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Synthesis of Orthogonally Protected (*R*)- and (*S*)-2-Methylcysteine via an Enzymatic Desymmeterization and Curtius Rearrangement

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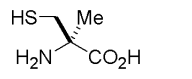
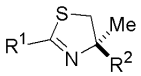
Abstract: A synthesis of differentially protected (*R*)- and (*S*)-2-methylcysteines is described. Monomethylation of dimethylmalonate followed by alkylation with *tert*-butylchloromethyl sulfide gave an achiral diester. Desymmeterization by selective hydrolysis of one ester with pig-liver esterase gave the acid in 97% chemical yield and 91% enantiomeric excess. Heating this acid with diphenylphosphoryl azide followed by 4-methoxybenzyl alcohol gave protected (*R*)-2-methylcysteine. Alternately, the acid and ester groups were interchanged and heated with diphenylphosphoryl azide followed by 4-methoxybenzyl alcohol, giving protected (*S*)-2-methylcysteine.

The amino acid 2-methylcysteine (**1**) occurs naturally in both (*R*)- and (*S*)-stereochemical configurations. It is present in the thiazoline rings (**2**) of a number of natural products including mirabazoles A−C,[1a,b] tantazoles A−F,[1b,c] thiangazole,[1d,e] thiazohalostatin,[1f,g] yersiniabactin,[1h] and 4-methylaeruginoic acid.[1i]

The key to any synthesis of 2-methylcysteine is control of stereochemistry at the tetrasubstituted α-carbon. A number of different synthetic strategies have been reported that address this issue. The first reported synthesis of 2-methylcysteine uses valine as a chiral auxiliary to direct the thiomethylation of an alanine derivative at its α-position.[2] Two other methods utilize strategies based on the principles of self-regeneration of stereocenters[3] to stereoselectively thiomethylate an alanine derivative[4] and methylate a cysteine derivative[5] at their α-positions, respectively. The forth method accesses 2-methylcysteine by nucleophilic opening of the *β*-lactone derived from (*R*)- or (*S*)-*N*-(*t*-Boc)-2-methylserine with a thiolate nucleophile.[6a,b] Finally, 2-methylcysteine has been synthesized from 2-methylglycidol, by way of 2-methylserine.[7a,b] With the exception of the methods reported by Fukuyama and Goodman,[6a,b] all of these methods utilize starting materials from the chiral pool.



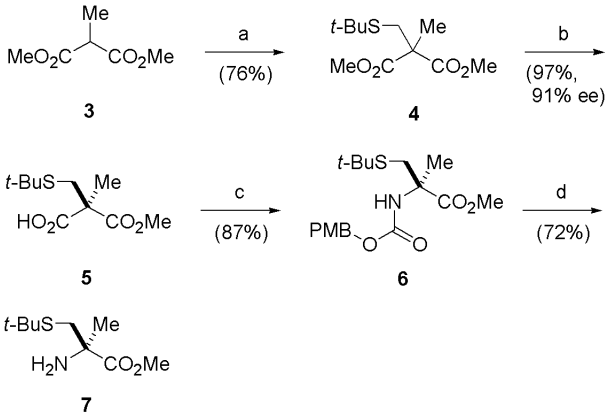
(*R*)-2-methylcysteine (**1**)



thiazoline of (*R*)-2-methylcysteine (**2**)

FIGURE 1.

SCHEME 1. Protected (*R*)-2-Methylcysteine[a]



[a] Reagents and conditions: (a) LHMDS, *t*-BuSCH$_2$Cl, THF, 20 h; (b) PLE, pH 7.2 phosphate buffer, 2 N NaOH, 8 h; (c) (i) diphenylphosphoryl azide (DPPA), Et$_3$N, (CH$_2$Cl)$_2$, reflux, 100 min; (ii) PMBOH, reflux, 4 h; (d) 10% TFA/CH$_2$Cl$_2$.

Our synthetic efforts toward the tantazoles and mirabazoles required significant quantities of both enantiomers of 2-methylcysteine, with orthogonal protection of all functionalities. Furthermore, we wanted a method that was as short as possible and utilized inexpensive starting materials to facilitate large-scale preparations. Therefore, we developed the synthesis of 2-methylcysteine described in Scheme 1.

Dimethyl malonate was monomethylated by a literature procedure[8] to give dimethyl 2-methylmalonate (**3**). This compound was then deprotonated with lithium bis(trimethylsilyl)amide (LHMDS) in THF and alkylated with *tert*-butylchloromethyl sulfide[9] to give achiral diester **4**.

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The next step involved an enzymatic hydrolysis of one ester of **4** with pig-liver esterase (PLE). Compound **4** was treated with PLE in a pH 7.2 phosphate buffer, with rapid stirring. The PLE was used as supplied [EC 3.1.1.1, pH 8 suspension in 3.2 M $(NH_4)_2SO_4$], at a loading level of 90 units per mmol of substrate. This enzyme level was selected because it gave convenient reaction times; however, lower loading levels also seem feasible. The acidity of the mixture was monitored throughout the reaction, and 2 N NaOH solution was added dropwise as needed to maintain a constant pH of 7.2. The reaction started off as biphasic, but became nearly homogeneous near the end. The reaction's end point could be estimated by monitoring the amount of NaOH consumed, and by the rate of pH change. After 1 equiv of NaOH had been consumed, the rate of pH change slowed dramatically, indicating a nearly complete reaction. The acid (**5**) was isolated by extraction as a white solid.

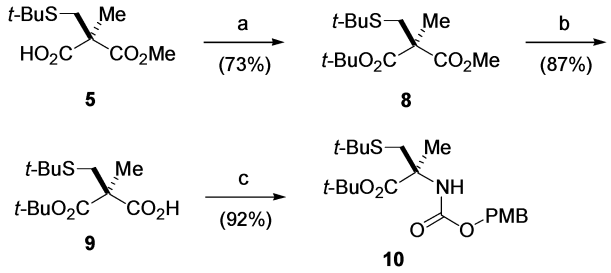
To determine the optical purity of **5**, a salt with (*S*)-α-methylbenzylamine was formed and analyzed by ^{1}H NMR. For comparison, racemic **5** was synthesized from **4** by saponification with lithium hydroxide. The resulting racemic acid was treated with 1 equiv of (*S*)-α-methylbenzylamine and analyzed by ^{1}H NMR. The resulting diastereomeric salts contained several well-resolved peaks, including methyl ester peaks at 3.58 and 3.56 ppm. Through integration of these peaks, the ratio of enantiomers obtained in the PLE reaction was determined to be 96% in favor of (*R*)-2-methylcysteine, for an enantiomeric excess (ee) of 91%.

There are several literature accounts of 2,2-disubstituted malonate diesters being selectively hydrolyzed by PLE.[6a,10a,b] The selectivity of the reaction reportedly depends greatly on substrate substitution. The most favorable results are obtained when the malonate diesters contain a methyl group in the 2-position and the other 2-substituent is bulky. Such substrates are reported to favor formation of the (*R*)-enantiomer, which was also observed in this study. It has also been reported that using DMSO as a cosolvent can help improve selectivity in some reactions with PLE. However, with **4** a decline in both chemical and optical yields was observed with use of a 5% DMSO cosolvent.

The acid **5** was next treated with diphenylphosphoryl azide and triethylamine in 1,2-dichloroethane, which resulted in rapid formation of an acyl azide (not isolated). Refluxing this solution promoted a Curtius rearrangement to the corresponding isocyanate (not isolated), which was treated with *p*-methoxybenzyl alcohol (PMBOH) to give **6**. These reactions resulted in retention of configuration to give protected (*R*)-2-methylcysteine. The sequence was carried out without predrying of solvents and reagents. The choice of alcohol (PMBOH) used in this reaction was based on the ease with which the resulting carbamate is cleaved with mild acid. Other alcohols could potentially be used, which would alter the properties of the resulting nitrogen protecting group.

To confirm the absolute stereochemistry of **6**, and to check its optical purity, it was converted to compound **7**. The enantiomer of **7** (*ent*-**7**) is known in optically pure form.[2,11] The magnitude of the reported optical rotation of *ent*-**7** compares very favorably with that of **7** obtained in this study, and is opposite in sign.[12]

SCHEME 2. Protected (*S*)-2-Methylcysteine[a]



[a] Reagents and conditions: (a) *t*-BuOH, H_2SO_4, $MgSO_4$, CH_2Cl_2, 24 h; (b) LiOH, H_2O, THF, $(n\text{-Bu})_4NHSO_4$; (c) (i) DPPA, Et_3N, $(CH_2Cl)_2$, reflux, 100 min; (ii) PMBOH, reflux, 4 h.

The conversion of acid **5** into protected (*S*)-2-methylcysteine involves swapping the ester and acid functionalities, followed by a Curtius rearrangement. In Scheme 2 the acid **5** was converted into ester **8** by treatment with acid adsorbed on magnesium sulfate and *tert*-butyl alcohol.[13] Saponification of the methyl ester with lithium hydroxide gave acid **9**. Finally, **9** was subjected to the Curtius rearrangement conditions used previously, and gave protected (*S*)-2-methylcysteine (**10**) in 92% yield.

In summary, we have developed syntheses of orthogonally protected (*R*)- and (*S*)-2-methylcysteine from dimethyl malonate that proceed in four steps and six steps, respectively. Key steps in this sequence include an enzymatic desymmeterization of an achiral malonate diester and a Curtius rearrangement to selectively form the carbon−nitrogen bond. This new method is amenable to large-scale preparations and should prove useful in future syntheses of 2-methylcysteine-containing compounds.

Experimental Section

Dimethyl 2-*tert*-Butylsulfanylmethyl-2-methylmalonate (4). A 1 M solution of LHMDS in THF (95.4 mL, 95.4 mmol) was cooled to 0 °C under an atmosphere of N_2. A solution of dimethyl 2-methylmalonate (13.94 g, 95.40 mmol) in THF (28 mL) was added over 5 min, with stirring. After an additional 15 min, *tert*-butylchloromethyl sulfide (14.55 g, 104.9 mmol, 1.1 equiv) was added dropwise over 5 min, with stirring. The cooling bath was removed and the solution was stirred at room temperature for 20 h. The solution was then diluted with ether (330 mL), washed twice with 1 N HCl, washed with brine, dried over $MgSO_4$, and filtered, and the solvents were evaporated under vacuum. The resulting liquid was vacuum distilled (74−80 °C, 0.26 Torr), giving the clear colorless liquid product (18.12 g, 76%): TLC R_f 0.35 (4:1 hexane/Et_2O); IR (NaCl, cm^{-1}) 2957, 1739, 1459, 1290, 1238, 1172, 1110; ^{1}H NMR ($CDCl_3$, δ ppm) 3.74 (s, 6 H), 3.04 (s, 2 H), 1.50 (s, 3 H), 1.31 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 171.5, 54.0, 52.6, 42.3, 33.5, 30.6, 19.8; FAB LRMS *m*/*z* (M + H) 249. Anal. Calcd for $C_{11}H_{20}O_4S$: C, 53.20; H, 8.12; S, 12.91. Found: C, 53.34; H, 8.44; S, 13.12.

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(11) The authors synthesized the compound in (*S*)-form but mistakenly refer to it as (*R*).

(12) For **7** obtained in this study $[\alpha]^{25}_D$ +19.6 (*c* 1.00, EtOH), purity 91% ee. Reported value for *ent*-**7** $[\alpha]^{20}_D$ −16.3 (*c* 1.00, EtOH), reported purity >95% ee.[2]

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(*R*)-2-*tert*-Butylsulfanylmethyl-2-methylmalonic Acid Monomethyl Ester (5). Diester **4** (17.74 g, 71.43 mmol) was mixed with 0.1 N NaH_2PO_4 solution (713 mL) and adjusted to pH 7.2 with 2 N NaOH. Pig-liver esterase [EC 3.1.1.1, 1.8 mL of a suspension in 3.2 M $(NH_4)_2SO_4$, 6430 units] was added, and the heterogeneous mixture was stirred rapidly. The pH was maintained between 7 and 7.2 by addition of 2 N NaOH, with stirring. After 8 h the reaction had consumed 1 molar equiv of NaOH and the pH change slowed dramatically. The reaction was worked up by addition of 2 N NaOH to reach pH 9, and the mixture was washed once with ether. The pH was then adjusted to 2 by addition of 2 N HCl, and the mixture was extracted with ether three times. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the ether was removed under vacuum to give the product as a clear colorless oil that crystallized (16.26 g, 97%, 91% ee): TLC R_f 0.26 (16:4:1 hexane/Et_2O/AcOH); mp 43−45 °C; $[\alpha]^{26}_D$ −1.0 (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3100 (br), 2961, 1738, 1723, 1460, 1292, 1239, 1206, 1164, 1114; ^{1}H NMR ($CDCl_3$, δ ppm) 3.78 (s, 3 H), 3.08 (d, J = 12.0 Hz, 1 H), 3.02 (d, J = 12.0 Hz, 1 H), 1.54 (s, 3 H), 1.32 (s, 9 H); ^{1}H NMR as the salt of (*S*)-α-methylbenzylamine ($CDCl_3$, δ ppm) 7.42−7.29 (m, 5 H), 6.69 (br s, 3 H), 4.30 (m, 1 H), 3.58 (s, −OC*H*$_3$, major *S*,*R*-diastereomeric salt, 3 H), 3.56 (s, −OC*H*$_3$, minor *S*,*S*-diastereomeric salt, 4% the intensity of the major isomer), 2.99 (d, J = 11.6 Hz, 1 H), 2.79 (d, J = 11.6 Hz, 1 H), 1.57 (d, J = 6.8 Hz, 3 H), 1.27 (apparent s, 12 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.6, 171.3, 54.1, 52.8, 42.4, 33.3, 30.5, 19.8; FAB LRMS *m*/*z* (M + H) 235, (M − isobutene) 179. Anal. Calcd for $C_{10}H_{18}O_4S$: C, 51.26; H, 7.74; S, 13.69. Found: C, 51.24; H, 7.77; S, 13.53.

(±)-2-*tert*-Butylsulfanylmethyl-2-methylmalonic Acid Monomethyl Ester (5). Diester **4** (53.0 mg, 0.213 mmol) was mixed with MeOH (0.25 mL) and 2 N NaOH (0.12 mL), and the solution was stirred for 4 h at 40 °C. MeOH was evaporated and the aqueous layer was acidified to pH ≤2 with 2 N HCl and extracted three times with ether. The combined extracts were washed with brine, dried over $MgSO_4$, and filtered, and the ether was removed by rotovapping. The product was purified by flash chromatography (75:25:2 hexane/EtOAc/AcOH), giving the pure racemic product as a clear colorless oil (38.0 mg, 76%): ^{1}H NMR as a 1:1 mixture of diastereomeric salts of (*S*)-α-methylbenzylamine ($CDCl_3$, δ ppm) 7.42−7.28 (m, 10 H), 6.47 (br s, 6 H), 4.30 (m, 2 H), 3.58 (s, 3 H, −OC*H*$_3$, *S*,*R*-diastereomeric salt), 3.56 (s, 3 H, −OC*H*$_3$, *S*,*S*-salt), 2.99 (d, J = 11.6 Hz, 1 H, *S*,*R*-salt), 2.96 (d, J = 12.0 Hz, 1 H, *S*,*S*-salt), 2.79 (d, J = 11.6 Hz, 1 H, *S*,*R*-salt), 2.76 (d, J = 12.0 Hz, 1 H, *S*,*S*-salt), 1.57 (d, J = 6.8 Hz, 6 H), 1.27 (apparent s, 21 H), 1.24 (s, 3H).

(*R*)-*N*-4-Methoxybenzyloxycarbonyl-*S*-*tert*-butyl-2-methylcysteine Methyl Ester (6). Acid **5** (0.748 g, 3.19 mmol) was dissolved in 1,2-dichloroethane (5.5 mL) and Et_3N (738 μL, 5.30 mmol) was added followed by diphenylphosphoryl azide (700 μL, 3.25 mmol), with stirring. After 15 min at room temperature the solution was heated at reflux for 100 min, after which it was converted completely to the isocyanate by TLC. Next, liquefied *p*-methoxybenzyl alcohol (660 μL, 5.30 mmol) was added and refluxing was resumed for 4 h. The solution was concentrated giving a yellow oil, which was purified directly by flash chromatography (6:1 hexane/EtOAc). This gave the product as a clear colorless oil (1.03 g, 87%): TLC R_f 0.10 (4:1 hexane/Et_2O); $[\alpha]^{26}_D$ +5.3 (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3362, 2958, 1739, 1724, 1515, 1304, 1247, 1176, 1054; ^{1}H NMR ($CDCl_3$, δ ppm) 7.30 (AA′XX′ pattern, J = 8.8 Hz, 2 H), 6.89 (AA′XX′ pattern, J = 8.8 Hz, 2 H), 5.73 (br s, 1 H), 5.02 (s, 2 H), 3.81 (s, 3 H), 3.77 (br s, 3 H), 3.31 (br d, J = 12.0 Hz, 1 H), 3.01 (d, J = 12.0 Hz, 1 H), 1.64 (s, 3 H), 1.27 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 173.4, 159.4, 154.6, 129.8, 128.4, 113.8, 66.3, 59.6, 55.2, 52.7, 42.2, 34.8, 30.7, 23.4; FAB LRMS *m*/*z* (M + H) 370, (M − PMB) 248, (PMB) 121. Anal. Calcd for $C_{18}H_{27}NO_5S$: C, 58.51; H, 7.37; N, 3.79; S, 8.68. Found: C, 58.76; H, 7.43; N, 3.51; S, 8.92.

(*R*)-*S*-*tert*-Butyl-2-methylcysteine Methyl Ester (7). Carbamate **6** (0.206 g, 0.557 mmol) was dissolved in CH_2Cl_2 (5.0 mL), and TFA (0.56 mL) was added, with stirring. The solution developed an intense purple color, and after 30 min was complete. Addition of H_2O (3 mL), with stirring, discharged the color. The CH_2Cl_2 was evaporated, and the remaining aqueous layer was washed once with hexane. The aqueous layer was decanted from a sticky residue and treated with aqueous ammonia to pH 9. The mixture was extracted twice with CH_2Cl_2, and the combined extracts dried over Na_2SO_4 and filtered. The solution was rotovapped, and the resulting liquid was purified by flash chromatography (1:1 hexane/EtOAc), giving the product as a clear colorless liquid (82.7 mg, 72%): $[\alpha]^{25}_D$ +19.6 (*c* 1.00, EtOH); IR (NaCl, cm^{-1}) 3372, 2962, 1738, 1459, 1198, 1161, 1097; ^{1}H NMR ($CDCl_3$, δ ppm) 3.67 (s, 3H), 2.91 (d, J = 12.0 Hz, 1 H), 2.63 (d, J = 12.0 Hz, 1 H), 1.87 (br s, 2H), 1.34 (s, 3 H), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 176.6, 57.8, 52.2, 42.1, 38.7, 30.7, 26.4; FAB LRMS *m*/*z* (M + H) 206.2. Anal. Calcd for $C_9H_{19}NO_2S$: C, 52.65; H, 9.33; N, 6.82; S, 15.62. Found: C, 52.33; H, 9.61; N, 6.59; S, 15.40.

(*S*)-*tert*-Butyl Methyl 2-*tert*-Butylsulfanylmethyl-2-methylmalonate (8). Concentrated H_2SO_4 (0.203 mL, 3.62 mmol) was added dropwise to a stirred suspension of anhydrous $MgSO_4$ (1.75 g, 14.50 mmol) and CH_2Cl_2 (14 mL). This resulted in some solid clumping, which was broken up mechanically, and stirring was continued for 15 min. A solution of acid **5** (0.849 g, 3.62 mmol) in CH_2Cl_2 (4.2 mL) and then *t*-BuOH (1.74 mL, 18.1 mmol) were added dropwise, with stirring. The flask was tightly stopped and the reaction mixture was stirred for 24 h. The mixture was vacuum filtered, and the $MgSO_4$ was rinsed with CH_2Cl_2. The filtrate was then washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and rotovapped to a liquid. Purification by bulb-to-bulb distillation (∼100 °C, 0.3 Torr) gave **8** as a clear colorless liquid (0.7711 g, 73%): TLC R_f 0.57 (6:1 hexane/Et_2O); $[\alpha]^{25}_D$ −7.6 (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 2974, 1733, 1368, 1293, 1245, 1159, 1111; ^{1}H NMR ($CDCl_3$, δ ppm) 3.70 (s, 3 H), 2.98 (d, J = 12.0 Hz, 1 H), 2.95 (d, J = 12.0 Hz, 1 H), 1.42 (s, 12 H), 1.28 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 171.9, 170.0, 81.8, 54.5, 52.3, 42.0, 33.3, 30.6, 27.7, 19.6; EI LRMS *m*/*z* (M^+) 290, (M − isobutene) 234, (M − 2 isobutenes) 178. Anal. Calcd for $C_{14}H_{26}O_4S$: C, 57.90; H, 9.02; S, 11.04. Found: C, 57.78; H, 9.14; S, 11.25.

(*S*)-2-*tert*-Butylsulfanylmethyl-2-methylmalonic Acid Mono-*tert*-butyl Ester (9). Diester **8** (0.548 g, 1.89 mmol) was dissolved in THF (9.5 mL) and H_2O (2.4 mL) was added, followed by $LiOH·H_2O$ (0.158 g, 3.78 mmol). The mixture was stirred for 20 h, and tetra-*n*-butylammonium hydrogensulfate (3.2 mg, 0.0094 mmol, 0.5 mol %) was then added. After another 28 h of stirring at room temperature, the reaction was complete. THF was evaporated, and the reaction was diluted with water and acidified to pH 3 with 2 N HCl. The mixture was extracted three times with ether, and the combined extracts were washed with brine, dried over $MgSO_4$, and filtered. Rotary evaporation gave the product as a clear colorless oil that crystallized (0.453 g, 87%): mp 58−59 °C; $[\alpha]^{25}_D$ −4.4 (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}) 3252, 2974, 1736, 1710, 1368, 1158; ^{1}H NMR ($CDCl_3$, δ ppm) 8.95 (br s, 1 H), 2.94 (d, J = 12.0 Hz, 1 H), 2.90 (d, J = 12.0 Hz, 1 H), 1.39 (s, 3 H), 1.38 (s, 9 H), 1.23 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 177.0, 169.8, 82.2, 54.4, 42.0, 33.2, 30.5, 27.7, 19.6; FAB LRMS *m*/*z* (M^+) 276.1.

(*S*)-*N*-4-Methoxybenzyloxycarbonyl-*S*-*tert*-butyl-2-methylcysteine *tert*-Butyl Ester (10). Acid **9** (0.374 g, 1.35 mmol) was dissolved in 1,2-dichloroethane (2.7 mL) and Et_3N (369 mL, 2.71 mmol) was added followed by diphenylphosphoryl azide (350 mL, 2.706 mmol), with stirring. After 15 min at room temperature the solution was heated at reflux for 100 min, after which it was converted completely to the isocyanate by TLC. Next liquefied *p*-methoxybenzyl alcohol (337 mL, 2.71 mmol) was added and refluxing was resumed for 4 h. The solvent was evaporated giving a yellow oil, which was purified by flash chromatography (6:1 hexane/EtOAc). This gave the product as an oil, which crystallized upon standing. Recrystallization from hexane gave the product as fine white needles (0.512 g, 92%): TLC R_f 0.32 (6:1 hexane/EtOAc); mp 78−79 °C; $[\alpha]^{24}_D$ +6.8 (*c* 1.00, $CHCl_3$); IR (NaCl, cm^{-1}, $CDCl_3$) 2975, 1716, 1514, 1247; ^{1}H NMR ($CDCl_3$, δ ppm) 7.27 (AA′XX′ pattern, J = 8.6 Hz, 2 H), 6.85 (AA′XX′ pattern, J = 8.6 Hz, 2 H), 5.75 (br s, 1 H), 4.99 (s, 2 H), 3.80 (s, 3 H), 3.32 (br d, J = 11.9 Hz, 1 H), 2.95 (d,

J = 11.9 Hz, 1 H), 1.44 (s, 9 H), 1.25 (s, 9 H); ^{13}C NMR ($CDCl_3$, δ ppm) 172.0, 159.5, 154.7, 129.9, 128.8, 113.9, 82.4, 66.2, 59.9, 55.3, 42.1, 34.8, 30.9, 27.9, 23.7.

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Supporting Information Available: General experimental conditions and ^{1}H NMR data for all new compounds, including spectra used for enantiomeric purity determinations. This material is available free of charge via the Internet at http://pubs.acs.org.

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