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Synthesis of Functionalized Pyrrolidin-2-ones and (*S*)-Vigabatrin from Pyrrole

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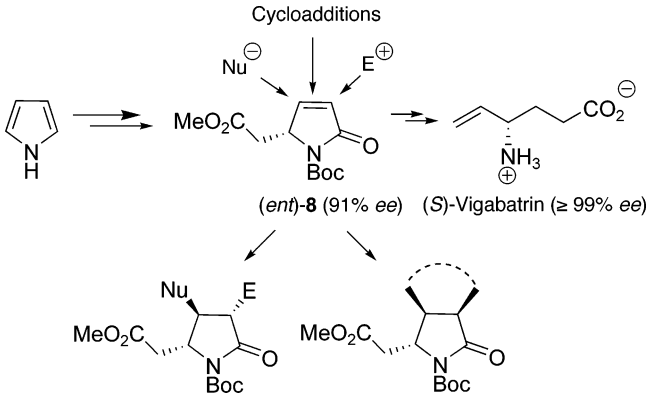

Starting from pyrrole, the novel 3,4-didehydropyrohomoglutamate **8** or (*ent*)-**8** can be efficiently synthesized in up to 91% ee, which can be utilized as a versatile building block toward functionalized pyrrolidin-2-ones. Moreover, (*ent*)-**8** can be readily converted to (*S*)-Vigabatrin, being an irreversible inhibitor for GABA-T, which is used as adjunctive therapy in patients that suffer from epilepsy.

Chiral 5-substituted 3-pyrrolin-2-ones are ideally suited as versatile templates toward functionalized pyrrolidin-2-ones, which are important due to their biological activity and their widespread occurrence as a substructure in alkaloids.

The combination of the chiral center being located adjacent to the β-center of the enone and the topology of the five-membered ring provides a high degree of regio- and stereocontrol for the functionalization of specific sites in the molecule. For example, the α,β-unsaturated lactam moiety can be stereoselectively alkylated by the conjugate addition of nucleophiles.[1] Alternatively, the double bond can be hydroxylated, leading to valuable intermediates, for example, toward glycosidase inhibitors or sphingosines.[2] Moreover, complex molecules can be synthesized by using the 3,4-didehydropyrohomoglutamate moiety as a dienophile in cycloaddition reactions.[3]

Consequently, a number of 5-substituted-3-pyrrolin-2-ones have been introduced as chiral building blocks (Figure 1), utilizing pyroglutamic acid (synthesis of **1**,[4] **2**,[1h] and **6**[5]), malic acid or enzymatic resolutions of lactams (synthesis of **3**[3c,6]), 2-siloxy substituted pyrroles (synthesis of **4**[7]), or chiral nitrones (synthesis of **5**[8]) as starting materials.

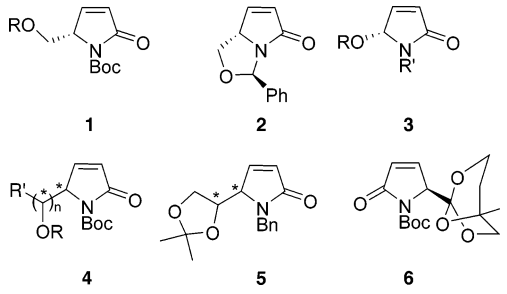

FIGURE 1. Chiral 5-substituted-3-pyrrolin-2-ones.

In contrast, the 3,4-didehydropyroglutamic ester **7**, being arguably the most readily accessible pyrroline-2-one starting from pyroglutamic acid, cannot not be used as a chiral building block as a result of its lability toward racemization and isomerization[9] and has so far only been trapped with cyclopentadiene in a Diels−Alder reaction in 50% ee.[10] We envisioned that the corresponding homoglutamic ester **8** should be less prone to these unwanted side reactions. Here we would like to report an efficient access to this new building block in either enantiomeric form starting from **9**, which in turn can be readily synthesized from pyrrole on a multigram scale, and its scope and limitation for synthetic applications (Figure 2).

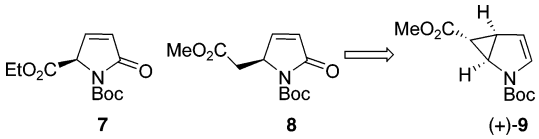

FIGURE 2. 3,4-Didehydropyroglutamic esters as chiral building blocks.

Based on our interest in developing an asymmetric methodology toward chiral intermediates and natural products from

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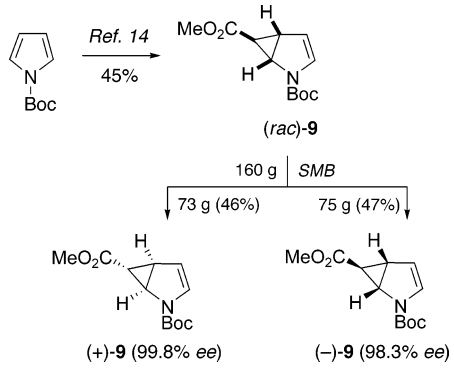
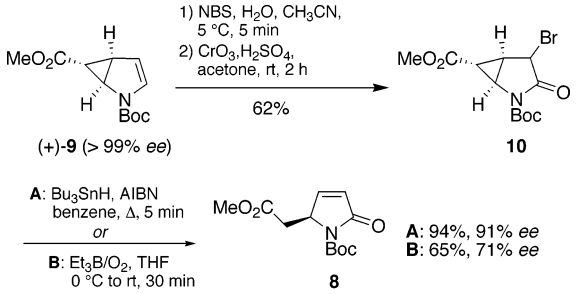
SCHEME 1



inexpensive heteroarenes,[11] we have been able to synthesize as a starting point for β−aminocyclopropanecarboxylic acids[12] the bicyclic adduct **9**,[13,14] enantiomerically pure in either form, by cyclopropanation of N-Boc-pyrrole, followed by enzymatic resolution[14]. However, the latter step was not amenable to accessing optically pure **9** on a large scale, making an alternative desirable. Unfortunately, we were not able to render the cyclopropanation of pyrrole with diazoacetates asymmetric by employing a suitable chiral catalyst, in contrast to the use of furans as starting materials.[15] However, we discovered that (*rac*)-**9** can be separated in its enantiomers by simulated moving bead (SMB) chromatography,[16] having cellulose-tris-(3,5-dimethylphenylcarbamate) Chiralcel OC (20 μm) as the stationary phase, with extraordinary productivity (separation of 1958 g of (*rac*)-**9**/kg stationary phase and day). The SMB chromatography was performed on a 160 g scale with ethanol as an eluent and with a feed concentration of 20 g/L to provide (+)-**9** (73 g, 99.8% ee) and (−)-**9** (75 g, 98.3% ee), along with 6 g of recovered (*rac*)-**9** (Scheme 1).

SCHEME 2



Having (+)-**9** in good quantities in hand, we next investigated its conversion to **8** (Scheme 2). Bromohydrine formation with NBS in water followed by oxidation smoothly gave rise to the α-bromo ketone **10** in 62% yield (2 steps). Utilizing the well-known process of rapid ring opening of cyclopropylmethyl radicals, upon treatment of **10** with tributyltin hydride, **8** was rapidly obtained in excellent yield (94%) by the exclusive fission of the exocyclic cyclopropane bond. Unfortunately, the optical purity of **8** was somewhat reduced (91% ee) compared to the starting material. In the same way, (*ent*)-**8** is obtained from (−)-**9**. Alternatively, the transformation of (+)-**9** to **8** could also be achieved with Et_3B/O_2, however, in this case the results were inferior (65% yield, 71% ee).

8 appears to be considerably more stable compared to **7**: it can be stored at −20 °C over months with no epimerization or isomerization being observed, and even upon standing in solution (CH_2Cl_2) for several hours at room temperature, no loss of optical purity is observed. A broad variety of functionalizations can be performed (Scheme 3) with **8**, such as the conjugate addition of nucleophiles with or without the combination of trapping the resulting enolate with electrophiles, cycloadditions, hydrogenations, or dihydroxylations. For all transformations, complete anti selectivity was observed. However, reactions carried out with basic reagents gave rise to some erosion of the stereochemistry, which could be remedied by a recrystallization of some of the products. This complication was especially severe in the addition of 2-nitropropane in the presence of DBU, for which **17** was only obtained in racemic form. Apparently, under basic conditions at room temperature (20 °C) for several hours α-deprotonation and thus racemization of **8** occurs.

As a further application, the conversion of (*ent*)-**8** into the pharmacologically active (*S*)-enantiomer[17] of Vigabatrin[18] could be demonstrated (Scheme 4), which is being commercialized as Sabril in racemic form for the treatment of epilepsy.[19]

Conjugate reduction of the enone (*ent*)-**8**, followed by *N*-Boc deprotection, afforded **18**,[20] which could be recrystallized to

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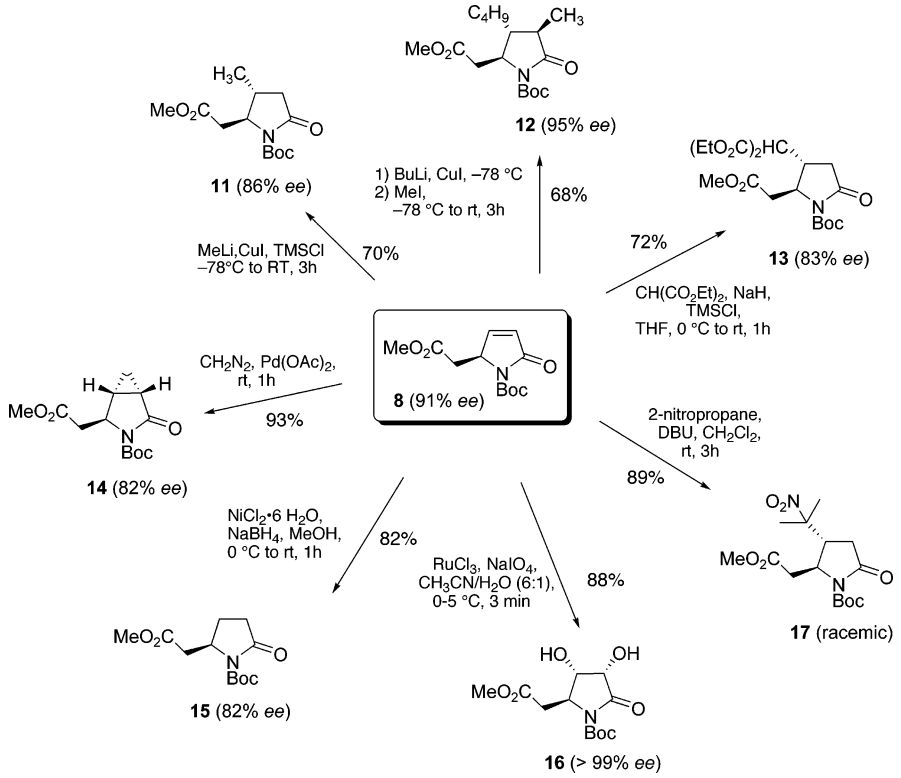
SCHEME 3



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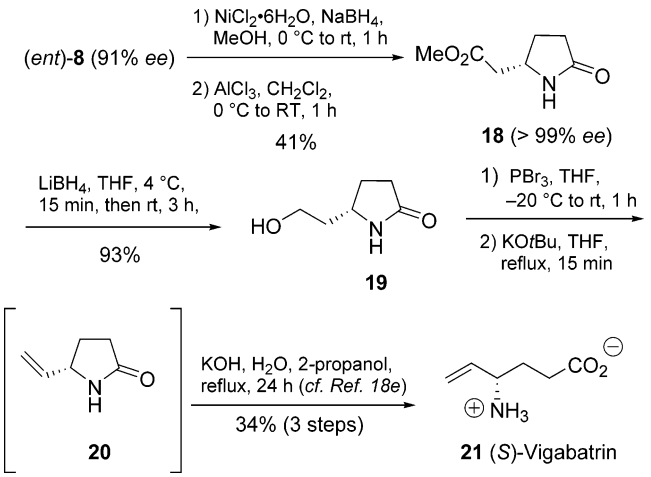

enantiopurity. Subsequent reduction of the methyl ester to the alcohol **19** could be achieved with $LiBH_4$ in high yield. Final transformation of **19** to (*S*)-Vigabatrin (**21**) was best carried out by a three-step protocol, forming first the bromide with PBr_3, followed by dehydrobromination with KO*t*-Bu, and finally hydrolysis of the vinylpyrrolidinone **20** with KOH, as previously described by Knaus and Wey.[18e]

In conclusion, starting from inexpensive pyrrole, we could develop a 4-step synthesis of the new 5-substituted 3-pyrrolin-2-one **8** and (*ent*)-**8** in 91% ee and demonstrate its scope and limitation for the synthesis of functionalized pyrrolidinones.

Experimental Section

(1*R*,5*R*,6*R*)-2-*tert*-Butyl 6-Methyl 2-Azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate, (+)-9, and (1*S*,5*S*,6*S*)-2-*tert*-Butyl 6-Methyl 2-Azabicyclo[3.1.0]hex-3-ene-2,6-dicarboxylate, (−)-9. (*rac*)-**9**[14] was separated into its constituent enantiomers using a preparative chiral SMB chromatographic unit (Licosep Lab) composed of a set of eight columns (2.5 cm × 10 cm) interconnected in series and packed with Chiralcel OC, 20 μm. The mobile phase was ethanol at room temperature. Feed concentration = 20.0 g/L, and feed rate = 16.0 mL/min. (+)-**9**: t_R 4.07 min (analytical HPLC, Chiralcel OC, 20 μm); 73 g (46%; theoretical maximum, 50%), 99.8% ee; $[\alpha]^{20}_D = 260.9$ (*c* 1, CH_2Cl_2). (−)-**9**: t_R 6.64 min (analytical HPLC, Chiralcel OC, 20 μm); 75 g (47%; theoretical maximum, 50%), 98.3% ee; $[\alpha]^{20}_D = -254.2$ (*c* 1, CH_2Cl_2).

(1*R*, 5*R*, 6*R*)-4-Bromo-3-oxo-2-aza-bicyclo[3.1.0]hexane-2,6-dicarboxylic Acid 2-*tert*-Butyl Ester 6-Methyl Ester (10). To a solution of olefin (+)-**9** (2.50 g, 10.46 mmol) in acetonitrile (10 mL) and water (20 mL) was added NBS (1.86 g, 10.46 mmol) in small portions at 5 °C. After stirring 5 min at the same temperature, the reaction mixture was extracted with CH_2Cl_2 (3 × 25 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated in vacuo at room temperature to afford 2.94 g of bromohydrine (84% crude yield). The bromohydrine was unstable at room temperature, and purification by column chromatography failed. The crude bromohydrine (2.94 g, 8.78 mmol) was dissolved in acetone (40 mL), and Jones reagent (17.5 mmol) was added. The reaction mixture was stirred at 20 °C under a N_2 atmosphere for 2 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$ (50 mL). CH_2Cl_2 (50 mL) was added to the mixture, and the organic phase was separated. The organic layer was washed with brine (2 × 25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude ketone was purified by flash column chromatography (silica gel, 20% EtOAc in hexanes) to afford **10** as a yellowish solid, mp 103−105 °C (2.16 g, 62% from olefin (+)-**9**). $R_f = 0.6$ (silica gel, hexanes/ethyl acetate, 3:2). $[\alpha]^{20}_D = -122$ (*c* 0.20, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.54 (s, 9H), 1.76 (dd, J = 1.6, 4.1 Hz, 1H), 2.54 (dd, J = 4.1, 7.2 Hz, 1H), 3.71 (s, 3H), 4.17 (dt, J = 1.2, 7.9 Hz, 1H), 4.45 (d, J = 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.5, 27.9, 31.1, 41.2, 41.8, 52.5, 84.9, 149.2, 167.8, 168.6. IR (KBr): 3074, 2982, 1796, 1443, 1410, 1368, 1302, 1150, 1041, 1012, 952, 914, 889, 839, 773 cm^{-1}. LRMS

[CI, (M + NH_4^+)]: 351/353. Anal. Calcd for $C_{12}H_{16}BrNO_5$: C, 43.13; H, 4.83; N, 4.19. Found: C, 43.16; H, 4.93; N, 4.14.

(2*R*)-2-Methoxycarbonylmethyl-5-oxo-2,5-dihydro-pyrrole-1-carboxylic Acid *tert*-Butyl Ester (8). Method A. To a stirred solution of **10** (2.0 g, 6.0 mmol) in dry benzene (25 mL) at reflux were added tributyltin hydride (1.58 mL, 6.0 mmol) and AIBN (98 mg, 0.6 mmol). The reaction mixture was stirred for 5 min, and then the solvent was evaporated. The crude mixture was dissolved in EtOAc (50 mL), and a saturated solution of KF (50 mL) was added. The mixture was stirred at 20 °C for 18 h. The white precipitate was removed by filtration, and the organic phase was concentrated in vacuo. Flash column chromatography (silica gel, 30% EtOAc in hexanes) afforded **8** as a yellowish oil (1.44 g, 94% yield). $[\alpha]^{20}_D = +176.4$ (*c* 0.81, CH_2Cl_2) with 91% ee; 20.67 min for minor (*S*) and 25.53 min for major (*R*). $R_f = 0.26$ (silica gel, hexanes/ethyl acetate, 3:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56 (s, 9H), 2.43 (dd, $J = 10.0$, 16.1 Hz, 1H), 3.33 (dd, $J = 4.0$, 16.1 Hz, 1H), 3.71 (s, 3H), 4.88 (ddd, $J = 1.9$, 3.8, 10.0 Hz, 1H), 6.12 (dd, $J = 1.6$, 6.1 Hz, 1H), 7.34 (dd, $J = 2.0$, 6.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 36.5, 52.1, 58.7, 83.6, 127.0, 149.3, 149.9, 168.6, 170.4. IR (neat): 3097, 2981, 1782, 1741, 1439, 1363, 1323, 1257, 1161, 1105, 1049, 988, 918, 820, 744 cm^{-1}. LRMS [CI, (M + NH_4^+)]: +273. Anal. Calcd for $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.49. Found: C, 56.32; H, 6.61; N, 5.40.

Method B. To a solution of **10** (90 mg, 0.27 mmol) in dry THF (4 mL) was added Et_3B (1 M in THF; 0.54 mL, 0.54 mmol) under nitrogen at 0 °C. Then dry air (10 mL) was introduced with a syringe. The reaction mixture was stirred for 30 min and allowed to warm to 20 °C. The reaction was quenched with a saturated solution of $Na_2S_2O_4$ (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic phases were concentrated in vacuo. Flash column chromatography (silica gel, 30% EtOAc in hexanes) afforded **8** (45 mg, 65% yield). $[\alpha]^{20}_D = +137.5$ (*c* 0.25, CH_2Cl_2) with 71% ee.

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Supporting Information Available: Chromatograms for the SMB separation of (*rac*)-**9**, and experimental details and analytical data for compounds **11**−**20**, (*ent*-**8**), and (*ent*-**15**). Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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