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Synthesis of ACAT inhibitors through substitution using allylic picolinate and copper reagent

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ABSTRACT

Amide of an octanoic acid possessing an aryl group at C3 position is a highly potent ACAT inhibitor. In this paper, we describe a synthetic access to this class of compounds as optically active forms. The key reaction is substitution of the allylic picolinate of (*S*,*Z*)-8-(benzyloxy)oct-5-en-4-ol with a copper reagent derived from (benzo[*d*][1,3]dioxol-4-yl)MgBr and CuBr·Me_2S to produce *anti* S_N2' product regio- and stereo-selectively. The product was hydrogenated to afford (*S*)-3-benzo[*d*][1,3]dioxol-4-yloctan-1-ol, which upon oxidation furnished the octanoic acid. Finally, the acid was converted with 2,6-(*i*-Pr)$_2$ $C_6H_3NH_2$ to the target amide via acid chloride. In a similar way, the one-carbon long homolog was synthesized.

Recently, we have reported allylic picolinates that are suited for allylic substitution with organocopper reagents derived from Grignard reagents and CuBr·Me_2S to deliver *anti* S_N2' products highly efficiently in terms of yields and regio/stereoselectivity.[1,2] One of the significant advantages of using the picolinate is its compatibility with a wide range of aryl copper reagents, whereas the previous methods with aryl copper reagents had suffered from low selectivity[3] except for specific substrates.[4] The picolinate method was then extended to organolithium-based copper reagents,[5] which in the presence of $MgBr_2$ furnished *anti* S_N2' products as well, thus allowing us to use several preparations of organolithiums for the substitution. With these results in mind we have interest in developing a synthesis of an optically active form of acylcoenzyme cholesterol acyltransferase (ACAT) inhibitors of the general structure **1** shown in Figure 1.[6] Among them, racemic octanoic acid derivative *rac*-**1a**[7] inhibits ACAT in human hepatoma cells (HepG2) with IC_{50} = 0.018 μM. Synthesis of *rac*-**1a** was accomplished by amide formation of the corresponding acid chloride with 2,6-(*i*-Pr)2$C_6H_3NH_2$,[6] and the acid was in turn prepared from the aryl aldehyde (Ar^1CHO) by constructing the octanoic acid structure on it through the nor-acid.[8] The method is, however, inconvenient in the preparation of derivatives with varying aryl groups since the group is involved in the synthesis from the beginning.

To avoid the strategic inconvenience, we envisioned a method illustrated in Scheme 1, in which the aryl copper reagent is installed to the octanoic chain **2** by using allylic substitution to produce *anti* S_N2' product **4** as the key intermediate. Herein, we present results of the investigation.

The requisite picolinate **2** was prepared by using a sequence of reactions summarized in Scheme 2. 3-Butyn-1-ol (**6**) was converted

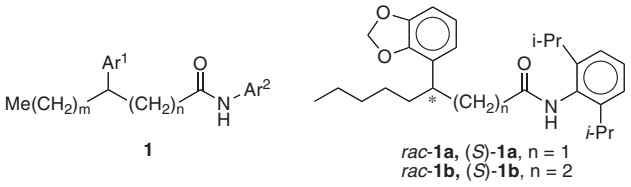
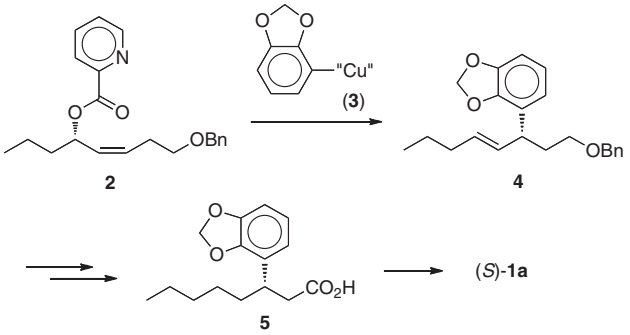


Figure 1. The general structure for the ACAT inhibitors and targets we have chosen.



Scheme 1. Strategy for synthesis of (*S*)-**1a**.

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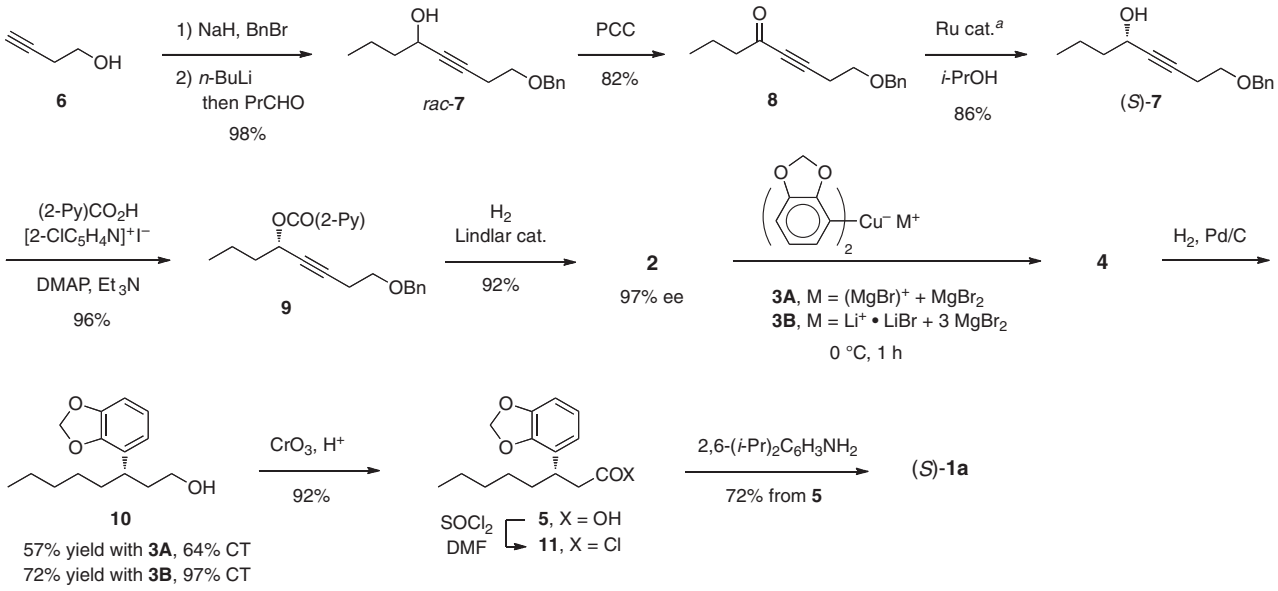
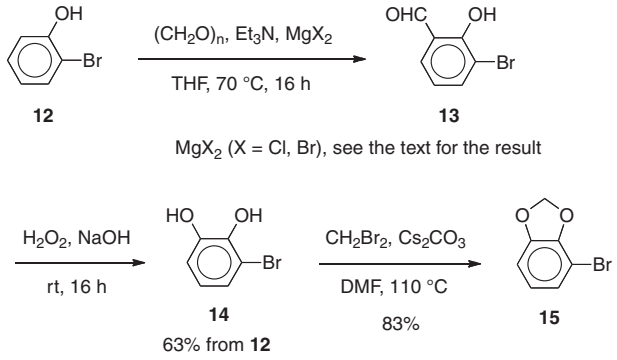


Scheme 2. Synthesis of (*S*)-**1a**. [a]Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene).

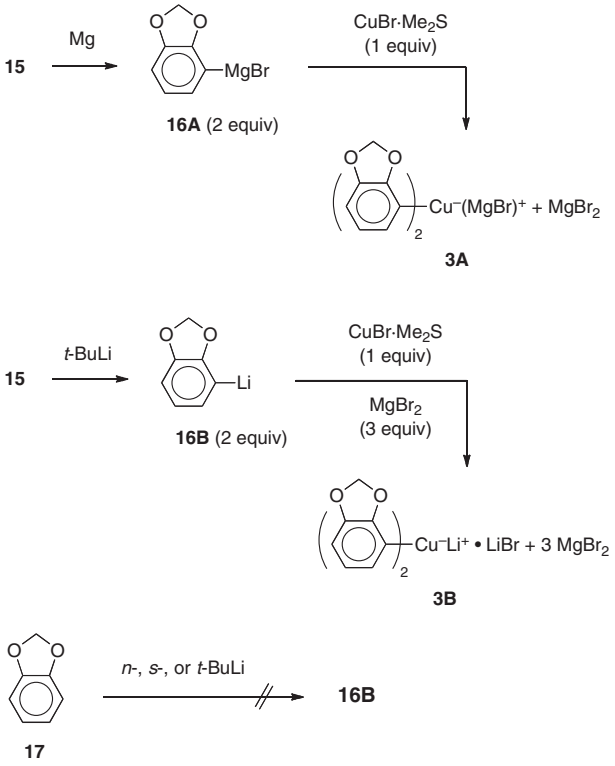
to ketone **8** in three steps using the standard reactions. Asymmetric reduction of **8** with Ru[(*S*,*S*)-TsDPEN](*p*-cymene)[9] as a catalyst in *i*-PrOH gave (*S*)-**7**, which was transformed to the key picolinate **2** by esterification with (2-Py)CO_2H followed by Lindlar hydrogenation. Enantiomeric excess (ee) of **2** was 97% by chiral HPLC analysis and purity of the *cis* olefin was >99% by ^1H NMR spectroscopy (δ 2.49–2.69 (m, 2 H) for **2**; 2.32–2.43 (m, 2H) for the trans isomer[10]).

For preparation of the bromide **15** via bromocatechol **14** we followed the literature protocol[11] consisting of the *ortho* formylation of bromophenol **12** using $(CH_2O)_n$, Et_3N, and $MgCl_2$ followed by the Dakin oxidation of the resulting aldehyde with H_2O_2 in one-pot (Scheme 3). However, a mixture of **14**, 3-bromo-2-hydroxybenzyl alcohol, and unidentified products were obtained in our hand. The first-step was then re-examined to find that the reaction with $MgBr_2$ at 70 °C proceeded cleanly to afford aldehyde **13**, whereas the use of original $MgCl_2$ gave a mixture of **13** and others. The Dakin oxidation of the aldehyde proceeded well to produce catechol **14** in 63% yield from **12**.[12] The yield was higher than that published[11] (55% yield). Finally, reaction with CH_2Br_2 gave **15** in 83% yield.

The Grignard reagent **16A** in THF was derived from bromide **15** and Mg turnings as usual and mixed with CuBr·Me_2S in a 2:1 ratio at 0 °C for 30 min to prepare the copper reagent **3A** (Scheme 4), which was subjected to reaction with allylic picolinate **2** at 0 °C for 1 h to produce the desired product **4** and the residue(s) derived

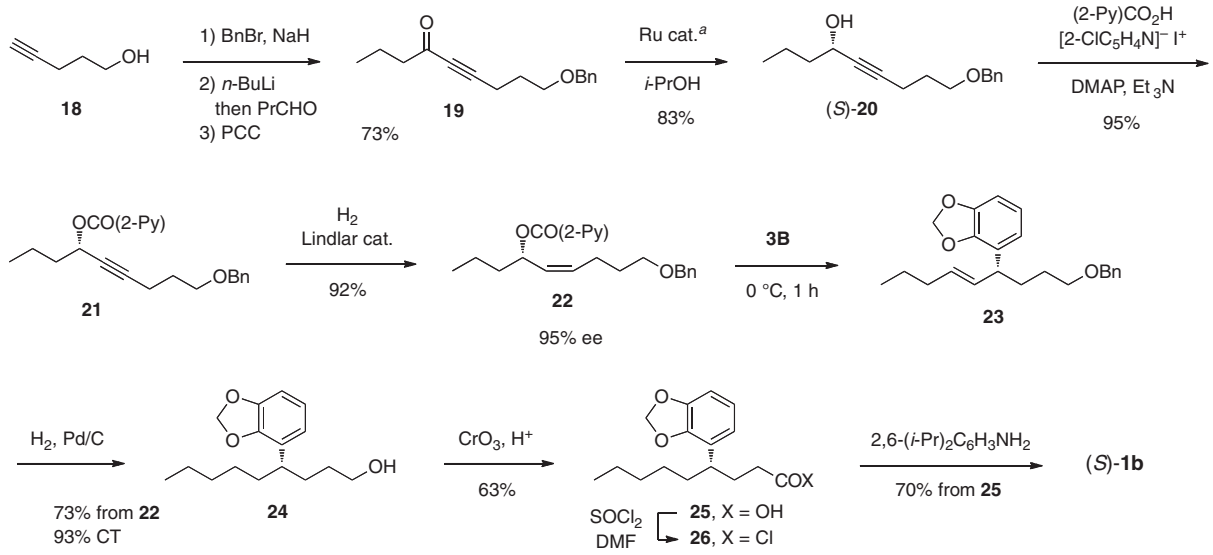


Scheme 3. Preparation of bromide **15**.



Scheme 4. Preparation of copper reagents **3A** and **3B**.

from the reagent. Due to the close R_f values of the products on TLC, the mixture was hydrogenated with 10% Pd/C under hydrogen to afford the polar octanol derivative **10**, which was isolated easily by chromatography on silica gel. However, the yield was 57% and chirality transfer (CT) determined by chiral HPLC analysis was insufficiently 64%. The observed suspension of **16A** in THF might be responsible for the unsatisfactory result.[13] We then investigated substitution with a lithium-based copper reagent. Although *ortho* lithiation[14] of catechol derivative **17** with *n*-, *s*-, and *t*-BuLi was unsuccessful,[15] halogen–lithium exchange of **15** with *t*-BuLi



Scheme 5. Synthesis of (*S*)-**1b**. [a]Ru cat. = Ru[(*S*,*S*)-TsDPEN](*p*-cymene).

cleanly produced anion **16B**,[15] which was subsequently mixed with $CuBr{\cdot}Me_2S$ to afford the other copper reagent **3B**. Substitution of picolinate **2** with the reagent **3B** (1 equiv) at 0 °C proceeded cleanly in the presence of $MgBr_2$ (5 equiv) to deliver *anti* S_N2' product **4**, which was converted to alcohol **10** in 72% yield over two steps with 97% CT.[16] Jones oxidation furnished acid **5** in 92% yield. Finally, the acid was transformed to (*S*)-**1a** in 72% yield through the acid chloride **11**.[17,18]

To show flexibility of the method, we then targeted the homolog (*S*)-**1b**. As shown in Scheme 5, allylic picolinate **22** was prepared from **18** in a similar manner to picolinate **2**. Briefly, ketone **19** was prepared from alcohol **18** in 73% yield and reduced with Ru[(*S*,*S*)-TsDPEN](*p*-cymene) in *i*-PrOH to afford alcohol (*S*)-**20**, which upon esterification with $(2\text{-Py})CO_2H$ and reduction with Lindlar catalyst delivered picolinate **22** with 95% ee by chiral HPLC analysis. Allylic substitution of **22** and **3B** in the presence of $MgBr_2$ proceeded smoothly and subsequent hydrogenation gave alcohol **24** in 73% yield from picolinate **22**. Finally, Jones oxidation followed by amide formation of the resulting acid **25**[17] with $2,6\text{-}(i\text{-Pr})_2C_6H_3NH_2$ afforded (*S*)-**1b** in good yield.

In summary, the potential ACAT inhibitor (*S*)-**1a** was synthesized as an optically active form. Total yield from **6** in 11 steps was 29%, whereas that of *rac*-**1a** calculated for the 12 steps from benzo[*d*][1,3]dioxole-4-carbaldehyde in the literature is 6.7%.[6,8] Furthermore, the flexibility of the method is demonstrated by synthesis of the homolog (*S*)-**1b**.

Acknowledgment

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References and notes

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7. (*S*)-**1a** was also synthesized via the nor-acid, which was obtained by optical resolution in 39% yield, whereas the potency of (*S*)-**1a** is not reported.
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9. Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738–8739.
10. The trans isomer was prepared by reduction of *rac*-**7** with $LiAlH_4$ followed by esterification with picolinic acid: ^1H NMR (300 MHz, $CDCl_3$) δ (diagnostic signals) 1.64–1.77 (m, 1H), 1.80–1.93 (m, 1H), 2.32–2.43 (m, 1H), 3.51 (t, J = 7 Hz, 2H), 4.50 (s, 2H), 5.56 (q, J = 7 Hz, 1H), 5.66 (ddt, J = 15, 7.5, 1 Hz, 1H), 5.86 (dt, J = 15, 7 Hz, 1H).
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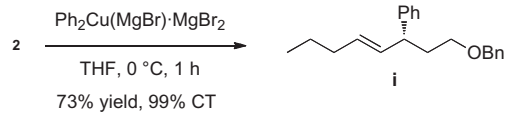
12. Isolated yields of **13** from **12** and **14** from **13** in repeated reactions were 65% and 80% yields, respectively.
13. In contrast, PhMgBr in THF was prepared (as a clean solution), and converted to $Ph_2Cu^-(MgBr)^+$, which upon reaction with **2** successfully gave the product **i** with 99% CT. The result suggests that purity of the reagent **3A** is a likely reason for the low efficiency of the reaction.



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15. Checked by addition reaction to $p\text{-}MeOC_6H_4CHO$.
16. To a solution of bromide **15** (58 mg, 0.288 mmol) in THF (1 mL) was added *t*-BuLi (0.37 mL, 1.57 M in *n*-pentane, 0.581 mmol) dropwise at −78 °C. The resulting mixture was stirred at −78 °C for 30 min, and added to an ice-cold mixture of $CuBr{\cdot}Me_2S$ (30 mg, 0.146 mmol) and a THF solution of $MgBr_2$ (3.6 mL, 0.20 M, 0.720 mmol). After 30 min at 0 °C, a solution of picolinate **2** (49 mg, 0.144 mmol) in THF (1 mL) was added to the mixture. The reaction was carried out at 0 °C for 1 h and quenched by addition of saturated NH_4Cl. The resulting mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford **4**, which was passed through a short silica gel column for the next reaction. A mixture of **4** prepared above and 10% Pd/C (30 mg) in MeOH (2 mL) was stirred at rt overnight under hydrogen, diluted with EtOAc, and filtered through a pad of Celite. The filtrate was concentrated and the residue was purified by chromatography on silica gel with (hexane/EtOAc) to afford alcohol **10** (26 mg,

72% over two steps from **2**): $[\alpha]_D^{24}$ +4.9 (*c* 0.72, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7 Hz, 3 H), 1.10–1.32 (m, 4 H), 1.48 (br s, 1 H), 1.53–1.85 (m, 3 H), 1.88–2.01 (m, 1 H), 2.83–2.95 (m, 1 H), 3.45 (ddd, *J* = 11, 8, 6 Hz, 1H), 3.57 (dq, *J* = 11, 5 Hz, 1H), 5.91 (d, *J* = 1.5, 1H), 5.93 (d, *J* = 1.5, 1H), 6.66 (dd, *J* = 8, 1.5 Hz, 1H), 6.69 (dd *J* = 8, 1.5 Hz, 1H), 6.79 (dd, *J* = 8, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (−), 27.3 (−), 31.9 (−), 35.1 (−), 36.4 (+), 38.4 (−), 61.2 (−), 100.4 (−), 106.5 (+), 120.8 (+), 121.9 (+), 126.6 (−), 145.5 (−), 147.0 (−).

17. The ^1H NMR spectra of **5**, (*S*)-**1a**, and **25** were consistent with the data reported.[6]
18. Characterization data: acid **5**: $[\alpha]_D^{24}$ 0 (*c* 0.38, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J* = 7 Hz, 3H), 1.08–1.35 (m, 6 H), 1.54–1.76 (m, 2H), 2.66 (dd, *J* = 16, 8 Hz, 1H), 2.72 (dd, *J* = 16, 8 Hz, 1H), 3.11–3.24 (m, 1H), 5.92 (s, 2H), 6.65 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.69 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (−), 27.1 (−), 31.7 (−), 34.4 (−), 37.2 (+), 39.5 (−), 100.6 (−), 106.9 (+), 121.4 (+), 121.6 (+), 125.6 (−), 145.2 (−), 147.3 (−), 178.4 (−). Amide (*S*)-**1a**: $[\alpha]_D^{24}$ +26 (*c* 0.34, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7 Hz, 3 H), 1.08 (d, *J* = 7 Hz, 12H), 1.15–1.35 (m, 8 H), 1.62–1.80 (m, 2 H), 2.77 (dd, *J* = 14.5, 5.5 Hz, 1 H), 2.87 (dd, *J* = 14.5, 10.5 Hz, 1H), 3.29–3.37 (m, 1H), 5.94 (s, 1H), 5.96 (s, 1H), 6.56 (s, 1H), 6.73–6.76 (m, 2H), 6.80 (dd, *J* = 9, 7 Hz, 1H), 7.09 (d, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (−), 23.6 (+), 23.8 (+), 27.1 (−), 28.6 (+), 31.8 (−), 35.3 (−), 38.8 (+), 42.0 (−), 100.6 (−), 107.1 (+), 122.0 (+), 122.1 (+), 123.4 (+), 125.8 (−), 128.4 (+), 131.0 (−), 145.1 (−), 146.3 (−), 147.4 (−), 171.2 (−). Alcohol **24**: $[\alpha]_D^{26}$ −4 (*c* 0.811, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 6.5 Hz, 3H), 1.10–1.32 (m, 6H), 1.34–1.78 (m, 7H), 2.71 (dq, *J* = 7, 7 Hz, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 5.91 (s, 2H), 6.64 (dd, *J* = 8, 1 Hz, 1H), 6.68 (dd, *J* = 8, 1 Hz, 1H), 6.77 (t, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5 (+), 22.6 (−), 27.3 (−), 31.0 (−), 31.4 (−), 31.9 (−), 35.3 (−), 40.1 (+), 63.1 (−), 100.3 (−), 106.3 (+), 121.0 (+), 121.6 (+), 127.4 (−), 145.4 (−), 147.0 (−). Acid **25**: $[\alpha]_D^{26}$ −7 (*c* 0.21, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J* = 6.5 Hz, 3H), 1.10–1.32 (m, 6H), 1.47–1.78 (m, 2H), 1.82–2.07 (m, 2 H), 2.22 (t, *J* = 6.5 Hz, 2H), 2.65–2.78 (m, 1H), 5.91 (s, 2 H), 6.62 (dd, *J* = 8, 1 Hz, 1H), 6.69 (dd, *J* = 8, 1 Hz, 1H), 6.77 (t, *J* = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (−), 27.3 (−), 29.9 (−), 31.9 (−), 32.2 (−), 35.0 (−), 39.9 (+), 100.5 (−), 106.6 (+), 121.0 (+), 121.7 (+), 126.1 (−), 145.5 (−), 147.1 (−), 179.7 (−). Amide (*S*)-**1b**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7 Hz, 3H), 1.19 (d, *J* = 7 Hz, 12H), 1.00–1.32 (m, 8H), 1.49–2.37 (m, 4H), 2.76–2.89 (m, 1H), 2.96–3.16 (m, 2H), 5.92 (d, *J* = 1.5 Hz, 1H), 5.93 (d, *J* = 1.5 Hz, 1H), 6.58 (br s, 1H), 6.69 (d, *J* = 8 Hz, 1H), 6.73 (d, *J* = 8 Hz, 1H), 6.82 (t, *J* = 8 Hz, 1H), 7.16 (d, *J* = 7 Hz, 2H), 7.25–7.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1 (+), 22.6 (−), 23.8 (+), 27.3 (−), 28.8 (+), 31.3 (−), 31.9 (−), 35.0 (−), 35.3 (−), 40.2 (+), 100.4 (−), 106.7 (+), 121.2 (+), 121.9 (+), 123.5 (+), 126.6 (−), 128.4 (+), 131.2 (−), 145.5 (−), 146.4 (−), 147.1 (−), 172.4 (−).