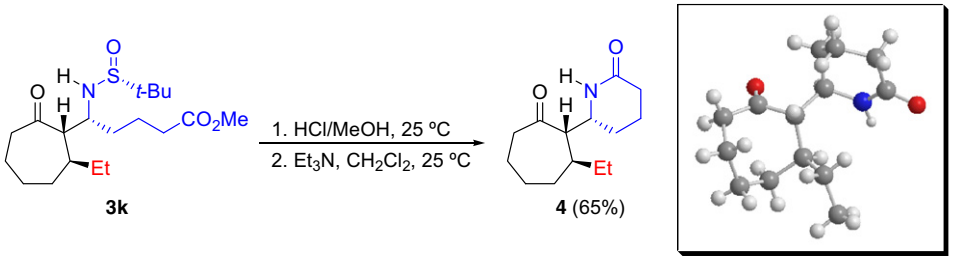
Following a recently reported procedure,[27] piperidone **4** was obtained in good yield by acidic deprotection of compound **3k** and subsequent cyclization mediated by Et_3N. Crystals of **4** were obtained from Et_2O, and X-ray crystallography revealed the stereochemistry as shown in Scheme 3. This stereochemical outcome can be explained in terms of the models proposed above for the addition of enolates

Table 2
Scopes and limitations



Entry	Equiv of R_2Zn/enone	R_2Zn	R′	*n*	Yield[a] (%) (product)
1	4:3	Et_2Zn	Ph	1	65 (**3a**)
2	4:3	Et_2Zn	Ph	2	66 (**3c**)
3	4:3	Et_2Zn	*p*-ClC_6H_4	1	68 (**3d**)
4	4:3	Et_2Zn	*p*-$MeOC_6H_4$	1	nd[b]
5	3:1.5	Et_2Zn	*n*-C_8H_{17}	1	84 (**3e**)
6	3:1.5	Et_2Zn	*n*-C_8H_{17}	2	95 (**3f**)
7	3:1.5	Et_2Zn	$(CH_2)_2Ph$	1	86 (**3g**)
8	3:1.5	Me_2Zn	$(CH_2)_2Ph$	1	86 (**3h**)
9	3:1.5	Bu_2Zn	*n*-C_8H_{17}	1	90 (**3i**)
10	3:1.5	Et_2Zn	$(CH_2)_3CO_2Me$	1	82 (**3j**)
11	3:1.5	Et_2Zn	$(CH_2)_3CO_2Me$	2	85 (**3k**)

[a] Isolated yield after column chromatography. A single stereoisomer was observed by ^1H NMR analysis of crude reaction mixtures.
[b] Not determined.



Scheme 3. Synthesis and X-ray structure of **4**.

to *t*-BS imines (Fig. 1). This situation is consistent with our presumption that the stereocontrol at the Mannich stereocentre arises purely as a result of the asymmetric *t*-BS imine induction. Interestingly, an intramolecular hydrogen bond between the amidic NH and the carbonyl group is not observed in compound **4**.

In summary, we have extended the reactivity of homochiral zinc/copper enolates to include trapping with chiral *t*-BS imines. Three contiguous stereocentres and two carbon–carbon bonds can be generated in a truly multicomponent reaction with excellent stereocontrol. We observed that whereas the enantioselection at the cycle stereocentres is governed by the phosphoramidite auxiliary, in the case of the aminic α-C stereocentre the asymmetric induction comes from the *tert*-butylsulfinyl moiety. Moreover, the present methodology allows access to four diastereomeric β-amino ketones in enantiomerically pure form, with good functional-group tolerance. The reaction can be applied to a wide range of substrates and is especially efficient when enolisable *t*-BS imines are used. Application of this stereoselective multicomponent reaction to the synthesis of diverse heterocyclic scaffolds can be easily envisioned.

Acknowledgements

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26. Typical procedure for the enantioselective synthesis of amino ketones **3**: $Cu(OTf)_2$ (6 mg, 0.016 mmol), phosphoramidite **L** (18 mg, 0.032 mmol), enone (0.75 mmol) and the corresponding *tert*-butanesulfinimine (0.50 mmol) were suspended in CH_2Cl_2 (4.0 mL) and stirred at room temperature for 20 min before cooling to −40 °C. A solution of R_2Zn (1.50 mL, 1.0 M in hexane, 3 equiv) was added dropwise and the reaction mixture was allowed to reach −20 °C while stirring overnight (12–14 h). The reaction was quenched at −20 °C by adding a saturated solution of NH_4Cl in 1:1 H_2O/MeOH (1.50 mL) and left stirring over 15 min at room temperature. The generated

precipitate was filtered through a short pad of Celite and after evaporation of solvents, ^{1}H NMR analysis of the crude sample was performed to determine the sulfinimine conversion and diastereomeric ratio of products. Purification by silica gel column chromatography, using a gradient from 3:1 to 1:1 *n*-hexane/EtOAc, gave the analytically pure compound **3**. Compound **3a**: mp 122–125 °C; $[\alpha]_D^{20}$ −115 (*c* 1.9, $CHCl_3$); R_f: 0.32 (1:1 *n*-hexane/EtOAc); HPLC analysis [HPLC analyses were performed on a JASCO 200-series equipped with a Chiralpak OD-H column] (0.7 mL/min, $\lambda = 210$, 99:1 *n*-hexane/*i*-PrOH), $t_R = 31.8$ min; ^{1}H NMR δ 7.30 (m, 5H), 5.10 (d, *J* 8.6, 1H), 4.63 (dd, *J* 8.6/5.9, 1H), 2.96 (dd, *J* 9.1/5.9, 1H), 2.30 (m, 1H), 1.90 (m, 2H), 1.70 (m, 2H), 1.40 (m, 1H), 1.16 (s, 9H), 0.93 (t, *J* 7.5, 3H); ^{13}C NMR δ 213.7, 139.9, 128.7 (CH), 128.4 (CH), 127.6 (CH), 60.7 (CH), 60.4 (CH), 56.0, 42.0 (CH_2), 40.8 (CH), 28.0 (CH_2), 25.8 (CH_2), 23.5 (CH_2), 22.7 (CH_3), 10.5 (CH_3); IR ν (cm^{-1}) 3500–3200 (br), 2960 (m), 2918 (m), 1700 (s), 1454 (s), 1039 (s), 703 (s); MS (MALDI): *m*/*z* 358 (M+Na); HRMS (MALDI) calcd for $C_{19}H_{29}NNaO_2S$ $[M+Na]^+$ 358.1817, found 358.1811. Compound *ent*-**3a**: $[\alpha]_D^{20}$ +122.7 (*c* 1.1, $CHCl_3$); HPLC analysis (0.7 mL/min, $\lambda = 210$, 99:1 *n*-hexane/*i*-PrOH), $t_{Rmaj} = 30.4$ min; other physical and spectroscopic data were found to be the same than for **3a**. Compound *ent*-**3b**: mp 108–111 °C; $[\alpha]_D^{20}$ +46.5 (*c* 1.0, $CHCl_3$); R_f: 0.35 (1:1 *n*-hexane/EtOAc); HPLC analysis (0.7 mL/min, $\lambda = 210$, 99:1 *n*-hexane/*i*-PrOH), $t_{Rmaj} = 26.9$ min, $t_{Rmin} = 31.2$ min; ^{1}H NMR δ 7.30 (m, 5H), 4.68 (dd, *J* 7.0/5.0, 1H), 4.40 (d, *J* 5.0, 1H), 2.57 (t, *J* 7.0, 1H), 2.45 (m, 1H), 2.30 (m, 1H), 1.80–2.00 (m, 4H), 1.52 (m, 2H), 1.35 (m, 1H), 1.17 (s, 9H), 0.84 (t, *J* 7.4, 3H); ^{13}C NMR δ 215.0, 141.5, 128.5 (CH), 127.7 (CH), 127.6 (CH), 61.8 (CH), 58.1 (CH), 56.0, 41.1 (CH_2), 40.3 (CH), 26.4 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 10.7 (CH_3); IR ν (cm^{-1}) 3301 (br), 2959 (s), 2872 (m), 1698 (s), 1455 (s), 1072 (s), 702 (s); MS (MALDI): *m*/*z* 358 (M+Na). Compound **3b**: $[\alpha]_D^{20}$ −41.0 (*c* 1.1, $CHCl_3$); HPLC analysis (0.7 mL/min, $\lambda = 210$, 99:1 *n*-hexane/*i*-PrOH), $t_{Rmaj} = 26.1$ min, $t_{Rmin} = 21.8$ min; other physical and spectroscopic data were found to be the same than for *ent*-**3b**. Compound **3c**: $[\alpha]_D^{20}$ −97 (*c* 2.6, $CHCl_3$); R_f: 0.30 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 7.30 (m, 3H), 7.20 (m, 2H), 4.82 (t, *J* 4.6, 1H), 4.61 (d, *J* 4.2, 1H), 2.68 (dd, *J* 9.5/4.6, 1H), 2.04 (m, 1H), 1.80–1.30 (m, 8H), 1.23 (s, 9H), 1.16 (m, 2H), 0.96 (t, *J* 7.3, 3H); ^{13}C NMR δ 216.2, 138.8, 128.7 (CH), 128.3 (CH), 128.0 (CH), 64.4 (CH), 57.9 (CH), 55.9, 44.0 (CH_2), 37.3 (CH), 32.5 (CH_2), 28.3 (CH_2), 26.7 (CH_2), 26.6 (CH_2), 22.8 (CH_3), 10.4 (CH_3); IR ν (cm^{-1}) 3302 (br), 2958 (s), 2925 (s), 2866 (m), 1695 (s), 1450 (s), 1075 (s); MS (MALDI): *m*/*z* 372.4 (M+Na). HRMS (MALDI) calcd for $C_{20}H_{31}NNaO_2S$ $[M+Na]^+$ 372.1973, found 372.1979. Compound **3d**: mp 119–122 °C; $[\alpha]_D^{20}$ −137.2 (*c* 1.1, $CHCl_3$); R_f: 0.22 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 7.25 (m, 4H), 5.13 (d, *J* 8.8, 1H), 4.59 (dd, *J* 5.7/8.8, 1H), 2.98 (dd, *J* 3.8/9.5, 1H), 2.30 (m, 2H), 1.90 (m, 2H), 1.70–1.40 (m, 4H), 1.16 (s, 9H), 0.94 (t, *J* 7.3, 3H); ^{13}C NMR δ 213.6, 138.4, 133.4, 130.1 (CH), 128.6 (CH), 60.4 (CH), 59.8 (CH), 56.0, 42.2 (CH_2), 40.9 (CH), 28.3 (CH_2), 25.7 (CH_2), 23.7 (CH_2), 22.7 (CH_3), 10.4 (CH_3); IR ν (cm^{-1}) 3292 (br), 2959 (s), 2851 (m), 1696 (s), 1488 (s), 1450 (m), 1055 (s), 1008 (m); MS (MALDI): *m*/*z* 392.3 (M+Na). HRMS (MALDI) calcd for $C_{19}H_{28}ClNNaO_2S$ $[M+Na]^+$ 392.1427, found 392.1417. Compound **3e**: $[\alpha]_D^{20}$ −51 (*c* 1.0, $CHCl_3$); R_f: 0.25 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 4.51 (d, *J* 10.7, 1H), 3.25 (t, *J* 10.8, 1H), 2.92 (dd, *J* 4.0/11.6, 1H), 2.31 (m, 2H), 2.05 (m, 1H), 1.88 (m, 1H), 1.70 (m, 2H), 1.55 (m, 3H), 1.26 (m, 15), 1.20 (s, 9H), 0.97 (t, *J* 7.3, 3H), 0.88 (t, *J* 6.8, 3H); ^{13}C NMR δ 214.4, 59.3 (CH), 57.0 (CH), 56.2, 42.7 (CH_2), 41.9 (CH), 31.9 (CH_2), 30.0 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 27.0 (CH_2), 25.3 (CH_2), 22.9 (CH_3), 22.8 (CH_2), 14.2 (CH_3), 9.9 (CH_3); IR ν (cm^{-1}) 3418 (br), 2925 (s), 2854 (m), 1696 (s), 1463 (s), 1455 (m), 1070 (s); MS (MALDI): *m*/*z* 394 ($M+Na^+$). HRMS (MALDI) calcd for $C_{21}H_{41}NNaO_2S$ $[M+Na]^+$ 394.2756, found 394.2761. Compound **3f**: $[\alpha]_D^{20}$ −39 (*c* 1.2, $CHCl_3$); R_f: 0.40 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 4.26 (d, *J* 9.3, 1H), 3.33 (m, 1H), 2.91 (dd, *J* 8.4/4.0, 1H), 2.48 (m, 2H), 1.80–1.40 (m, 12H), 1.30 (m, 11H), 1.22 (s, 9H), 0.96 (t, *J* 7.5, 3H), 0.88 (t, *J* 6.6, 3H); ^{13}C NMR δ 217.4, 61.7 (CH), 58.5 (CH), 56.1, 44.6 (CH_2), 37.8 (CH), 32.7 (CH_2), 31.9 (CH_2), 31.4 (CH_2), 29.6 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 27.0 (CH_2), 26.9 (CH_2), 26.8 (CH_2), 25.4 (CH_2), 22.9 (CH_3), 22.8 (CH_2), 14.2 (CH_3), 10.4 (CH_3); IR ν (cm^{-1}) 3258 (br), 2965 (s), 2925 (s), 2851 (m), 1696 (s), 1455 (s), 1075 (s); MS (MALDI): *m*/*z* 408 ($M+Na^+$). HRMS (MALDI) calcd for $C_{22}H_{43}NNaO_2S$ $[M+Na]^+$ 408.2912, found 408.2923. Compound **3g**: $[\alpha]_D^{20}$ −31 (*c* 3.0, $CHCl_3$); R_f: 0.20 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 7.26 (m, 3H), 7.15 (m, 2H), 4.63 (d, *J* 10.6, 1H), 3.26 (t, *J* 11.2, 1H), 2.89 (m, 2H), 2.52 (m, 1H), 2.29 (m, 2H), 2.12 (m, 1H), 1.95 (m, 1H), 1.82 (m, 1H), 1.60 (m, 3H), 1.44 (t, *J* 11.5, 1H), 1.26 (s, 9H), 1.06 (m, 1H), 0.83 (t, *J* 7.3, 3H); ^{13}C NMR δ 214.4, 141.9, 128.7 (CH), 128.5 (CH), 126.0 (CH), 59.2 (CH), 56.2, 55.9 (CH), 42.6 (CH_2), 41.9 (CH), 33.0 (CH_2), 32.2 (CH_2), 29.7 (CH_2), 25.3 (CH_2), 24.9 (CH_2), 22.9 (CH_3), 9.8 (CH_3); IR ν (cm^{-1}) 3307 (br), 2957 (s), 2866 (m), 1696 (s), 1454 (s), 1067 (s); MS (MALDI): *m*/*z* 386 ($M+Na^+$). HRMS (MALDI) calcd for $C_{21}H_{33}NNaO_2S$ $[M+Na]^+$ 386.2130, found 386.2139. Compound **3h**: $[\alpha]_D^{20}$ −27.7 (*c* 0.92, $CHCl_3$); R_f: 0.19 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 7.26 (m, 3H), 7.17 (m, 2H), 4.64 (d, *J* 10.8, 1H), 3.28 (t, *J* 11.0, 1H), 2.90 (m, 1H), 2.80 (dd, *J* 11.7/3.9, 1H), 2.53 (m, 1H), 2.30 (m, 2H), 1.95 (m, 1H), 1.77 (m, 1H), 1.60 (m, 3H), 1.44 (m, 1H), 1.26 (s, 9H), 0.83 (d, *J* 6.4, 3H); ^{13}C NMR δ 213.9, 141.9, 128.7 (CH), 128.5 (CH), 126.0 (CH), 61.7 (CH), 56.3 (CH), 56.2, 42.6 (CH_2), 36.6 (CH), 34.2 (CH_2), 33.0 (CH_2), 32.0 (CH_2), 25.5 (CH_2), 22.9 (CH_3), 19.4 (CH_3); IR ν (cm^{-1}) 3301 (br), 2956 (s), 2867 (m), 1697 (s), 1455 (m), 1066 (s); MS (MALDI): *m*/*z* 372 ($M+Na^+$). HRMS (MALDI) calcd for $C_{20}H_{31}NNaO_2S$ $[M+Na]^+$ 372.1973, found 372.1979. Compound **3i**: $[\alpha]_D^{20}$ −33.0 (*c* 1.75, $CHCl_3$); R_f: 0.35 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 4.50 (d, *J* 10.6, 1H), 3.27 (m, 1H), 2.89 (dd, *J* 11.7/4.0, 1H), 2.29 (m, 2H), 1.95 (m, 2H), 1.70 (m, 2H), 1.60–1.25 (m, 20H), 1.20 (s, 9H), 0.92 (t, *J* 6.7, 3H), 0.88 (t, *J* 7.0, 3H); ^{13}C NMR δ 59.9 (CH), 57.0 (CH), 56.2, 42.7 (CH_2), 40.9 (CH), 32.4 (CH_2), 32.0 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.0 (CH_2), 27.0 (CH_2), 25.4 (CH_2), 23.0 (CH_2), 22.9 (CH_3), 22.8 (CH_2), 14.2 (CH_3), 14.1 (CH_3); IR ν (cm^{-1}) 3307 (br), 2955 (s), 2926 (s), 2856 (m), 1698 (s), 1456 (m), 1071 (s); MS (MALDI): *m*/*z* 422 ($M+Na^+$), 400.4 (M+H). HRMS (MALDI) calcd for $C_{23}H_{45}NNaO_2S$ $[M+Na]^+$ 422.3069, found 422.3079. Compound **3j**: $[\alpha]_D^{20}$ −56 (*c* 2.7, $CHCl_3$); R_f: 0.22 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 4.54 (d, *J* 10.7, 1H), 3.67 (s, 3H), 3.27 (m, 1H), 2.94 (dd, *J* 11.7/4.0, 1H), 2.30 (m, 4H), 2.10–1.30 (m, 11H), 1.20 (s, 9H), 0.97 (t, *J* 7.3, 3H); ^{13}C NMR δ 214.4, 174.0, 59.1 (CH), 56.2, 51.6 (CH), 42.7 (CH_2), 41.9 (CH_3), 33.6 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 22.9 (CH_3), 9.8 (CH_3); IR ν (cm^{-1}) 3299 (br), 2951 (s), 2866 (m), 1732 (s), 1696 (s), 1449 (s), 1362 (m), 1161 (m), 1061 (s), 881 (m); MS (MALDI): *m*/*z* 382.4 ($M+Na^+$), 360.5 (M+H). HRMS (MALDI) calcd for $C_{18}H_{33}NNaO_4S$ $[M+Na]^+$ 382.2028, found 382.2035. Compound **3k**: $[\alpha]_D^{20}$ −52.5 (*c* 3.5, $CHCl_3$); R_f: 0.30 (1:1 *n*-hexane/EtOAc); ^{1}H NMR δ 4.24 (d, *J* 9.8, 1H), 3.67 (s, 3H), 3.31 (m, 1H), 2.97 (dd, *J* 7.7/4.0, 1H), 2.45 (m, 2H), 2.32 (t, *J* 6.9, 2H), 1.80–1.40 (m, 13H), 1.22 (s, 9H), 0.97 (t, *J* 7.1, 3H); ^{13}C NMR δ 214.4, 174.0, 59.1 (CH), 56.2, 51.6 (CH), 42.7 (CH_2), 41.9 (CH_3), 33.6 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 25.3 (CH_2), 25.1 (CH_2), 22.9 (CH_3), 9.8 (CH_3); IR ν (cm^{-1}) 3299 (br), 2951 (s), 2866 (m), 1732 (s), 1696 (s), 1449 (s), 1362 (m), 1161 (m), 1061 (s), 881 (m); MS (ES): MS (MALDI): *m*/*z* 396 ($M+Na^+$), 374.3 (M+H). HRMS (MALDI) calcd for $C_{19}H_{35}NNaO_4S$ $[M+Na]^+$ 396.2184, found 396.2195. Compound **4**: mp (Et_2O): 100–101 °C; $[\alpha]_D^{20}$ −57 (*c* 0.9, $CHCl_3$); ^{1}H NMR δ 6.15 (s, 1H), 3.93 (m, 1H), 2.45 (m, 4H), 2.25 (m, 1H), 1.90 (m, 1H), 1.80–1.40 (m, 11H), 1.30 (t, *J* 13.0, 1H), 0.95 (t, *J* 7.3, 3H); ^{13}C NMR δ 213.9, 172.6, 61.0 (CH), 53.1 (CH), 43.4 (CH_2), 33.6 (CH), 31.6 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 26.5 (CH_2), 24.7 (CH_2), 23.2 (CH_2), 20.2 (CH_2), 11.9 (CH_3); IR ν (cm^{-1}) 3389 (br), 2929 (s), 2888 (m), 1698 (s), 1649 (s), 1462 (s), 1348 (m), 1175 (m); MS (EI): *m*/*z* 237 (M^+); HRMS (EI) calcd for $C_{14}H_{23}NO_2$ $[M]^+$: 237.1729, found 237.1719.

27. Voituriez, A.; Ferreira, F.; Chemla, F. *J. Org. Chem.* **2007**, *72*, 5358.