Copper-Catalyzed Asymmetric Michael Reactions with α-Amino Acid Amides: Synthesis of an Optically Active Piperidine Derivative

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Quaternary stereocenters are obtained at room temperature in copper-catalyzed asymmetric Michael reactions with α-amino acid amides as chiral auxiliaries. L-Valine diethylamide was applied as a chiral auxiliary, and an optically active piperidine derivative was prepared with 97% *ee*. The optical purity of the product was established by GLC after cyclization to a hexahydroisoquinolonecarboxylate.

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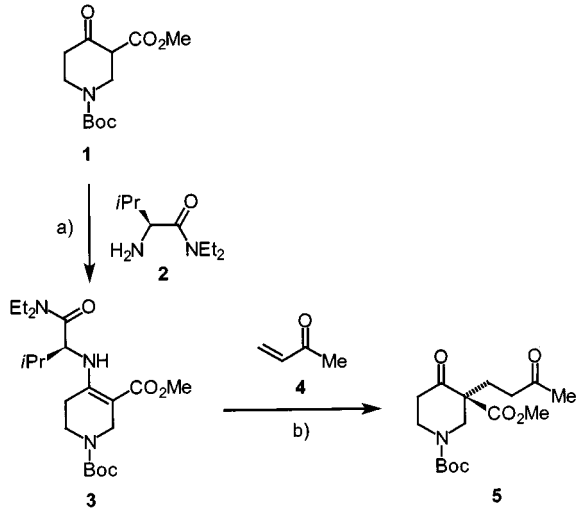
Introduction

Asymmetric conjugate additions are valuable stereoselective C−C bond forming reactions.[1−3] Metal-catalyzed Michael reactions are an important alternative to base catalysis, since the chemoselectivity is improved in most cases.[4,5] In the field of metal-catalyzed enantioselective Michael reactions the heterobimetallic catalysts developed by Shibasaki are presently defining the state-of-the-art.[6,7] Applying Shibasaki's method tertiary stereocenters are generally formed with excellent selectivities at ambient temperature, whereas low temperatures are required for the generation of quaternary stereocenters.[8−11] More problematic, however, is the incompatibility of the Lewis acidic catalyst with substrates containing donor groups like amino functions or carbamate moieties. Recently, we reported the application of α-amino acid dialkyl amides as chiral auxiliaries for copper-catalyzed asymmetric Michael reactions.[12,13] Herein we wish to prove the compatibility of our method with substrates with carbamate functions. Therefore, we have prepared an optically active piperidine derivative bearing a quaternary stereocenter with 97% *ee* at room temperature applying the method recently developed in our laboratory.

Results and Discussion

The acid-catalyzed conversion of β-ketocarboxylate **1** with equimolar amounts of the auxiliary L-valine diethylamide **2** yielded the enamino ester **3** (82%) (Scheme 1). Treatment of the Michael donor **3** with a catalytic amount of copper(II) acetate and a small excess of methyl vinyl ketone (**4**) gave the optically active product **5** in 74% yield after acidic hydrolysis. The reaction was performed at 23 °C in acetone as solvent and the exclusion of moisture or air was not necessary. The carbamate protective group of **5** seemed to be stable under workup conditions (1 M hydrochloric acid). The auxiliary could be recovered from the aqueous layer by extraction. The absolute configuration of the Michael reaction product was assigned as (*S*)-**5**.[12−14]



Scheme 1. Copper-catalyzed asymmetric Michael reaction with L-valine diethylamide **2** as auxiliary: a) **2**, cat. HCl, molecular sieves 4 Å, toluene, 50 °C, 16 h, 82%; b) 1. 10 mol % $Cu(OAc)_2 \cdot H_2O$, **4**, acetone, 23 °C, 16 h, 2. HCl/H_2O (1 M), 0 °C, 2 h, 74%

Derivatives had to be prepared in order to determine the enantiopurity of the product **5**. First of all we synthesized the *O*-acetyl mandelic amide **7** by deprotection (95%) of **5** followed by conversion of the secondary amine **6** with *O*-acetyl-L-mandelic acid and DCC (70% yield; Scheme 2). Careful analysis of the ^1H and ^{13}C NMR spectra of **7**,

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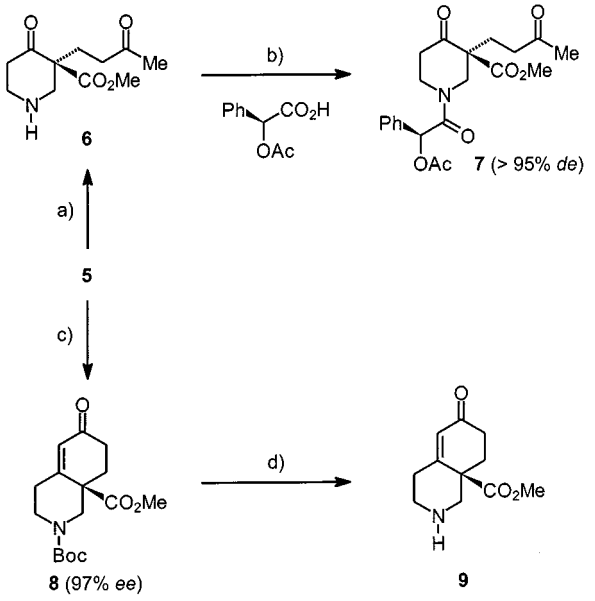
which was not to trivial due to rotamers of the amide moiety, showed that our material had a purity of at least 95% *de*. Of course, we also prepared the epimeric mixture of **7** from racemic **5** for comparison. However, we were not sure whether we might have lost the other diastereoisomer during the purification. Therefore, we also cyclized piperidine **5** to compound **8** (70%), which gave sufficient baseline-resolution in GC on a chiral phase in a racemic sample. Finally, the optical purity of compound **8** was determined to be 97% *ee*. Cleavage of the carbamate protective group in **8** yielded compound **9** (94%), which is a very interesting, enantiopure building block with three different functionalities for further transformations: a secondary amine, an enone, and a methyl ester.



Scheme 2. Determination of the optical purity after derivatization: a) TFA, CH_2Cl_2, 23 °C, 16 h, 95%; b) acetylmandelic acid, DCC, CH_2Cl_2, 23 °C, 16 h, 70%; c) pyrrolidine, AcOH, CH_2Cl_2, 23 °C, 16 h, 70%; d) TFA, CH_2Cl_2, 23 °C, 16 h, 94%

Conclusion

In conclusion, the copper-catalyzed, auxiliary-mediated Michael reaction has proved to be compatible with carbamate functions in the substrate and therefore superior to lanthanide-based methods. The piperidine derivative **5** bearing a quaternary stereocenter was obtained with 97% *ee* enantioselectivity at room temperature. In order to determine the enantiopurity the bicyclic derivative **8** was prepared, which yields the hexahydroisoquinolone **9** on a multigram scale after deprotection. This compound is a very interesting optically active chiral building block.

Experimental Section

General Remarks: Chiral GC analysis was performed with a HRGC Mega 2 series (Fisons instruments) with FID, a SP4270 integrator, and a Bondex unβ column[15] (20 m × 0.3 mm) with hydrogen carrier gas (0.4 bar). Column chromatography was accomplished on Merck silica gel (Type 60, 0.063−0.200 mm) or ICN alumina (Al_2O_3 90, basic, activity stage I) using ethyl acetate (EA) and hexanes (PE) as solvents. (*S*)-(+)-*O*-Acetylmandelic acid[16] and the auxiliary **2**[13] were synthesized according to literature procedures.

1-*tert*-Butyl-3-methyl-4-oxopiperidine-1,3-dicarboxylate (1): A solution of Boc_2O (7.41 g, 33.9 mmol) in MeOH (25 mL) was added to a solution of 3-methoxycarbonyl-4-oxopiperidinium chloride (6.57 g, 33.9 mmol) and K_2CO_3 (2.34 g, 17.0 mmol) in MeOH (25 mL), and the resulting mixture was stirred for 16 h at 23 °C. After all volatile materials had been removed under vacuum, the residue was partitioned between CH_2Cl_2 and H_2O (40 mL, 1:1), the layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 50 mL). After drying of the combined organic layers ($MgSO_4$), filtration, and removal of the solvent under vacuum, carbamate **1** (8.52 g, 33.1 mmol, 98%) was obtained as a colorless, crystalline material, m.p. 59 °C. Only the enol tautomer is observed in the NMR spectra. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 2.37 (t, *J* = 5.9 Hz, 2 H), 3.57 (t, *J* = 5.9 Hz, 2 H), 3.78 (s, 3 H), 4.06 (s, 2 H), 11.98 (s, 1 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 28.41 (CH_3), 28.86 (CH_2), 39.18 (CH_2), 40.32 (CH_2), 51.56 (CH_3), 80.11 (C), 96.20 (C), 154.54 (CO), 170.09 (CO), 171.04 (CO). IR (KBr): $\tilde{\nu}$ = 1701, 1678, 1633 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 257 (1) [M$^+$], 200 (66) [M$^+$ − *t*Bu], 168 (62) [M$^+$ − MeOH − *t*Bu]. $C_{12}H_{19}NO_5$ (257.28): calcd. C 56.02, H 7.44, N 5.44; found C 56.12, H 7.43, N 5.32.

***N*-(4-*tert*-Butyloxycarbonyl-2-methoxycarbonyl-4-aza-1-cyclohexenyl)-L-valine Diethylamide (3):** L-Valine amide **2** (2.12 g, 7.77 mmol), molecular sieves (8.0 g, 4 Å), and conc. hydrochloric acid (ca. 50 mg) were added to a solution of piperidone **1** (2.00 g, 7.77 mmol) in toluene (20 mL). After stirring the reaction mixture for 16 h at 50 °C and filtration, the residue was washed with CH_2Cl_2, and the filtrate evaporated under vacuum. Chromatography on Al_2O_3 [PE/EA 1:1, R_f (SiO_2) = 0.25] gave enamine **3a** (2.62 g, 6.36 mmol, 82%) as a colorless solid, m.p. 131 °C. $[\alpha]_D^{20}$ = +94.1 (*c* = 6.95 g dm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.00 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.7 Hz, 3 H), 1.12 (t, *J* = 7.1 Hz, 3 H), 1.20 (t, *J* = 7.1 Hz, 3 H), 1.47 (s, 9 H), 1.99−2.10 (m, 1 H), 2.22 (ddd, *J* = 16.2, *J* = 6.1, *J* = 6.1 Hz, 1 H), 2.36 (dt, *J* = 16.2, *J* = 5.6 Hz, 1 H), 3.17−3.19 (m, 1 H), 3.27−3.31 (m, 1 H), 3.39−3.46 (m, 2 H), 3.59 (br. s, 2 H), 3.70 (s, 3 H), 4.08 (br. s, 3 H), 9.27 (d, *J* = 9.2 Hz, 1 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 12.86 (CH_3), 14.67 (CH_3), 17.61 (CH_3), 19.98 (CH_3), 26.34 (CH_2), 28.45 (CH_3), 32.29 (CH), 39.05 (CH_2), 40.30 (CH_2), 41.52 (CH_2), 41.76 (CH_2), 50.76 (CH_3), 57.58 (CH), 79.78 (C), 89.00 (C), 154.77 (CO), 155.86 (C), 168.96 (CO), 170.42 (CO). IR (KBr): $\tilde{\nu}$ = 1696, 1670, 1650, 1603, 1415, 1260, 1175 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 411 (8) [M$^+$], 354 (100) [M$^+$ − *t*Bu], 311 (50) [M$^+$ − $CONEt_2$]. $C_{21}H_{37}N_3O_5$ (411.54): calcd. C 61.29, H 9.06, N 10.21; found C 61.21, H 9.01, N 10.05.

(+)-(*S*)-1-*tert*-Butyl-3-methyl-4-oxo-3-(3-oxobutyl)piperidine-1,3-dicarboxylate (5): After stirring a mixture of enamine **3** (800 mg, 1.94 mmol), $Cu(OAc)_2 \cdot H_2O$ (39 mg, 0.19 mmol) and acetone (5 mL) for 30 min at 23 °C, MVK **4** (409 mg, 5.84 mmol) was added, and the mixture stirred for a further 16 h at 23 °C. All volatile materials were removed under vacuum, the residue was diluted with hydrochloric acid (5 mL, 1 mol dm^{-3}) and stirred for 2 h at 0 °C. The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent, chromatography on SiO_2 (PE/EA 2:1, R_f = 0.21) yielded **5** as a

colorless solid (473 mg, 1.44 mmol, 74%), m.p. 64 °C. $[\alpha]_D^{20} = +26$ ($c = 5.7$ g dm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 1.89 (ddd, $J = 14.4$, $J = 10.0$, $J = 5.4$ Hz, 1 H), 2.03−2.13 (m, 1 H), 2.13 (s, 3 H), 2.49 (dt, $J = 14.8$, $J = 5.0$ Hz, 2 H), 2.59−2.76 (m, 2 H), 3.24 (br. s, 1 H), 3.41 (br. s, 1 H), 3.74 (s, 3 H), 4.02 (br. s, 1 H), 4.41 (d, $J = 13.4$ Hz, 1 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.24 (CH_2), 28.24 (CH_3), 29.91 (CH_3), 38.64 (CH_2), 39.61 (CH_2), 43.25 (CH_2), 51.01 (CH_2), 52.58 (CH_3), 60.57 (C), 80.64 (C), 154.06 (CO), 170.73 (CO), 205.12 (CO), 207.07 (CO). IR (KBr): ṽ = 1725, 1697, 1436 cm^{-1}. MS (EI, 70 eV), *m*/*z* (%) = 327 (6) [M$^+$]. $C_{16}H_{25}NO_6$ (327.29): calcd. C 58.70, H 7.70, N 4.28; found C 58.78, H 7.71, N 4.21.

***rac*-1-*tert*-Butyl-3-methyl-4-oxo-3-(3-oxobutyl)piperidine-1,3-dicarboxylate (*rac*-5):** MVK **4** (699 mg, 9.97 mmol) was added to a mixture of piperidone **1** (1.28 g, 4.99 mmol), $FeCl_3 \cdot 6H_2O$ (67 mg, 0.25 mmol), and CH_2Cl_2 (3 mL). After stirring for 16 h at 23 °C, all volatile materials were removed under vacuum and the residue was chromatographed on SiO_2 (PE/EA 2:1) to yield *rac*-**5** (1.29 g, 3.95 mmol, 79%) as a colorless solid, m.p. 48 °C.

(*S*)-Methyl-4-oxo-3-(3-oxobutyl)piperidine-3-carboxylate (6): A solution of piperidone **5** (700 mg, 2.14 mmol) in a mixture of CH_2Cl_2 (6 mL) and TFA (3 mL) was stirred for 16 h at 23 °C. All volatile materials were removed under vacuum and the residue partitioned between sat. $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). After drying ($MgSO_4$), filtration, and evaporation of the solvent, chromatography on SiO_2 (MeOH/EA 1:4, $R_f = 0.19$) yielded **6** as a colorless oil (464 mg, 2.02 mmol, 95%). $[\alpha]_D^{20} = +140$ ($c = 4.5$ g dm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.81 (ddd, $J = 14.4$, $J = 9.6$, $J = 5.7$ Hz, 1 H), 1.96 (s, 1 H), 2.11 (ddd, $J = 14.6$, $J = 9.4$, $J = 5.3$ Hz, 1 H), 2.13 (s, 3 H), 2.34−2.45 (m, 2 H), 2.50−2.65 (m, 3 H), 2.92 (ddd, $J = 12.7$, $J = 11.5$, $J = 3.8$ Hz, 1 H), 3.35 (ddt, $J = 12.8$, $J = 6.5$, $J = 2.5$ Hz, 1 H), 3.71 (dd, $J = 13.4$, $J = 2.0$ Hz, 1 H), 3.76 (s, 3 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 25.35 (CH_2), 29.89 (CH_3), 38.55 (CH_2), 42.85 (CH_2), 47.86 (CH_2), 52.61 (CH_3), 55.79 (CH_2), 62.30 (C), 171.93 (CO), 205.46 (CO), 207.40 (CO). IR (neat): ṽ = 1720 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 227 (10) [M$^+$], 196 (14), 170 (26), 168 (37), 139 (100). $C_{11}H_{17}NO_4$ (227.26): calcd. 227.1158; found 227.1166 (HRMS).

(*S*,*S*)-Methyl-1-(2-acetoxy-2-phenylacetyl)-4-oxo-3-(3-oxobutyl) piperidine-3-carboxylate (7): A solution of the deprotected piperidone **6** (104 mg, 0.456 mmol) in CH_2Cl_2 (1 mL) was added to a mixture of DCC (94 mg, 0.46 mmol) and *O*-acetyl-L-mandelic acid (89 mg, 0.456 mmol) in CH_2Cl_2 (1 mL). After stirring for 16 h at 23 °C, the reaction mixture was chromatographed on SiO_2 (PE/EA 1:4, $R_f = 0.38$) to yield amide **7** (130 mg, 0.322 mmol, 70%) as a colorless oil. $[\alpha]_D^{20} = +150$ [$c = 5.2$ g dm^{-3}, $CHCl_3$, (*S*,*S*)-diastereoisomer]. The NMR spectra show a doubled signal set due to hindered rotation of the amide C−N bond. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.65−1.74 (m, 0.5 H), 1.83−2.01 (m, 1.5 H), 2.12 (s, 3.5 H), 2.17 (s, 3 H), 2.26−2.49 (m, 2 H), 2.54−2.59 (m, 0.5 H), 2.67−2.90 (m, 2 H), 3.27 (d, $J = 13.6$ Hz, 0.5 H), 3.56−3.62 (m, 2 H), 3.74−3.88 (m, 2 H), 4.36 (d, $J = 13.9$ Hz, 0.5 H), 4.73 (d, $J = 13.6$ Hz, 0.5 H), 4.85 (d, $J = 8.9$ Hz, 0.5 H), 6.26 (s, 0.5 H), 6.49 (s, 0.5 H), 7.41−7.46 (m, 5 H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): rotamer 1: δ = 20.78 (CH_3), 25.19 (CH_2), 29.89 (CH_3), 38.53 (CH_2), 38.85 (CH_2), 44.34 (CH_2), 48.52 (CH_2), 52.63 (CH_3), 60.40 (C), 73.34 (CH), 128.39 (CH), 129.22 (CH), 129.70 (CH), 133.55 (C), 166.88 (CO), 170.18 (CO), 170.69 (CO), 203.59 (CO), 206.89 (CO); rotamer 2: δ = 20.78 (CH_3), 25.74 (CH_2), 29.89 (CH_3), 38.53 (CH_2), 42.31 (CH_2), 42.55 (CH_2), 52.20 (CH_2), 53.60 (CH_3), 59.85 (C), 73.69 (CH), 128.67 (CH), 129.39 (CH), 129.70 (CH), 133.79 (C), 166.88 (CO), 170.38 (CO), 170.79 (CO), 203.74 (CO), 206.89 (CO). IR (neat): ṽ = 1745, 1730, 1675 cm^{-1}. MS (70 eV, EI): *m*/*z* (%) = 403 (1) [M$^+$], 343 (20) [M$^+$ − CO − MeOH], 224 (90), 56 (100). $C_{21}H_{25}NO_7$ (403.43): calcd. 403.1631; found 403.1626 (HRMS). Data for the (*R*,*S*)-diastereoisomer *epi*-**7** (resulting from conversion of racemic **5**, only a single signal set is observed): ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 20.79 (CH_3), 25.25 (CH_2), 29.97 (CH_3), 38.22 (CH_2), 38.59 (CH_2), 44.12 (CH_2), 47.73 (CH_2), 52.79 (CH_3), 60.99 (C), 73.34 (CH), 128.44 (CH), 129.39 (CH), 129.82 (CH), 133.34 (C), 166.88 (CO), 170.09 (CO), 170.52 (CO), 203.87 (CO), 206.82 (CO).

(+)-(*R*)-3-*tert*-Butyl-1-methyl-8-oxo-3-azabicyclo[4.4.0]-6-decene-1,3-dicarboxylate (8): A mixture of carbamate **5** (2.00 g, 6.11 mmol), CH_2Cl_2 (10 mL), pyrrolidine (370 mg, 5.19 mmol), and AcOH (312 mg, 5.19 mmol) was stirred for 16 h at 23 °C. All volatile materials were removed under vacuum, and the residue was chromatographed on SiO_2 (PE/EA 2:1, $R_f = 0.22$) to yield **8** as a colorless oil (1.32 g, 4.28 mmol, 70%). $[\alpha]_D^{20} = +152$ ($c = 5.2$ g dm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.84 (td, $J = 14.3$, $J = 5.5$ Hz, 1 H), 2.29−2.47 (m, 4 H), 2.64 (d, $J = 12.8$ Hz, 1 H), 2.82 (br. s, 2 H), 3.75 (s, 3 H), 4.42 (br. s, 1 H), 4.67 (d, $J = 13.4$ Hz, 1 H), 5.98 (s, 1 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 28.28 (CH_3), 30.75 (CH_2), 32.93 (CH_2), 34.48 (CH_2), 43.21 (CH_2), 48.96 (C), 52.82 (CH_3), 52.96 (CH_2), 80.28 (C), 127.64 (CH), 153.88 (C), 158.77 (CO), 172.02 (CO), 197.90 (CO). IR (KBr): ṽ = 1731, 1685, 1229, 1162, 1128 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 309 (6) [M$^+$]. $C_{16}H_{23}NO_5$ (309.36): calcd. 309.1576; found 309.1576 (HRMS). GC: Bondex un β, temperature program: 3 min 100 °C isotherm, then 2 K min^{-1} gradient to 200 °C: t_R (*R*-**8**) = 47.25 min, t_R (*S*-**8**) = 47.52 min, 97% *ee*.

(+)-(*R*)-Methyl-8-oxo-3-azabicyclo[4.4.0]-6-decene-1-carboxylate (9): A solution of amine **8** (180 mg, 0.582 mmol) in CH_2Cl_2 (2 mL) and TFA (1 mL) was stirred for 16 h at 23 °C. All volatile materials were removed under vacuum, the residue partitioned between CH_2Cl_2 (10 mL) and sat. $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Filtration and evaporation of the solvent gave **9** as a colorless oil (114 mg, 0.545 mmol, 94%). $[\alpha]_D^{20} = +282$ ($c = 1.3$ g dm^{-3}, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.88 (td, $J = 13.6$, $J = 6.0$ Hz, 1 H), 2.09 (br. s, 1 H), 2.25 (ddd, $J = 13.8$, $J = 4.8$, $J = 3.1$ Hz, 1 H), 2.31−2.50 (m, 3 H), 2.49 (d, $J = 12.8$ Hz, 1 H), 2.54 (ddd, $J = 14.4$, $J = 6.0$, $J = 2.1$ Hz, 1 H), 2.73 (td, $J = 12.2$, $J = 3.4$ Hz, 1 H), 3.23 (ddt, $J = 12.3$, $J = 6.0$, $J = 1.6$ Hz, 1 H), 3.64 (dd, $J = 12.8$, $J = 1.6$ Hz, 1 H), 3.79 (s, 3 H), 5.96 (d, $J = 1.9$ Hz, 1 H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ = 30.63 (CH_2), 34.41 (CH_2), 34.73 (CH_2), 46.93 (CH_2), 49.60 (C), 52.78 (CH_3), 57.14 (CH_2), 126.82 (CH), 160.33 (C), 173.41 (CO), 198.28 (CO). IR (neat): ṽ = 3430, 1735, 1680, 1600 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 209 (100) [M$^+$]. $C_{11}H_{15}NO_3$ (209.24): calcd. 290.1052; found 290.1052 (HRMS).

Acknowledgments

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