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Asymmetric Synthesis of *N,O*-Heterobicyclic Octanes and (−)-Geissman−Waiss Lactone

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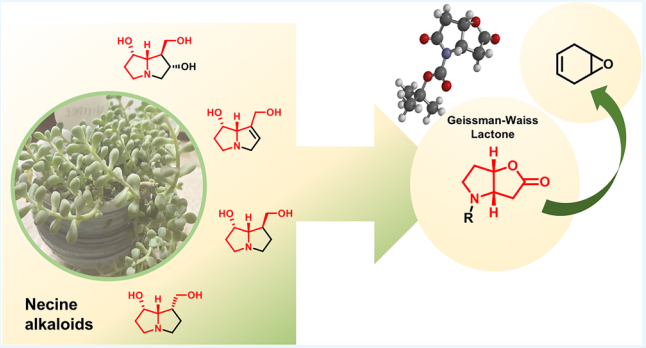
ABSTRACT: A short, asymmetric synthesis of tetrahydro-2*H*-furo[3,2-*b*]pyrrole derivatives and (−)-Geissman−Waiss lactone starting from *meso*-cyclohexadiene epoxide is described. Pivotal transformations in the developed synthetic procedure include asymmetric epoxide ring opening to install the requisite 1*S*,5*S* stereocenters and oxidative lactonization/lactamization sequences. This route provides a streamlined synthetic pathway toward necine alkaloids.



INTRODUCTION

Tetrahydro-2*H*-furo[3,2-*b*]pyrroles are nitrogen- and oxygen-containing heterobicyclo[3.3.0]octane structures present in a number of complex alkaloid natural products. They also constitute important synthetic intermediates used for the synthesis of pyrrolizidine[1] and indole alkaloids.[2] The Geissman−Waiss lactone (GWL, **1**) features a 2-oxa-6-azabicyclo[3.3.0]octan-3-one framework, which has been a key building block to access saturated, unsaturated, and polyhydroxylated necine alkaloids such as croalbinecine (**2**),[3] platynecine (**3**),[4] retronecine (**4**),[5−8] and turneforcidine (**5**)[9] (Figure 1). In a recent study, GWL was utilized for the synthesis of 11-methoxymitragynine pseudoindoxyl (**6**),[2] a potent opioid agonist alkaloid. Considering the focal role of GWL and its substituted derivatives in alkaloid synthesis, considerable efforts have been invested to innovate efficient enantioselective approaches to synthesize its 1*R*,5*R* and 1*S*,5*S* stereoisomers. Nonracemic derivatives have been prepared through linear sequences starting from "chiral pool" reagents, kinetic resolution, and chiral auxiliary-based diastereoselective reactions.[8,10−26] Previous illustrations on the synthesis of natural necine alkaloids were inspired by utilization of the 1*R*,5*R* enantiomer of GWL, which can be obtained from enantiomerically pure 2,5-dihydropyrroles via [2+2] cycloaddition of enecarbamates,[27] stereocontrolled synthesis of (4*R*,5*R*)-5-allyl-4-methoxy-2-oxazolidinones from 3-[(1*S*)-2-*exo*-alkoxy-1-apocamphanecarbonyl]-2-oxazolones,[22] or regio- and diastereoselective reductive ethoxycarbonylmethylation of protected (*S*)-maleimides.[23]

Synthetic methodologies toward GWL not relying on a chiral pool approach are limited. To the best of our knowledge, the only example known makes use of the Katsuki−Sharpless

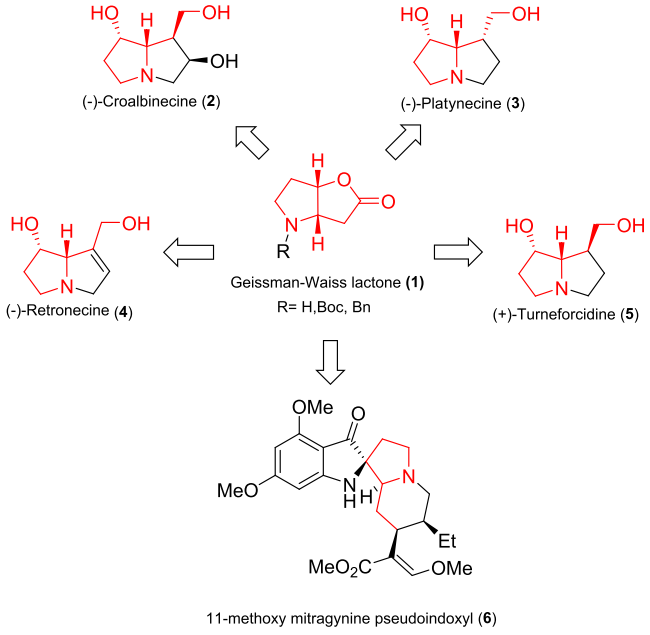


Figure 1. Alkaloids derived from Geissman−Waiss lactone intermediates.

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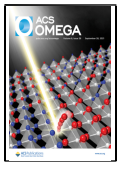

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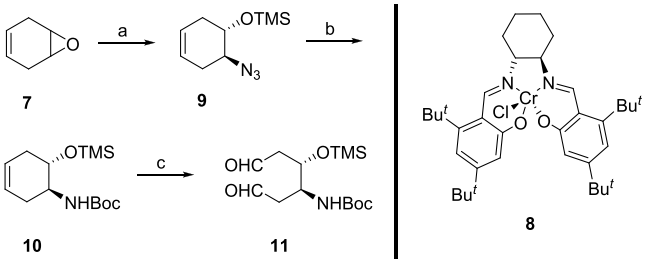
kinetic resolution of racemic *N*-benzyloxycarbonyl-3-hydroxy-4-pentenylamine.[19]

As part of an effort to develop efficient synthetic methodologies for the preparation of heterocyclic compounds,[28,29] we herein report the synthesis of GWL (**1**) via sequential transformations involving oxidative lactonization/lactamization sequences from *meso*-cyclohexadiene epoxide.

RESULTS AND DISCUSSION

We envisioned a short route for the synthesis of (−)-GWL (**1**) via facile installation of the requisite 1*S*,5*S* stereocenters bridging the lactam/lactone rings by desymmetrization of readily available *meso*-cyclohexadiene epoxide (**7**). *Meso*-epoxides are attractive starting materials for preparing enantiopure intermediates due to the propensity of the nucleophilic oxygen atom in the oxirane moiety to be activated by electrophilic reagents such as chiral Lewis acids and allowing stereoselective entry of nucleophilic reagents. Utilizing the method developed by Jacobsen using Cr complex **8**, the six carbons and the desired oxygenated and aminated stereocenters present in GWL (**1**) can be installed in a single synthetic operation. Thus, treatment of cyclohexadiene epoxide (**7**) with trimethylsilylazide using a salen catalyst complex (**8**) afforded (1*S*,2*S*)-1-azido-2-trimethylsiloxycyclohexene **9**, in 63% yield and 85% enantiomeric excess. The azide moiety in **9** was reduced next using $Pd(OH)_2/C$ and triethylsilane, and the resulting amine was protected with di-*tert*-butyldicarbonate to give **10** in 88% isolated yield. This step was required to avoid the formation of unnecessary products such as cross-conjugated ester or amide derivatives in the following transformations. To produce the requisite carbonyl functionalities, the olefin in **10** was cleaved oxidatively under reductive ozonolysis conditions to dialdehyde **11** in modest yields (62%) (Scheme 1). Further oxidation of **11** using Jones

Scheme 1. Synthesis of GWL Synthetic Precursors 10 and 11[a]

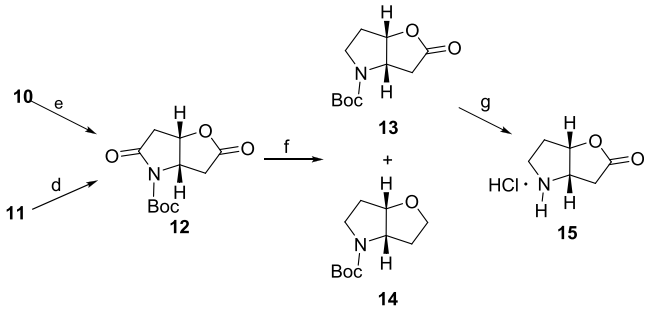


[a]Reagents and conditions: (a) (*R*,*R*)-salen complex **8** (2 mol %), $TMSN_3$ (1.05 equiv.), Et_2O, rt., 46 h, 63%. (b) Boc_2O (1.5 equiv.), $Pd(OH)_2/C$, Et_3SiH (1.5 equiv.), EtOH, rt., 20 h, 88%. (c) O_3, DMS, DCM, −78 °C, 18 h, 62%.

oxidation directly afforded, via in situ formation of the corresponding diacid with concomitant lactonization and lactamization cascades, the *S*,*S*-configured *N*,*O*-heterobicycle **12** in quantitative yield (Scheme 2).

While this sequence is high-yielding, the use of stoichiometric amounts of chromium oxide (Jones reagent) was not satisfactory. Gratifyingly, the sequence could be greatly improved by oxidation of **10** with $NaIO_4$ in the presence of catalytic amounts of $RuCl_3$[29] giving rise to **12** in 68% yield. The structure of **12** could be unambiguously established by single crystal X-ray structure analysis (Figure 2).

Scheme 2. Synthesis of (−)-GWL Hydrochloride Salt 15[a]



[a]Reagents and conditions: (d) Jones reagent (2.5 M), acetone, 10 °C, 15 min, quant. (e) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4-AcCN-H_2O, 0 °C, 8 h, 68%. (f) H_3B-SMe_2 (3.0 equiv.), THF, 24 h, 54% for **12** and 11% for **13**. (g) HCl/EtOAc, 0 °C, 3 h, 64%.

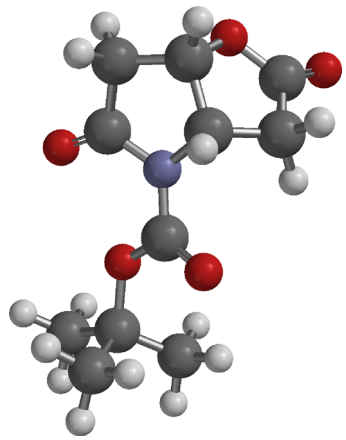


Figure 2. X-ray structure of **12**.

Finally, the lactam carbonyl in **12** was chemoselectively reduced using borane-dimethylsulfide to afford *N*,*O*-heterobicycle **13** (54%), along with the fully reduced heterobicycle **15** (11%), which could be readily separated using column chromatography. Subsequent deprotection of **13** under acidic conditions furnished the (1*S*,5*S*)-GWL **15** hydrochloride salt[30] in 64% yield. *N*-Protected **14** also constitutes an important synthetic intermediate in pyrrolizidine alkaloid synthesis.

CONCLUSIONS

In summary, we demonstrated a short stereoselective synthesis of the hydrochloride salt (**15**) of (−)-Geissman−Waiss lactone (**1**), a key building block for biologically active indole and pyrrolizidine alkaloids, starting from *meso*-cyclohexene epoxide in a linear fashion employing Cr(salen)-enabled desymmetrization, Pd-catalyzed azide reduction/*N*-Boc protection, and oxidative lactonization and lactamization sequences. This streamlined, modular strategy provides easy access to many important alkaloidal natural products.

MATERIALS AND METHODS

General. All reactions were performed in flame-dried flasks under a N_2 atmosphere using anhydrous solvents unless otherwise stated. Commercial reagents of high purity were purchased and used. All reactions were monitored by TLC (thin layer chromatography). Flash chromatography was performed on silica (Merck Kieselgel 60, 0.04−0.063 mm) using mixtures of hexanes/EtOAc. NMR spectra were recorded

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on a Bruker Avance 300 (300 MHz for ^{1}H, 75 MHz for ^{13}C) and a Bruker Avance III 600 Kryo (600 MHz for ^{1}H, 150 MHz for ^{13}C). Chemical shifts are reported in parts per million (ppm) based on the internal standard for $CHCl_3$ (7.26 ppm (^{1}H), 77.16 ppm (^{13}C)) on the δ scale. Coupling constants are given in Hertz (Hz). The following notations indicate the multiplicity of the signals for the ^{1}H NMR spectra: s = singlet, d = doublet, t = triplet, dd = doublet of doublet, ddt = doublet of doublet of triplet, and m = multiplet. High-resolution mass spectra were recorded on a Thermoquest Finnigan TSQ 7000. ATR-IR spectroscopy was carried out on a Biorad Excalibur FTS 3000 spectrometer, equipped with a Specac Golden Gate Diamond Single Reflection ATR system. The optical rotation was determined using a PerkinElmer 241 polarimeter with a 589 nm wavelength (sodium-d-line) on a 1.0 dm measuring cell of ca. 2 mL volume. High-performance liquid chromatography was carried out using the following conditions: for the column, LabID 80/Daicel Chemical Industries Ltd./CHIRALCEL (OD-H) (Lot No. ODH0CE-GB060)/cellulose tris (3,5-dimethylphenyl carbamate)/coated on 5 μm silica gel/250 mm × 4.6 mm ID/part DAIC 14325 and CHIRALCEL OJ-H, 4.6 × 250 mm, 10 μm; for the LC system, Agilent 1100/3, DAD G1315B [DE03010828].

((1*S*,6*S*)-(6-Azidocyclohex-3-en-1-yl)oxy)-trimethylsilane (9). To a mixture of epoxide 7[31] (610 mg, 6.32 mmol, 1 equiv.) in 2.1 mL of diethyl ether was added catalyst complex L-**8** (88 mg, 0.12 mmol, 2 mol %). The mixture was stirred for 15 min, and trimethylsilylazide (0.88 mL, 6.63 mmol, 1.05 equiv.) was added slowly. After the mixture was stirred for 46 h at room temperature, the solvent was evaporated to give a yellowish crude product, which was purified by column chromatography on a silica gel (hexanes/EtOAc, 9:1) to yield **9** (840 mg, 63%) as a yellowish oil. R_f = 0.83 (SiO_2, hexanes/EtOAc 9:1); α_D^{25} of −14.8 (c = 0.4, DCM), 85% *ee* (72%, 81% *ee*).[32] IR (film): $\tilde{\nu}$; = 2957, 2905, 2107, 1438, 1250, 1140, 881, 840, 748, 667 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.48−5.61 (m, 2H), 3.73−3.84 (m, 1H), 3.49−3.59 (m, 1H), 2.32−2.48 (m, 2H), 2.08−2.20 (m, 1H), 1.90−2.03 (m, 1H), 1.98 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 124.6, 123.9, 71.9, 62.9, 34.7, 30.9. MS [CI, NH_3]: m/z (%) = 212.1 (11) $[M + H]^+$, 184.1 (29.9) $[(M + H)^+ - N_2]$.

***tert*-Butyl ((1*S*,6*S*)-6-((Trimethylsilyl)oxy)cyclohex-3-en-1-yl)carbamate (10).** To a stirred mixture of azido trimethylsiloxy cyclohexene **9** (200 mg, 1.02 mmol, 1 equiv.) in 3.4 mL of ethanol, *tert*-butoxycarbonyl (Boc_2O) (450 mg, 2.04 mmol, 2 equiv.) and 20% $Pd(OH)_2/C$ (10.2 mg) were added at room temperature. To this mixture, triethylsilane (0.33 mL, 2.04 mmol, 2 equiv.) was added, and the mixture was stirred for another 20 h under nitrogen. The mixture was filtered through Celite, and the filtrate was concentrated to give a yellow solid, which was purified by silica gel column chromatography (hexanes/EtOAc, 15:0.5) to yield **10** (255 mg, 88%) as a yellow solid. R_f = 0.75 (SiO_2, hexanes/EtOAc 21:7); m.p. 79−81 °C. α_D^{25} of +35.5 (c = 0.4, DCM). IR (film): $\tilde{\nu}$; = 3340, 2976, 1689, 1531, 1366, 1309, 1249, 1170, 1102, 1067, 887, 840, 749, 661 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.46−5.57 (m, 2H), 4.45 (bs, IH), 3.67−3.76 (m, 1H), 3.53−3.65 (m, 1H), 2.55 (m, 1H), 2.26 (m, 1H), 2.05 (m, 1H), 1.88 (m, 1H), 1.48 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (75.5 MHz, CDCl3): δ 155.5, 124.2 (2×), 78.9, 68.9, 50.8, 32.9, 29.9, 28.2; MS [CI, NH_3]: m/z (%) = 285.1 (100); HRMS (Cl, NH_3): calculated for $C_{14}H_{27}NO_3Si$, 285.1760 $[M]^+$; found, 285.1758.

***tert*-Butyl ((3*S*,4*S*)-1,6-Dioxo-4-((trimethylsilyl)oxy)-hexan-3-yl)carbamate (11).** To a stirred solution of *N*-Boc-trimethylsiloxy cyclohexene amine **10** (1.01 g, 3.56 mmol, 1 equiv.), $NaHCO_3$ (30 mg, 0.36 mmol, 0.10 equiv.) and methanol (0.36 mL, 8.90 mmol) in DCM (4.5 mL) were treated with ozone at −78 °C. Subsequently, dimethylsulfide (0.54 mL, 7.33 mmol) was added, and the reaction mixture was allowed to warm to room temperature and stirred for an additional 12 h. The mixture was extracted with water (3×) (6 mL), dried over $MgSO_4$, filtered, and concentrated to give the crude dialdehyde, which was purified by column chromatography on a silica gel (hexanes/EtOAc, 15:3) to afford **11** (700 mg, 62%) as a colorless oil. R_f = 0.24 (SiO_2, hexanes/EtOAc 15:3); α_D^{25} of +20.5 (c = 0.4, DCM); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.78 (d, 1H), 9.72 (d, 1H), 5.41 (d, 1H, J = 4.1), 4.68 (m, 1H), 4.42 (m, 1H), 2.69 (m, 1H), 2.40 (m, 1H), 2.22 (m, 1H), 1.88 (m, 1H), 1.49 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 221.7 (2×), 154.1, 73.3, 70.2, 56.9, 42.3, 41.3, 28.6.

(3*aS*,6*aS*)-*tert*-Butoxycarbonyl-*cis*-dihydrofuro(3,2-*b*)-pyrrole-2,5-dione (12). *Method A.* To a stirred solution of **11** (233 mg, 0.70 mmol) in acetone (19 mL) was added at 10 to 15 °C over a period of 0.5 h a 2.5 M Jones reagent until the mixture turned green in color. A few drops of isopropanol followed by water (35 mL) were added to dissolve the precipitate that formed. The solvent was evaporated, and the product was extracted by ethyl acetate to afford **12** (quantitative).

Method B. To a stirred solution of **10** (530 mg, 1.8 mmol, 1 equiv.) in 55 mL of biphasic solution of CCl_4:AcCN:H_2O (1:1:2) was added $RuCl_3{\cdot}3H_2O$ (32 mg, 8.3 mol %) at 0 °C followed by $NaIO_4$ (1.58 g, 4.1 equiv.) portion-wise. The reaction mixture was stirred for 8 h at 0 °C. The mixture was diluted with 30 mL of water and extracted with DCM (15 mL × 3) followed by *n*-butanol (15 mL × 3). The combined organic layer was dried ($MgSO_4$), and the solvent was evaporated to give a brownish solid, which was purified by column chromatography on silica (hexanes/EtOAc, 9:1) to yield **12** (268 mg, 68%, 90% *ee*) as a white solid. R_f = 0.71 (SiO_2, EtOAc/MeOH 9:1); m.p. 162−164 °C (m.p. 163−164 °C);[33] +53.8 (c = 0.4, DMF), +61.7[32] (c = 1.0, DMF); IR (film): $\tilde{\nu}$; = 1781, 1768, 1721, 1356, 1324, 1251, 1225, 1186, 1149, 1047, 1022, 933, 907, 836 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.01−5.09 (ddd, J = 5.1, 5.5, 2.7, 1H), 4.74−4.81 (ddd, J = 4.8, 6.0, 2.2, 1H), 2.89−2.98 (m, 4H), 1.51 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 173.7, 169.8, 149.8, 84.7, 73.5, 57.9, 38.6, 35.6, 28.0. MS [CI, NH_3]: m/z (%) = 259.1 (44) $[M + NH_4]^+$; elemental analysis calcd (%) for $C_{11}H_{15}NO_5$ (241.1): C, 54.77; H, 6.27; N, 5.81; found: C, 54.99; H, 6.36; N, 5.44.

(3*aS*,6*aS*)-*tert*-Butyl 2-Oxotetrahydro-2*H*-furo(3,2-*b*) Pyrrole-4(5*H*) Carboxylate (13) and (3*aS*,6*aS*)-*tert*-Butyl Tetrahydro-2*H*-furo(3,2-*b*) Pyrrole-4(5*H*) Carboxylate (14). To a stirred solution of **12** (100 mg, 0.41 mmol, 1 equiv.) in 10 mL of dry THF was added BH_3-DMS (0.12 mL, 1.24 mmol, 3 equiv.) dropwise at 0 °C to room temperature, and the mixture was left stirring for 17 h under nitrogen. Methanol was added until no gas evolution was observed, and the solvent was removed *in vacuo* (3 times) to give a white solid, which was purified by column chromatography on silica (EtOAc/methanol, 4:6) to yield **13** (50 mg, 54%) as a white

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solid along with **14** (11%, 10 mg) also a white solid. **13**: R_f = 0.57 (SiO_2, hexanes/EtOAc 4:6); m.p. 105−107 °C (m.p. 106−107 °C);[17] +95.0 (c = 0.4, MeOH),[17] α_D^{25} of +96.0 (c = 0.4, MeOH). IR (film): $\tilde{\nu}$; = 2978, 2933, 2872, 1766, 1698, 1394, 1366, 1230, 1160, 1116, 1092, 1036, 982, 904, 843, 774 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.01−5.10 (m, 1H), 4.38−4.50 (m, 1H), 3.61−3.86 (m, 1H), 3.29−3.42 (m, 1H), 2.72−2.88 (m, 2H), 2.28−2.40 (dd, J = 14, 6.2 Hz, 1H), 1.96−2.12 (m,1H), 1.45 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 176.4, 154.5, 83.1, 80.5, 57.8, 44.2, 36.6, 30.7, 28.4; MS [CI, NH_3]: m/z (%) = 227.1 $[M]^+$. **14**: R_f = 0.42 (SiO_2, hexanes/EtOAc 4:6); m.p. 83−85 °C. α_D^{25} of +10.8 (c = 0.4, DCM). IR (film): $\tilde{\nu}$; = 2976, 2938, 2888, 1650, 1410, 1366, 1251, 1162, 1128, 1068, 1013, 980, 866, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 4.28−4.36 (m, 1H), 3.85−3.92 (bs, 1H), 3.55−3.72 (m, 2H), 3.20−3.35 (m, 2H), 3.55−2.02 (m, 4H), 1.38 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 155.8, 79.9, 70.7, 59.0, 57.8, 43.5, 31.1, 30.7, 28.4. MS [CI, NH_3]: m/z (%) = 213.1 $[M]^+$.

(3*aS*,6*aS*)-Hexahydro-2*H*-furo[3,2-*b*]pyrrol-2-one Hydrochloride (15). Compound **13** (31 mg, 0.14 mmol, 1 equiv.) was treated with saturated HCl in dry EtOAc (8 mL) at 0 °C for 3 h. The solvent was removed *in vacuo* to afford 14 mg of **15** (64%, 91% *ee*) as a white solid. M.p. 180−183 °C (m.p. 182−184 °C);[29] α_D^{25} of −40.0 (c = 0.4, MeOH), −42.0 (c = 0.4, MeOH).[30]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c03251.

^1H and ^{13}C NMR spectroscopic data for compounds **9**−**15** and X-ray crystallographic data for compound **12** (PDF)

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Author Contributions

M.T.M.A. took part in conceptualization, investigation, formal analysis, writing, and editing; Z.M.H. took part in conceptualization, investigation, and formal analysis; A.P.G.M. took part in conceptualization, investigation, supervision, formal analysis, editing, and reviewing.

Notes

The authors declare no competing financial interest.

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