

# 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

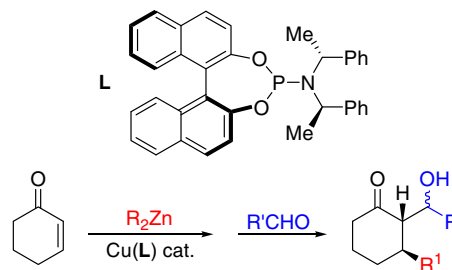
A convenient access to enantiopure  $\beta$ -amino ketones through a multicomponent reaction of dialkyl zinc reagents, cyclic enones and chiral *N*-*tert*-butanesulfinimines is disclosed. Four diastereoisomers can be selectively obtained by the appropriate choice of the chiral ligand (*L* or *ent-L*) and the chiral *N*-sulfinimine (*R<sub>S</sub>* or *S<sub>S</sub>*). The protocol is particularly efficient when enolisable *N*-sulfinimines are used.  
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**Keywords:** Conjugate addition; Multicomponent reaction; Chiral sulfinimines;  $\beta$ -Amino ketones; Dialkyl zincs

Chiral  $\beta$ -amino ketones are important building blocks for the asymmetric synthesis of biologically active molecules.<sup>1</sup> For example, these compounds have been used in the stereoselective synthesis of 1,3-aminoalcohols,<sup>2</sup> homoallylic amines,<sup>3</sup> piperidines,<sup>4</sup> indolizidines<sup>5</sup> and other alkaloids.<sup>6</sup> However, to the best of our knowledge, the only asymmetric synthesis of  $\alpha$ -substituted  $\beta$ -amino ketones is the diastereoselective addition of lithium enolates to chiral *N*-sulfinyl imines (sulfinimines) that was recently developed by Davis.<sup>7</sup> Chiral sulfinimines have been widely studied—in particular—by Davis, who proposed the use of *N*-*p*-tolyl-sulfinimines,<sup>8</sup> and by Ellman, who developed *N*-*tert*-butyl derivatives.<sup>9</sup> 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.<sup>10</sup> 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  $\beta$ -amino ketones.<sup>11</sup>

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.<sup>12</sup> 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  $\beta$  to the carbonyl group is usually formed in a stereorandom manner (Scheme 1).<sup>13</sup> Herein,



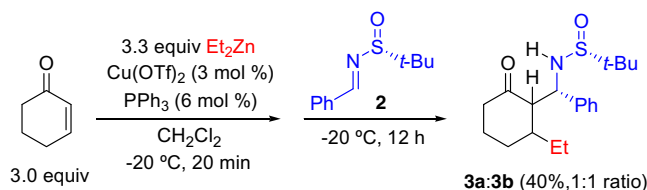
Scheme 1.

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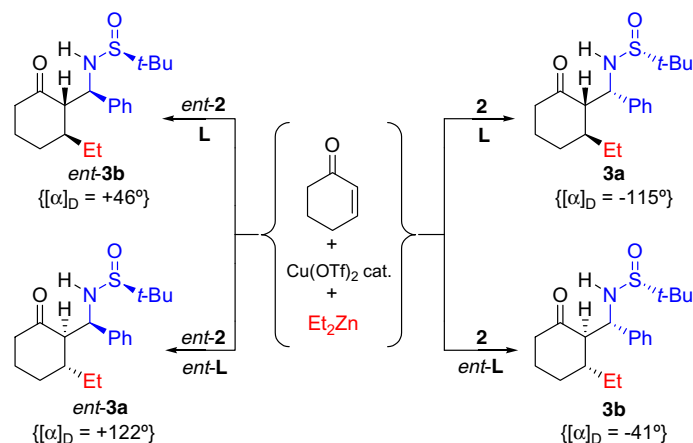
we outline our initial findings on the reactivity of homo-chiral zinc/copper<sup>14</sup> enolates with chiral sulfinimines.

*N*-*tert*-Butanesulfinimines (*t*-BS imines) are known to be less reactive with lithium enolates than other chiral sulfinimines.<sup>15</sup> However, we initially explored their reactivity due to the ready availability of both antipodes<sup>16</sup> and the high stereinduction of the *tert*-butyl group.<sup>17</sup> In a preliminary experiment, an excess of the enolate, generated by copper-catalyzed conjugate addition of diethylzinc to cyclohexenone, using PPh<sub>3</sub> 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).<sup>18</sup> 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.<sup>19</sup>



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

Table 1  
Screening and optimization of the reaction conditions<sup>a</sup>



| Entry | Ligand                | Imine                 | Equiv of Et <sub>2</sub> Zn/enone | CuL <sub>2</sub> (mol %) | Yield <sup>b</sup> (product) (%) | dr <sup>b</sup> |
|-------|-----------------------|-----------------------|-----------------------------------|--------------------------|----------------------------------|-----------------|
| 1     | <b>L</b>              | <b>2</b>              | 3.3:3                             | 3.5                      | 75 ( <b>3a</b> )                 | >98:2           |
| 2     | <b>L</b>              | <b>2</b>              | 3.3:3                             | 1.7                      | 42 ( <b>3a</b> )                 | >98:2           |
| 3     | <b>L</b>              | <b>2</b>              | 4:3                               | 3.5                      | 83 ( <b>3a</b> )                 | >98:2           |
| 4     | <b>L</b>              | <b>2</b>              | 4:2                               | 3.5                      | 66 ( <b>3a</b> )                 | >98:2           |
| 5     | <i>ent</i> - <b>L</b> | <i>ent</i> - <b>2</b> | 4:3                               | 3.5                      | 75 ( <i>ent</i> - <b>3a</b> )    | >98:2           |
| 6     | <i>ent</i> - <b>L</b> | <b>2</b>              | 4:3                               | 3.5                      | 70 ( <b>3b</b> )                 | 89:11           |
| 7     | <b>L</b>              | <i>ent</i> - <b>2</b> | 4:3                               | 3.5                      | 70 ( <i>ent</i> - <b>3b</b> )    | 91:9            |
| 8     | <b>L</b>              | <i>ent</i> - <b>2</b> | 5:3                               | 3.5                      | 75 ( <i>ent</i> - <b>3b</b> )    | >98:2           |

<sup>a</sup> A mixture of Cu(OTf)<sub>2</sub>, ligand, enone and sulfinimine was stirred over 30 min at room temperature in CH<sub>2</sub>Cl<sub>2</sub>. The reaction mixture was cooled down to –40 °C before Et<sub>2</sub>Zn was added and stirred overnight at –20 °C.

<sup>b</sup> Determined by <sup>1</sup>H NMR and chiral HPLC analysis of the crude reaction mixture.

We assumed that chiral *t*-BS imines overcome the directing effect of a chiral enolate at the Mannich stereocentre.<sup>20</sup> 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<sub>2</sub>Zn was added either before or after the sulfinimine,<sup>21</sup> indicating that enolate formation is possible in the presence of the electrophile and a truly multi-component reaction is taking place.<sup>22,23</sup> As illustrated in entries 2–4 of Table 1, 3.5 mol % of copper, 4 equiv of Et<sub>2</sub>Zn 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<sub>2</sub>Zn (entry 8).

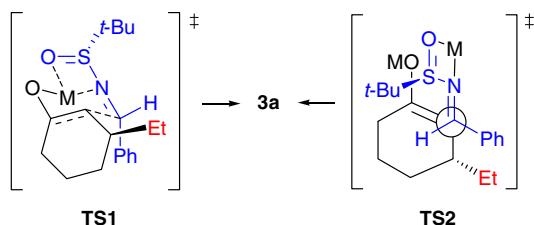


Fig. 1.

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).<sup>24</sup> 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.<sup>25</sup>

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<sub>2</sub>Zn was used (entry 9) and even with the less reactive Me<sub>2</sub>Zn (entry 8). Importantly, the *tert*-butanesulfinyl group minimizes the competitive  $\alpha$ -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.<sup>26</sup>

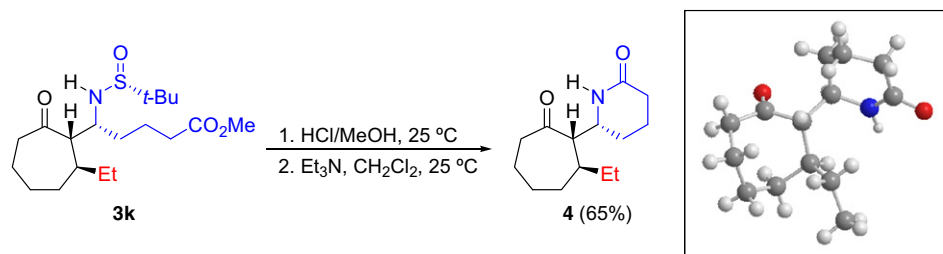
Following a recently reported procedure,<sup>27</sup> piperidone **4** was obtained in good yield by acidic deprotection of compound **3k** and subsequent cyclization mediated by Et<sub>3</sub>N. Crystals of **4** were obtained from Et<sub>2</sub>O, and X-ray crystallography revealed the stereochemistry 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 <sub>2</sub> Zn/enone | R <sub>2</sub> Zn  | R'                                                 | <i>n</i> | Yield <sup>a</sup> (%) (product) |
|-------|----------------------------------|--------------------|----------------------------------------------------|----------|----------------------------------|
| 1     | 4:3                              | Et <sub>2</sub> Zn | Ph                                                 | 1        | 65 ( <b>3a</b> )                 |
| 2     | 4:3                              | Et <sub>2</sub> Zn | Ph                                                 | 2        | 66 ( <b>3c</b> )                 |
| 3     | 4:3                              | Et <sub>2</sub> Zn | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>          | 1        | 68 ( <b>3d</b> )                 |
| 4     | 4:3                              | Et <sub>2</sub> Zn | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>         | 1        | nd <sup>b</sup>                  |
| 5     | 3:1.5                            | Et <sub>2</sub> Zn | <i>n</i> -C <sub>8</sub> H <sub>17</sub>           | 1        | 84 ( <b>3e</b> )                 |
| 6     | 3:1.5                            | Et <sub>2</sub> Zn | <i>n</i> -C <sub>8</sub> H <sub>17</sub>           | 2        | 95 ( <b>3f</b> )                 |
| 7     | 3:1.5                            | Et <sub>2</sub> Zn | (CH <sub>2</sub> ) <sub>2</sub> Ph                 | 1        | 86 ( <b>3g</b> )                 |
| 8     | 3:1.5                            | Me <sub>2</sub> Zn | (CH <sub>2</sub> ) <sub>2</sub> Ph                 | 1        | 86 ( <b>3h</b> )                 |
| 9     | 3:1.5                            | Bu <sub>2</sub> Zn | <i>n</i> -C <sub>8</sub> H <sub>17</sub>           | 1        | 90 ( <b>3i</b> )                 |
| 10    | 3:1.5                            | Et <sub>2</sub> Zn | (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me | 1        | 82 ( <b>3j</b> )                 |
| 11    | 3:1.5                            | Et <sub>2</sub> Zn | (CH <sub>2</sub> ) <sub>3</sub> CO <sub>2</sub> Me | 2        | 85 ( <b>3k</b> )                 |

<sup>a</sup> Isolated yield after column chromatography. A single stereoisomer was observed by <sup>1</sup>H NMR analysis of crude reaction mixtures.

<sup>b</sup> 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 stereo-centre 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 homo-chiral 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 multi-component 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  $\alpha$ -C stereocentre the asymmetric induction comes from the *tert*-butylsulfinyl moiety. Moreover, the present methodology allows access to four diastereomeric  $\beta$ -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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precipitate was filtered through a short pad of Celite and after evaporation of solvents,  $^1\text{H}$  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;  $[\alpha]_{\text{D}}^{20}$  –115 (c 1.9,  $\text{CHCl}_3$ );  $R_f$ : 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),  $t_{\text{R}}$  = 31.8 min;  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  213.7, 139.9, 128.7 (CH), 128.4 (CH), 127.6 (CH), 60.7 (CH), 60.4 (CH), 56.0, 42.0 (CH<sub>2</sub>), 40.8 (CH), 28.0 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 23.5 (CH<sub>2</sub>), 22.7 (CH<sub>3</sub>), 10.5 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 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  $\text{C}_{19}\text{H}_{29}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 358.1817, found 358.1811. Compound **ent-3a**:  $[\alpha]_{\text{D}}^{20}$  +122.7 (c 1.1,  $\text{CHCl}_3$ ); HPLC analysis (0.7 mL/min,  $\lambda$  = 210, 99:1 *n*-hexane/*i*-PrOH),  $t_{\text{Rmaj}}$  = 30.4 min; other physical and spectroscopic data were found to be the same than for **3a**. Compound **ent-3b**: mp 108–111 °C;  $[\alpha]_{\text{D}}^{20}$  +46.5 (c 1.0,  $\text{CHCl}_3$ );  $R_f$ : 0.35 (1:1 *n*-hexane/EtOAc); HPLC analysis (0.7 mL/min,  $\lambda$  = 210, 99:1 *n*-hexane/*i*-PrOH),  $t_{\text{Rmaj}}$  = 26.9 min,  $t_{\text{Rmin}}$  = 31.2 min;  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  215.0, 141.5, 128.5 (CH), 127.7 (CH), 127.6 (CH), 61.8 (CH), 58.1 (CH), 56.0, 41.1 (CH<sub>2</sub>), 40.3 (CH), 26.4 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 23.7 (CH<sub>2</sub>), 22.7 (CH<sub>3</sub>), 10.7 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3301 (br), 2959 (s), 2872 (m), 1698 (s), 1455 (s), 1072 (s), 702 (s); MS (MALDI):  $m/z$  358 (M+Na). Compound **3b**:  $[\alpha]_{\text{D}}^{20}$  –41.0 (c 1.1,  $\text{CHCl}_3$ ); HPLC analysis (0.7 mL/min,  $\lambda$  = 210, 99:1 *n*-hexane/*i*-PrOH),  $t_{\text{Rmaj}}$  = 26.1 min,  $t_{\text{Rmin}}$  = 21.8 min; other physical and spectroscopic data were found to be the same than for **ent-3b**. Compound **3c**:  $[\alpha]_{\text{D}}^{20}$  –97 (c 2.6,  $\text{CHCl}_3$ );  $R_f$ : 0.30 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  216.2, 138.8, 128.7 (CH), 128.3 (CH), 128.0 (CH), 64.4 (CH), 57.9 (CH), 55.9, 44.0 (CH<sub>2</sub>), 37.3 (CH), 32.5 (CH<sub>2</sub>), 28.3 (CH<sub>2</sub>), 26.7 (CH<sub>2</sub>), 26.6 (CH<sub>2</sub>), 22.8 (CH<sub>3</sub>), 10.4 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 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  $\text{C}_{20}\text{H}_{31}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 372.1971, found 372.1979. Compound **3d**: mp 119–122 °C;  $[\alpha]_{\text{D}}^{20}$  –137.2 (c 1.1,  $\text{CHCl}_3$ );  $R_f$ : 0.22 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  213.6, 138.4, 133.4, 130.1 (CH), 128.6 (CH), 60.4 (CH), 59.8 (CH), 56.0, 42.2 (CH<sub>2</sub>), 40.9 (CH), 28.3 (CH<sub>2</sub>), 25.7 (CH<sub>2</sub>), 23.7 (CH<sub>2</sub>), 22.7 (CH<sub>3</sub>), 10.4 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 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  $\text{C}_{19}\text{H}_{28}\text{ClNNaO}_2\text{S}$  [M+Na]<sup>+</sup> 392.1427, found 392.1417. Compound **3e**:  $[\alpha]_{\text{D}}^{20}$  –51 (c 1.0,  $\text{CHCl}_3$ );  $R_f$ : 0.25 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  214.4, 59.3 (CH), 57.0 (CH), 56.2, 42.7 (CH<sub>2</sub>), 41.9 (CH), 31.9 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 9.9 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3418 (br), 2925 (s), 2854 (m), 1696 (s), 1463 (s), 1455 (m), 1070 (s); MS (MALDI):  $m/z$  394 (M+Na<sup>+</sup>). HRMS (MALDI) calcd for  $\text{C}_{21}\text{H}_{41}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 394.2756, found 394.2761. Compound **3f**:  $[\alpha]_{\text{D}}^{20}$  –39 (c 1.2,  $\text{CHCl}_3$ );  $R_f$ : 0.40 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR

$\delta$  217.4, 61.7 (CH), 58.5 (CH), 56.1, 44.6 (CH<sub>2</sub>), 37.8 (CH), 32.7 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 31.4 (CH<sub>2</sub>), 29.6 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 26.9 (CH<sub>2</sub>), 26.8 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 10.4 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3258 (br), 2965 (s), 2925 (s), 2851 (m), 1696 (s), 1455 (s), 1075 (s); MS (MALDI):  $m/z$  408 (M+Na<sup>+</sup>). HRMS (MALDI) calcd for  $\text{C}_{22}\text{H}_{43}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 408.2912, found 408.2923. Compound **3g**:  $[\alpha]_{\text{D}}^{20}$  –31 (c 3.0,  $\text{CHCl}_3$ );  $R_f$ : 0.20 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  214.4, 141.9, 128.7 (CH), 128.5 (CH), 126.0 (CH), 59.2 (CH), 56.2, 55.9 (CH), 42.6 (CH<sub>2</sub>), 41.9 (CH), 33.0 (CH<sub>2</sub>), 32.2 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 24.9 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 9.8 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3307 (br), 2957 (s), 2866 (m), 1696 (s), 1454 (s), 1067 (s); MS (MALDI):  $m/z$  386 (M+Na<sup>+</sup>). HRMS (MALDI) calcd for  $\text{C}_{21}\text{H}_{33}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 386.2130, found 386.2139. Compound **3h**:  $[\alpha]_{\text{D}}^{20}$  –27.7 (c 0.92,  $\text{CHCl}_3$ );  $R_f$ : 0.19 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  213.9, 141.9, 128.7 (CH), 128.5 (CH), 126.0 (CH), 61.7 (CH), 56.3 (CH), 56.2, 42.6 (CH<sub>2</sub>), 36.6 (CH), 34.2 (CH<sub>2</sub>), 33.0 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 25.5 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 19.4 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3301 (br), 2956 (s), 2867 (m), 1697 (s), 1455 (m), 1066 (s); MS (MALDI):  $m/z$  372 (M+Na<sup>+</sup>). HRMS (MALDI) calcd for  $\text{C}_{20}\text{H}_{31}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 372.1973, found 372.1979. Compound **3i**:  $[\alpha]_{\text{D}}^{20}$  –33.0 (c 1.75,  $\text{CHCl}_3$ );  $R_f$ : 0.35 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  59.9 (CH), 57.0 (CH), 56.2, 42.7 (CH<sub>2</sub>), 40.9 (CH), 32.4 (CH<sub>2</sub>), 32.0 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>), 29.9 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.4 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 28.0 (CH<sub>2</sub>), 27.0 (CH<sub>2</sub>), 25.4 (CH<sub>2</sub>), 23.0 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 22.8 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3307 (br), 2955 (s), 2926 (s), 2856 (m), 1698 (s), 1456 (m), 1071 (s); MS (MALDI):  $m/z$  422 (M+Na<sup>+</sup>), 400.4 (M+H). HRMS (MALDI) calcd for  $\text{C}_{23}\text{H}_{45}\text{NNaO}_2\text{S}$  [M+Na]<sup>+</sup> 422.3069, found 422.3079. Compound **3j**:  $[\alpha]_{\text{D}}^{20}$  –56 (c 2.7,  $\text{CHCl}_3$ );  $R_f$ : 0.22 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  214.4, 174.0, 59.1 (CH), 56.2, 51.6 (CH), 42.7 (CH<sub>2</sub>), 41.9 (CH<sub>3</sub>), 33.6 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 9.8 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 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<sup>+</sup>), 360.5 (M+H). HRMS (MALDI) calcd for  $\text{C}_{18}\text{H}_{33}\text{NNaO}_4\text{S}$  [M+Na]<sup>+</sup> 382.2028, found 382.2035. Compound **3k**:  $[\alpha]_{\text{D}}^{20}$  –52.5 (c 3.5,  $\text{CHCl}_3$ );  $R_f$ : 0.30 (1:1 *n*-hexane/EtOAc);  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  214.4, 174.0, 59.1 (CH), 56.2, 51.6 (CH), 42.7 (CH<sub>2</sub>), 41.9 (CH<sub>3</sub>), 33.6 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 25.3 (CH<sub>2</sub>), 25.1 (CH<sub>2</sub>), 22.9 (CH<sub>3</sub>), 9.8 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 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<sup>+</sup>), 374.3 (M+H). HRMS (MALDI) calcd for  $\text{C}_{19}\text{H}_{35}\text{NNaO}_4\text{S}$  [M+Na]<sup>+</sup> 396.2184, found 396.2195. Compound **4**: mp (Et<sub>2</sub>O): 100–101 °C;  $[\alpha]_{\text{D}}^{20}$  –57 (c 0.9,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR  $\delta$  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);  $^{13}\text{C}$  NMR  $\delta$  213.9, 172.6, 61.0 (CH), 53.1 (CH), 43.4 (CH<sub>2</sub>), 33.6 (CH), 31.6 (CH<sub>2</sub>), 28.8 (CH<sub>2</sub>), 28.0 (CH<sub>2</sub>), 26.5 (CH<sub>2</sub>), 24.7 (CH<sub>2</sub>), 23.2 (CH<sub>2</sub>), 20.2 (CH<sub>2</sub>), 11.9 (CH<sub>3</sub>); IR  $\nu$  (cm<sup>–1</sup>) 3389 (br), 2929 (s), 2888 (m), 1698 (s), 1649 (s), 1462 (s), 1348 (m), 1175 (m); MS (EI):  $m/z$  237 (M<sup>+</sup>); HRMS (EI) calcd for  $\text{C}_{14}\text{H}_{23}\text{NO}_2$  [M]<sup>+</sup>: 237.1729, found 237.1719.

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