Supporting Information for

Functionalized cis- and trans-Fused Bicyclic α -Amino Acids via Stereoselective Double Annulation and Dequaternization Reactions

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Evidence with which stereochemical assignments were made, preparation and characterization of **3b**, **7b**, **13b**, **14b**, and **15b**, and spectra of **6b**, **7b**, **12**, and **Troc-20**, for which satisfactory elemental analyses were not obtained (16 pages).

Stereochemical Assignments

All stereochemical assignments were made by ^1H NMR spectroscopy.

Compound **4**: The methine H adjacent to the An group participated in one large and one small coupling (10.9 Hz and 2.3 Hz), establishing the equatorial orientation of the An group. A NOESY spectrum of a close analog of **4** (Ph in place of An) showed cross-peaks between the axial H atoms in the cyclohexane ring and the methine H at the ring junction. These cross-peaks would not have been observed in the lowest-energy conformation of the cis isomer, in which the methine H at the ring junction was equatorial with respect to the cyclohexane ring; instead, a strong cross-peak would have been observed between at least one of the axial H atoms of the cyclohexane ring and one of the axial H atoms of the piperidine ring.

Compounds **6a** and **6b**: In the ^1H NMR spectrum of the more abundant product **6a**, the methine H adjacent to the ester participated in only three small couplings (3.5 Hz, 3.5 Hz, and 1.3 Hz), establishing the ester to be axial, whereas in that of the less abundant product **6b**, the same H participated in one small and two large couplings (3.7 Hz, 11.7 Hz, and 11.7 Hz), establishing the ester to be equatorial.

Compound **8**: At rt, broad peaks attributable to fluxional behavior were observed (such behavior was absent in **3b**), but at elevated temperature the H atom adjacent to the CN group could be seen to participate in three fairly small couplings (each ≈ 4.4 Hz), establishing the relative configuration to be cis.

Compound **9**: The methine H adjacent to the carbonyl group participated in one large and two small couplings (12.6 Hz, 4.6 Hz, and 4.6 Hz), and the allylic methine H participated in only small couplings (< 3 Hz), establishing the cis configuration at the ring junction and the axial orientation of the allylic methine H with respect to the dihydropyridone ring. The ^1H NMR spectrum of the minor, trans isomer featured a very large coupling constant between the methine H atoms (15.2 Hz).

Compound **10**: The methine H adjacent to the An group participated in one large and one small coupling (11.4 Hz and 4.4 Hz), establishing the equatorial orientation of the An group.

Compounds **16a**, **17a**, and **17b**: The methine H atoms at the ring junctions participated in one large coupling (13.2–13.9 Hz), establishing the axial orientation of this H atom with respect to the pyridone ring in all three compounds. (Several small couplings (< 2 Hz) to this H atom were also observed in **16a** and **17a**; these were partly attributed to W-coupling to H atoms in the carbocyclic ring. In **17b**, only one additional coupling (5.3 Hz) to this H atom was observed.) Moreover, in the ^1H NMR spectrum of **16a**, the methine H adjacent to the An group participated only in small couplings (≤ 4.5 Hz), establishing its equatorial orientation, whereas in that of **17a** and **17b** the same H participated in one large and one small coupling (11.4 Hz and 3.6 Hz in **17a**, 11.5 Hz and 2.1 Hz in **17b**), establishing its axial orientation.

Compounds **22a** and **22b**: In **22b**, the two methine H atoms adjacent to the carbonyl groups showed NOEs to one another, and the axial H atom in the CH_2 group of the lactam ring showed an NOE to one of the H atoms of the ethylene bridge in the cyclopentane ring, establishing the all-cis stereochemistry about the cyclopentane ring. In **22a**, on the other hand, the H atom adjacent to the amide carbonyl group showed three medium coupling constants (8.4–9.5 Hz), not one small and two large ones, establishing the cis stereochemistry of the ring junction, and the H atom adjacent to

the CO₂Et group showed an NOE to the axial H atom in the CH₂ group of the lactam ring, establishing the trans orientation of the CO₂Et group to the other two substituents on the cyclopentane ring.

Compound **23**: Each H atom in the CH₂ group adjacent to N showed one large (geminal) coupling constant (12.4 Hz) and one small (vicinal) one (2.3 Hz or 3.6 Hz), confirming the cis stereochemistry of the ring junction.

Experimental Section

Dimethyl 3,3-Dicyano-2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,1-cyclohexanedicarboxylate (3b). This material, prepared from dimethyl 5,5-dicyanopentane-1,1-dicarboxylate¹ in the same way as **3a**, was obtained in 62% yield as a white solid, mp 132 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.02 (d, 9.0 Hz, 2H), 6.97 (d, 9.0 Hz, 2H), 3.88 (s, 3H), 3.87 (s, 3H), 3.84 (dd, 2.8 Hz, 6.4 Hz, 1H), 3.75 (dd, 2.8 Hz, 19.1 Hz, 1H), 3.66 (s, 3H), 3.41 (dd, 6.4 Hz, 19.1 Hz, 1H), 2.58 (dm, 13.6 Hz, 1H), 2.50 (dm, 13.6 Hz, 1H), 2.20 (dt, *J*_d = 4.4 Hz, *J*_t = 13.0 Hz, 1H), 2.02 (m, 1H), 1.96 (m, 1H), 1.80 (dt, *J*_d = 4.0 Hz, *J*_t = 13.5 Hz, 1H). ¹³C{¹H} NMR (50 MHz, CDCl₃): δ 193.4, 170.1, 168.9, 163.9, 130.5 (× 2), 129.2, 115.1, 114.3, 113.9 (× 2), 56.8, 55.4, 53.2, 52.8, 39.9, 39.5, 37.6, 35.5, 31.8, 19.0. IR (KBr): 2249, 1735, 1673 cm⁻¹. Anal. Calcd for C₂₁H₂₂N₂O₆: C, 63.31; H, 5.57. Found: C, 63.05; H, 5.48.

Ethyl (1*R,2*R*,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2-carboxylate**. Compound **6b** (330 mg, 0.96 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (12% EtOAc in petroleum ether) gave the protected amine (435 mg, 0.84 mmol, 88% yield) as a white solid, mp 100 °C. ¹H NMR (400 MHz, CDCl₃, 60 °C): δ 7.24 (d, 8.8 Hz, 2H), 6.84 (d, 8.8 Hz, 2H), 4.68 (d, 12.0 Hz, 1H), 4.67 (dd, 6.1 Hz, 10.4 Hz, 1H), 4.58 (d, 12.0 Hz, 1H), 4.22 (d, 13.7 Hz, 1H), 4.15 (dq, *J*_d = 11.1 Hz, *J*_q = 7.1 Hz, 1H), 4.12 (dq, *J*_d =

11.1 Hz, $J_q = 7.1$ Hz, 1H), 3.77 (s, 3H), 3.44 (d, 13.7 Hz, 1H), 2.53 (ddd, 3.7 Hz, 11.4 Hz, 11.7 Hz, 1H), 2.06 (m, 3H), 1.84 (m, 4H), 1.55 (m, 2H), 1.23 (t, 7.1 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (50 MHz, CDCl_3): δ 173.6, 158.7, 154.4, 133.8, 127.2 ($\times 2$), 120.4, 113.7 ($\times 2$), 95.0, 74.9, 60.4, 59.1, 54.9, 52.6, 44.9, 44.2, 41.2, 34.2, 33.3, 29.1, 21.7, 13.9. IR (KBr): 2234, 1729 cm^{-1} . Anal. Calcd for $\text{C}_{23}\text{H}_{27}\text{Cl}_3\text{N}_2\text{O}_5$: C, 53.35; H, 5.26. Found: C, 53.45; H, 5.42.

(1*R,2*R*,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-8-azabicyclo[4.4.0]decane-2,9-dicarboxylic acid, 2-Ethyl Ester (7b).** The previous compound (378 mg, 0.73 mmol) was subjected to the standard procedure for oxidation of the An group. The residue was crystallized from ether to give **7b** (271 mg, 0.60 mmol, 82% yield) as a white solid, mp 111 °C. ^1H NMR (400 MHz, CDCl_3 , 60 °C): δ 8.50 (br, 1H), 4.89 (d, 11.9 Hz, 1H), 4.65 (d, 11.9 Hz, 1H), 4.30 (d, 13.7 Hz, 1H), 4.18 (d, 7.1 Hz, 2H), 4.08 (m, 1H), 3.12 (d, 13.7 Hz, 1H), 2.52 (dt, $J_d = 3.7$ Hz, $J_t = 11.4$ Hz, 1H), 2.15 (m, 1H), 2.05 (m, 2H), 1.89 (m, 3H), 1.76 (ddd, 3.2 Hz, 11.2 Hz, 12.1 Hz, 1H), 1.51 (dq, $J_d = 5.1$ Hz, $J_q = 12.5$ Hz, 1H), 1.41 (dt, $J_d = 4.8$ Hz, $J_t = 12.5$ Hz, 1H), 1.28 (t, 7.1 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (100 MHz, CDCl_3 , 60 °C): δ 173.9, 173.1, 154.4, 119.9, 95.1, 76.1, 61.3, 57.9, 53.2, 45.7, 42.6, 41.1, 33.7, 29.7, 29.0, 21.9, 14.4. IR (KBr): 3220, 2229, 1719 cm^{-1} . $\text{C}_{17}\text{H}_{21}\text{Cl}_3\text{N}_2\text{O}_6$.

Ethyl 2-Cyano-2-(2-bromoethyl)-3-ethyl-3-pentenoate. Ethyl 2-cyano-3-ethyl-2-pentenoate² (18.1 g, 100 mmol) was added very slowly to a stirring solution of 60% NaH (4.4 g, 110 mmol) in DMF (100 mL) under N_2 . 1,2-Dibromoethane (26 mL, 300 mmol) was added, and the reaction was allowed to stir at rt for 4 h. The reaction was quenched with 1 N HCl and diluted with ether. The resulting mixture was washed with water, dried over MgSO_4 , and evaporated to give the crude product, which was purified by Kugelrohr distillation to give the title compound (25.5 g, 88.7 mmol, 89% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.89 (q, 6.8 Hz, 1H), 4.27 (m, 2H), 3.46 (m, 2H), 2.66 (ddd, 7.9 Hz, 9.5 Hz, 13.9 Hz, 1H), 2.46 (ddd, 6.8 Hz, 9.7 Hz, 13.9 Hz, 1H), 2.18 (q, 7.5 Hz, 2H), 1.73 (d, 6.8 Hz, 3H), 1.32 (t, 7.1 Hz, 3H),

1.02 (t, 7.5 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (50 MHz, CDCl_3): δ 166.4, 133.8, 125.7, 117.2, 62.9, 54.7, 37.8, 25.8, 20.6, 13.6, 13.5, 13.2. IR (neat): 2242, 1743 cm^{-1} . Anal. Calcd for $\text{C}_{12}\text{H}_{18}\text{BrNO}_2$: C, 50.01; H, 6.30. Found: C, 50.45; H, 6.36.

Triethyl 4-Cyano-5-ethyl-5-heptene-1,1,4-tricarboxylate. Diethyl malonate (13.8 mL, 90.78 mmol) was added very slowly to a stirring solution of 60% NaH (3.33 g, 83.22 mmol) in DMF (80 mL) under N_2 . The previous compound (21.8 g, 75.65 mmol) was added, and the reaction was allowed to stir at rt for 22 h. The reaction was quenched with 1 N HCl and diluted with ether. The resulting mixture was washed with water, dried over MgSO_4 , and evaporated to give the crude product, which was purified by Kugelrohr distillation to give the title compound (25.99 g, 70.73 mmol, 93% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 5.87 (q, 6.8 Hz, 1H), 4.24 (m, 6H), 3.35 (~t, 6.7 Hz, 1H), 2.08 (m, 6H), 1.72 (d, 6.8 Hz, 3H), 1.31 (t, 7.1 Hz, 3H), 1.28 (t, 7.1 Hz, 6H), 0.99 (t, 7.6 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (50 MHz, CDCl_3): δ 168.5 ($\times 2$), 167.3, 134.3, 125.5, 118.0, 62.8, 61.4 ($\times 2$), 55.0, 51.3, 32.4, 24.3, 20.7, 13.9 ($\times 2$), 13.7, 13.6, 13.2. IR (neat): 2256, 1742 cm^{-1} . Anal. Calcd for $\text{C}_{19}\text{H}_{29}\text{NO}_6$: C, 62.11; H, 7.96. Found: C, 62.18; H, 8.11.

Triethyl 4-Cyanobutane-1,1,4-tricarboxylate (13b). The previous compound (14.38g, 39.14 mmol) was dissolved in CH_2Cl_2 (100 mL), and the solution was cooled to -78°C . The solution was sparged with ozone (50 V, 1.2 L/min) until it turned blue. It was allowed to warm to rt, and the solvent was evaporated. The residue was dissolved in EtOH (100 mL), and $\text{TsOH}\cdot\text{H}_2\text{O}$ (1.10 g, 5.87 mmol) was added. The mixture was allowed to reflux for 2 h. The solvent was evaporated, and ether was added. The solution was shaken with dil. aq. NaHCO_3 and water, dried over MgSO_4 , and evaporated to give the crude product, which was purified by Kugelrohr distillation to give **13b** (10.75 g, 35.93 mmol, 92% yield) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 4.28 (q, 7.1 Hz, 2H), 4.22 (m, 4H), 3.53 (dd, 6.1 Hz, 7.7 Hz, 1H), 3.37 (t, 7.1 Hz, 1H), 2.06 (m, 4H), 1.33 (t, 7.1 Hz, 3H), 1.28 (t, 7.1 Hz, 6H). $^{13}\text{C}\{\text{H}\}$ NMR (50

MHz, CDCl_3): δ 168.7, 168.7, 165.8, 116.2, 63.0, 61.8 ($\times 2$), 51.2, 37.3, 27.4, 25.8, 14.1 ($\times 2$), 14.0. IR (neat): 2250, 1734 cm^{-1} . Anal. Calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_6$: C, 56.18; H, 7.07. Found: C, 55.97; H, 7.35.

Triethyl (2*R,3*S*)-3-Cyano-2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,1,3-cyclopentanetricarboxylate (14b).** This material, prepared from **13b** in the same way as **14a** was prepared from **13a**, was obtained in 71% yield as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.94 (d, 9.0 Hz, 2H), 6.93 (d, 9.0 Hz, 2H), 4.29 (m, 6H), 3.87 (s, 3H), 3.82 (dd, 3.1 Hz, 10.7 Hz, 1H), 3.68 (dd, 3.1 Hz, 19.6 Hz, 1H), 3.49 (dd, 10.7 Hz, 19.6 Hz, 1H), 2.66 (ddd, 7.3 Hz, 10.4 Hz, 13.0 Hz, 1H), 2.56 (ddd, 2.8 Hz, 7.3 Hz, 13.0 Hz, 1H), 2.45 (ddd, 2.8 Hz, 8.3 Hz, 13.0 Hz, 1H), 2.35 (ddd, 8.3 Hz, 10.4 Hz, 13.0 Hz, 1H), 1.35 (t, 7.1 Hz, 3H), 1.32 (t, 7.1 Hz, 3H), 1.25 (t, 7.1 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (50 MHz, CDCl_3): δ 195.6, 169.7 ($\times 2$), 169.6, 163.6, 130.2 ($\times 2$), 129.3, 118.3, 113.6 ($\times 2$), 63.2, 63.0, 61.9, 61.8, 55.3, 51.8, 47.9, 37.7, 36.6, 33.4, 14.0, 13.8, 13.8. IR (neat): 2245, 1732, 1678 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_8$: C, 62.73; H, 6.36. Found: C, 62.44; H, 6.50.

Triethyl (1*R,6*S*)-4-(4-Methoxyphenyl)-3-azabicyclo[4.3.0]non-4-en-2-one-1,7,7-tricarboxylate (15b).** Concentrated H_2SO_4 (18 mL) was slowly added to a stirred solution of **14b** (4.21 g, 9.16 mmol) in absolute EtOH (6 mL) at 0 °C. The reaction mixture was then allowed to warm to rt. After 19 h, the mixture was neutralized with sat. aq. NaHCO_3 solution and extracted with CH_2Cl_2 . The combined organic layers were dried over MgSO_4 and evaporated to give the crude product. Flash chromatography (20% EtOAc in petroleum ether) gave **15b** (2.63 g, 5.72 mmol, 62% yield) as a pale yellow oil. ^1H NMR (400 MHz, CDCl_3): δ 7.32 (d, 8.9 Hz, 2H), 7.16 (br, 1H), 6.89 (d, 8.9 Hz, 2H), 5.32 (dd, 1.6 Hz, 6.2 Hz, 1H), 4.16 (m, 6H), 3.94 (d, 6.2 Hz, 1H), 3.82 (s, 3H), 2.90 (ddd, 5.5 Hz, 7.7 Hz, 13.2 Hz, 1H), 2.50 (m, 2H), 2.18 (ddd, 5.7 Hz, 8.6 Hz, 13.2 Hz, 1H), 1.29 (t, 7.1 Hz, 3H), 1.23 (t, 7.1 Hz, 3H), 1.15 (t, 7.1 Hz, 3H). $^{13}\text{C}\{\text{H}\}$ NMR (50 MHz, CDCl_3): δ 171.9, 171.0, 170.2, 168.9, 160.3, 136.7, 127.3,

126.2 ($\times 2$), 114.3 ($\times 2$), 98.2, 66.4, 62.1, 61.7, 61.6, 58.1, 55.4, 49.7, 33.2, 33.0, 14.0, 13.9 ($\times 2$). IR (neat): 3330, 1733, 1683 cm^{-1} . Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{NO}_8$: C, 62.73; H, 6.36. Found: C, 63.10; H, 6.56.

Supporting Information References

- (1) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, 62, 5235.
- (2) Cope, A. C.; Hancock, E. M. *Org. Syn., Coll. Vol. III* **1955**, 399.

K2H-15-CL1 1n CDCL3
12/13/01 KZH

Pulse Sequence: s2pul

Solvent: CDCL3
Ambient temperature
INOVA-400 "old400"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 71.2 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

8 repetitions

OBSERVE H1: 399.727173 MHz

DATA PROCESSING

FT size 65536

Total time 0 min, 38 sec

Compound 6b

K2H-11-15-CL1 1n CDCL3
12/18/01 KZH
Solvent: CDCl3
Ambient temperature
GEMINI-28088 "gembb.chem.uxy.edu"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 1.081 sec
Width 12508.0 Hz
28439 repetitions
OBSERVE C13 50.281179 MHz
DECOUPLE H1 199.965123 MHz
Power 49.08
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 32768
Total time 11.4 hours

Compound 6b

KZH-III-24 in CDCl3 at 60C

Pulse Sequence: s2pul

Solvent: CDCl3

Temp: 60.0 C / 333.1 K

INOVA-400 "Old400"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 71.2 degrees

Acq. time 3.744 sec

Width 6000.6 Hz

32 repetitions

OBSERVE H1, 399.7271810 MHz

DATA PROCESSING

FT size 65536

Total time 2 min, 32 sec

Compound 7b

K2H-II-24 in CDCl3 at 60C

Pulse Sequence: s2pul

Solvent: CDCl3

Temp: 60.0 C / 333.1 K

INNOVA-400 "Old400"

PULSE SEQUENCE

Relax. delay 1.000 sec

Pulse 69.2 degrees

Acq. time 0.800 sec

Width 25000.0 Hz

18691 repetitions

OBSERVE C13, 100.511446 MHz

DECOUPLE H1, 399.7291893 MHz

Power 42. dB

continuously ON

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 20 hr, 5 min, 53 sec

Compound 7b

Compound 12

Compound 12

Troc-20 at 60 °C

Compound Troc-20 at 60 °C