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Functionalized Cis- and Trans-Fused Bicyclic α-Amino Acids via Stereoselective Double Annulation and Dequaternization Reactions

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Fused bicyclic α-amino acids can be prepared by a double Michael reaction of *p*-anisyl ethynyl ketone and a tethered diacid, cyclization via hydrogenation or hydration of a CN group, and oxidation of the *p*-anisyl group. The substitution level of the α-amino acids can be adjusted by decyanation or decarboethoxylation of the intermediates. Bicyclic α-amino acids prepared in this way include *cis*- and *trans*-perhydroisoquinoline-3-carboxylic acids and *cis*-perhydro-2-pyrindine-3-carboxylic acids of various substitutions and oxidation levels. The bicyclic α-amino acids may be regarded as functionalized and conformationally restricted analogues of proline, pipecolic acid, 2-aminoadipic acid, or glutamic acid.

The synthesis of unusual α-amino acids (that is, α-amino acids that are not coded by DNA) has recently become an area of intense study. Many unnatural α-amino acids display desirable pharmacological properties, and they can confer conformational rigidity and stability to enzymatic degradation on peptides into which they are incorporated.[1] Rigidified analogues of natural amino acids have been of particular interest. One common strategy for rigidification has been to incorporate one or two rings into the α-amino acid. Some examples of biologically significant bicyclic α-amino acids are shown in Figure 1.[2]

Over the past few years we have described a suite of reactions, "double annulation", that provides access to highly substituted and functionalized fused carbobicyclic and azabicyclic compounds in stereoselective fashion (Scheme 1).[3] A "tethered diacid", which consists of two carbon acids connected by a tether, is allowed to undergo a double Michael reaction with 3-butyn-2-one to give a new cyclic compound with moderate to high stereoselectivity. If the double Michael adduct contains an equatorial CN group, hydrogenation affords a trans-fused bicyclic piperidine; if it contains an equatorial NO_2 group, hydrogenation affords a trans-fused bicyclic pyrroline or pyrrolidine; and if it contains only an axial CN group, treatment with strong acid affords a cis-fused bicyclic 3,4-dihydro-2-pyridone.

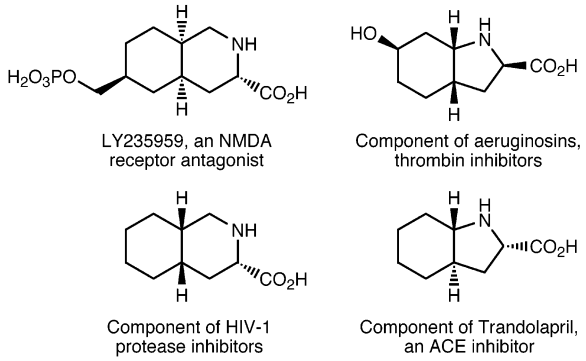
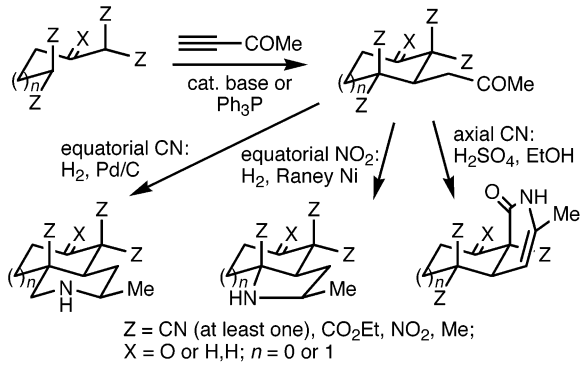


FIGURE 1. Some biologically significant bicyclic α-amino acids.

SCHEME 1



Because the double annulation provided access to novel azabicyclic compounds, we decided to develop it into a route to bicyclic analogues of the α-amino acids proline and pipecolic acid.[4] This application required that 3-butyn-2-one be replaced in the double Michael reaction with an ester of 2-oxo-3-butynoic acid (in Scheme 1, Me re-

* To whom correspondence should be addressed.

(1) Hanessian, S.; McNaughton-Smith, G.; Lombart, H. G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789. Gibson, S. E.; Guillo, N.; Tozer, M. J. *Tetrahedron* **1999**, *55*, 585.

(2) Brion, F.; Marie, C.; Mackiewicz, P.; Roul, J. M.; Buendia, J. *Tetrahedron Lett.* **1992**, *33*, 4889. Trova, M. P.; McGee, K. F., Jr. *Tetrahedron* **1995**, *51*, 5951. Hansen, M. M.; Bertsch, C. F.; Harkness, A. R.; Huff, B. E.; Hutchison, D. R.; Khau, V. V.; LeTourneau, M. E.; Martinelli, M. J.; Misner, J. W.; Peterson, B. C.; Rieck, J. A.; Sullivan, K. A.; Wright, I. G. *J. Org. Chem.* **1998**, *63*, 775. Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. *Chem.—Eur. J.* **2001**, *7*, 3446.

(3) Grossman, R. B. *Synlett* **2001**, 13.

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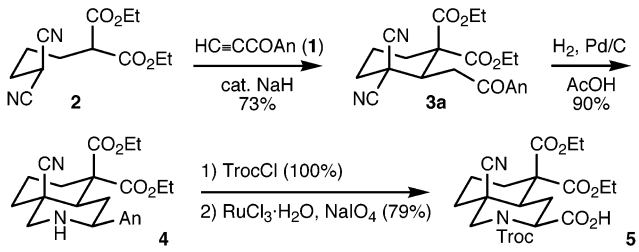
SCHEME 2

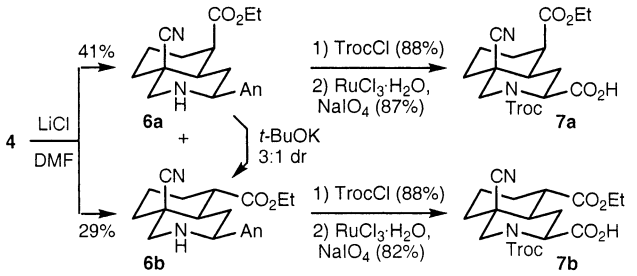


placed with CO_2R). The electron-withdrawing CO_2R group, though, was expected to render this ethynyl ketone exceedingly unstable. We chose to mask the CO_2R group as a *p*-methoxyphenyl (*p*-anisyl, An) group for three reasons: (1) *p*-anisyl ethynyl ketone (**1**) was known and stable,[5] (2) the An group was expected to be stable to catalytic hydrogenation and to strong acid, our two methods for azacyclization, and (3) the An group could be converted to a CO_2H group under conditions (excess $NaIO_4$, catalytic $RuCl_3 \cdot H_2O$) that did not generally affect amides, esters, nitriles, or unfunctionalized C−C and C−H σ bonds.[6,7]

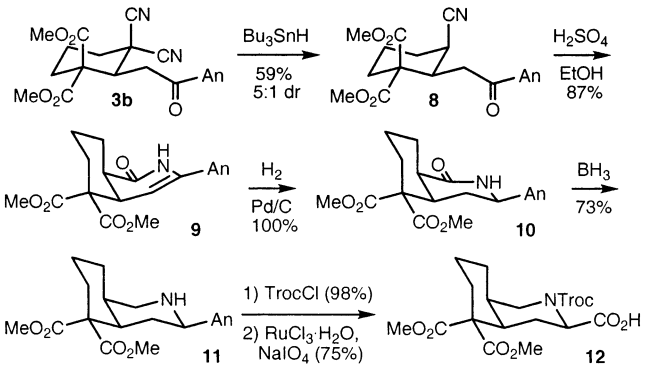
Results and Discussion

Tethered diacid **2**, prepared by a modification of our previously published procedures,[8] underwent a double Michael reaction with alkynone **1** catalyzed by NaH in THF to provide adduct **3a** in 73% yield (Scheme 2). Hydrogenation of **3a** over Pd/C in AcOH then afforded *trans*-perhydroisoquinoline **4** in 90% yield. (All stereochemical assignments were made by ^{1}H NMR; the reasoning is enumerated in the Supporting Information.) Hydrogenolysis of the new benzylic C−N bond was apparently not a problem under these reaction conditions. As expected from our previous observations, only the equatorial CN group of **3a** underwent reduction, and the two new stereocenters in **4** were formed with complete fidelity.[9,10] Protection of **4** with 2,2,2-trichloroethyl chloroformate (TrocCl) proceeded quantitatively, and oxidation of the An group with excess $NaIO_4$ and catalytic $RuCl_3 \cdot H_2O$ afforded *trans*-perhydroisoquinoline-3-carboxylic acid **5** in 79% yield. Similar results were obtained with the methyl carbamate of **4**, but neither the *tert*-butyl carbamate nor the trifluoroacetamide gave satisfactory results in the oxidation.[11] We did not try to deprotect **5**, but others have successfully deprotected *N*-Troc-α-amino acids.[11,12]

SCHEME 3



SCHEME 4



Although we considered it a strength of our method that two quaternary centers with rigidly disposed functional groups were installed in bicyclic α-amino acids **5**, we thought that the route would be more widely applicable if methods for producing less highly substituted analogues could be developed. Krapcho decarboxylations of **3a** and **5** did not proceed well, but the same reaction of **4** provided 41% and 29% yields of two separable monoesters, **6a** and **6b**, respectively (Scheme 3).[13] Apparently the CN group sterically inhibited protonation of the enolate or enol intermediate from the thermodynamically preferred direction, affording the more congested, higher energy isomer **6a** with slight selectivity, as has been observed in other systems.[14] A 1.1:1 mixture of **6a** and **6b** could be converted to a 3:1 mixture in favor of **6b** with catalytic *t*-BuOK in *t*-BuOH. In addition, both **6a** and **6b** could be carried on to *trans*-perhydroisoquinoline-3-carboxylic acids **7a** and **7b** stereospecifically and in very good yields.

To prepare a bicyclic α-amino acid that lacked a quaternary center at the ring junction, double Michael adduct **3b** (the methyl ester analogue of **3a**) was treated with Bu_3SnH to afford a mononitrile in 59% yield and as a 5:1 mixture of diastereomers (Scheme 4).[15] The major diastereomer **8** was separated by crystallization. The reaction of the intermediate decyanated radical with Bu_3SnH apparently occurred predominantly from the less hindered face to give the higher energy, cis isomer of the product. Hydrogenation of **8** gave poor yields, but treatment with 80% H_2SO_4 in EtOH caused it to rearrange to

(4) Couty, F. *Amino Acids* **1999**, *16*, 297. Hughes, F., Jr.; Grossman, R. B. *Org. Lett.* **2001**, *3*, 2911.
(5) Irving, F.; Johnson, A. W. *J. Chem. Soc.* **1948**, 2037.
(6) Ayres, D. C. *J. Chem. Soc., Perkin Trans. 1* **1978**, 585. Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. Tverezovsky, V. V.; Baird, M. S.; Bolesov, I. G. *Tetrahedron* **1997**, *53*, 14773. Badorrey, R.; Cativiela, C.; Diaz-de-Villegas, M. D.; Galvez, J. A. *Tetrahedron* **1999**, *55*, 14145. Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153.
(7) Martín-Martínez, M.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *Tetrahedron* **1996**, *52*, 13991.
(8) Grossman, R. B.; Varner, M. A. *J. Org. Chem.* **1997**, *62*, 5235. The Knoevenagel adduct of 3-pentanone and either malononitrile or ethyl cyanoacetate was alkylated with an α,ω-dibromide in DMF (instead of DMPU), the remaining Br was displaced with diethyl malonate (instead of diethyl isopentylidenemalonate), and the product was ozonolyzed and then refluxed in acidic EtOH.
(9) Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.
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(11) Walker, J. R.; Curley, R. W., Jr. *Tetrahedron* **2001**, *57*, 6695.
(12) Arakawa, Y.; Yasuda, M.; Ohnishi, M.; Yoshifuji, S. *Chem. Pharm. Bull.* **1997**, *45*, 255.
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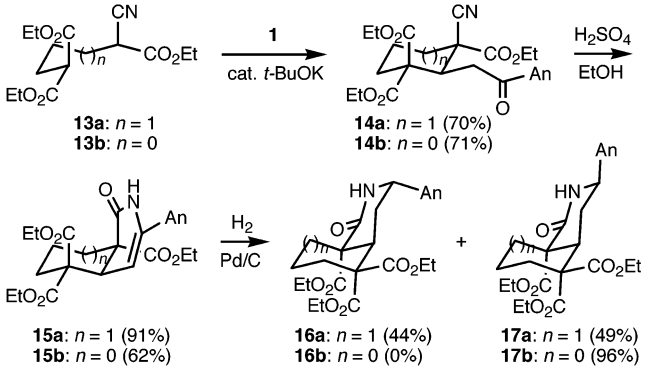
(14) Krapcho, A. P.; Weimaster, J. F. *J. Org. Chem.* **1980**, *45*, 4105.
(15) Curran, D. P.; Seong, C. M. *Synlett* **1991**, 107.

SCHEME 5

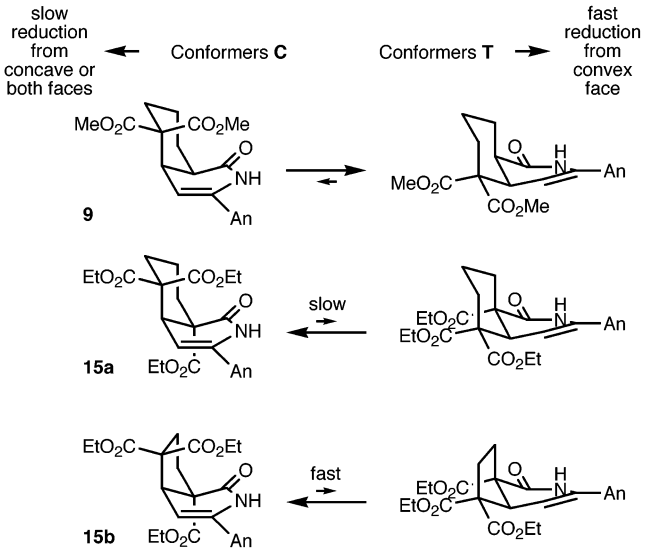


cis-hexahydroisoquinolin-1-one **9** in 87% yield.[16] An additional 9% of the trans isomer of **9** was also obtained. Hydrogenation of **9** over Pd/C proceeded on the convex face to give **10** quantitatively and with complete stereoselectivity. The oxidation of the An group of **10** provided none of the desired acid; instead, an imide was obtained in only 18% yield. This result was surprising, as **5**, **7a**, and **7b** were produced in excellent yield under the same conditions. An explanation for the different behavior of **10** is offered below. However, reduction of **10** with BH_3 gave amine **11** in 73% yield, and protection and oxidation of **11** afforded *cis*-perhydroisoquinoline-3-carboxylic acid **12** in 74% overall yield.

We also sought to prepare bicyclic amino acids with a cis ring fusion and an angular substituent at the ring junction (Scheme 5). Previously prepared tethered diacid **13a** and new tethered diacid **13b** were each prepared in three steps by the modified literature procedure.[8,17] These diacids underwent highly diastereoselective double Michael reactions with **1** to provide adducts **14a** (70% yield) and **14b** (71% yield), as expected from our previous work.[9] The H_2SO_4-catalyzed rearrangements of **14a** and **14b** afforded *cis*-hexahydroisoquinolin-1-one **15a** in 91% yield and *cis*-tetrahydro-2-pyrindin-1-one **15b** in 62% yield. Much to our surprise, hydrogenation of **15a** over Pd/C afforded both **16a** and **17a** in 49% and 44% isolated yields, respectively. The catalyst 20% $Pd(OH)_2$/C gave reversed but equally poor stereoselectivity, and PtO_2, 5% Rh/C, Raney Ni, and $(Ph_3P)_3RhCl$ failed to catalyze the hydrogenation at all. By contrast, hydrogenation of **15b** over Pd/C afforded only **17b** in 96% isolated yield; no resonances attributable to its diastereomer **16b** were seen in the ^1H NMR spectrum of the crude reaction mixture.

We have great difficulty explaining why the hydrogenation of **15a** proceeds with such poor selectivity, whereas the hydrogenations of **9** and **15b** proceed with perfect selectivity, but our best stab at it follows. Compounds **9**, **15a**, and **15b** can exist in two major conformations, **T** and **C** (Scheme 6). Hydrogenation of conformers **T** from the convex face is facile because approach of the catalyst is unhindered and because the reduction places the nascent piperidone ring in a half-chair conformation with an equatorial An group. By contrast, hydrogenation of conformers **C** from the convex face requires either that the nascent piperidone ring assume a half-boat conformation with a severe flagpole interaction or that the An group experience a severe steric interaction with the *endo*-CO_2Et group, and as a result, these hydrogenations are slow. For simple steric reasons, compound **9** resides primarily in conformation **T**, as shown by the very small coupling constant between the olefinic H atom and the adjacent methine H atom (2.4 Hz), so its hydrogenation is rapid and stereoselective. Compounds **15a** and **15b**, on the other hand, reside primarily in conformation **C**, as shown by the larger coupling constants between the olefinic H atoms and the adjacent methine H atoms (5.9 and 6.2 Hz, respectively). However, the five-membered ring in **15b** may make this compound more conformationally mobile, and as a result the concentration of **15b-T** may be sufficiently high that its hydrogenation (from the convex face) can proceed stereoselectively and at a reasonable rate. On the other hand, the concentration of conformer **T** of the more rigid **15a** may be so low that the hydrogenation of **15a-C** (from the concave face or from both faces) becomes competitive.

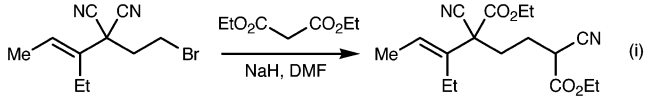
SCHEME 6



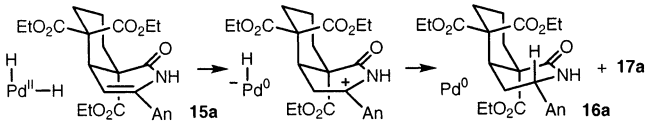
It remains to explain how **15a-C** can be hydrogenated from the concave face, even with the encumbrance of the *endo*-CO_2Et group. Perhaps the insertion of Pd−H into the convex face of the C=C π bond of **15a-C** is such a high-energy process, and the approach of Pd−H to the concave face is so hindered, that the mechanism of hydrogenation switches to an ionic protonation−hydride-transfer mechanism (Scheme 7): that is, protonation of **15a** by H−Pd(II)−H gives $[H-Pd(0)]^-$ and a carbocation stabilized by the NH and An groups, and hydride transfer then provides the product and regenerates neutral Pd(0). The hydride-transfer step may be much less sterically demanding than an insertion, and it would proceed with a stereoelectronic bias for axial delivery of H^-, providing the unexpected **16a** as well as **17a**. Others

(16) Grossman, R. B.; Pendharkar, D. S.; Rasne, R. M.; Varner, M. A. *J. Org. Chem.* **2000**, *65*, 3255.

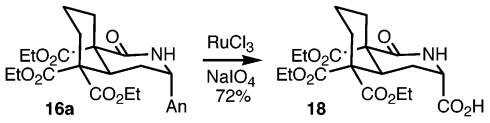
(17) Interestingly, an attempt to prepare diethyl 3,3-dicyanopropylmalonate, the analogue of **2** with a two-carbon tether, gave only the known diethyl 2,5-dicyanoadipate.[8] The exchange of the positions of a CN and a CO_2Et group apparently occurred in the second alkylation step (eq i). We mention this reaction because we believe it makes an excellent mechanism exercise for students.



SCHEME 7



SCHEME 8



have noted that the polarity of the Pd−H bond in homogeneous and heterogeneous hydrogenations depends on the electronic bias of the alkene.[18] In **15a**, of course, the alkene is very strongly polarized by the N and An groups, so the $Pd^{\delta-}-H^{\delta+}$ polarization induced by the alkene may be so pronounced, and the traditional insertion so disfavored by steric factors, that the mechanism changes from an organometallic one to an ionic one. Experiments to test this hypothesis are being designed, and the results will be reported in due course.

Oxidation of the An group of **16a** provided *cis*-perhydroisoquinolin-1-one-3-carboxylic acid **18** in 72% yield, with preservation of stereochemistry adjacent to the newly introduced CO_2H group (Scheme 8). By contrast, oxidation of **17a** provided an inseparable 3:1 mixture of the desired acid and the corresponding α,β-unsaturated acid in only 44% yield, and oxidation of **17b** provided the desired acid in only 30% yield. The common feature of the compounds whose oxidations proceeded in poor yield or that were overoxidized (**10**, **17a**, and **17b**) was an axial, benzylic C−H bond in a δ-lactam. By contrast, among the compounds whose oxidations proceeded smoothly (**16a** and protected **4**, **6a**, **6b**, and **11**), the benzylic C−H bond was equatorial in the first, and the others were not lactams. The benzylic C−H bonds in **10**, **17a**, and **17b** may have been particularly prone to oxidation due to hyperconjugation of the lone pairs of the lactam N atoms with these axially oriented bonds (Figure 2); on the other hand, in the protected **4**, **6a**, **6b**, and **11**, hyperconjugation with the benzylic C−H bonds would have been reduced because of a slightly different orientation of the N lone pair (and perhaps also because of the potent electron-withdrawing ability of the Troc group), and in **16a** it would have been nearly absent. This reasoning led us to reduce the amide moiety of **17a** (Scheme 9). Treatment of **17a** with Lawesson's reagent gave the thioamide **19** in 94% yield, and reductive desulfurization of **19** by nickel boride gave amine **20** in 80% yield.[7] (One-step reduction of **17a** to **20** with BH_3 gave an unsatisfactory yield.) Amine **20** was quantitatively protected with a Troc group, and oxidation of the An group afforded **21** cleanly and in a much more satisfying 64% yield. The NMR spectra of both Troc-**20** and **21** showed extra resonances due to restricted rotation.

To prepare a bicyclic α-amino acid lacking quaternary centers, perhydro-2-pyrindine **17b** was subjected to Krapcho decarboxylation to afford the two monoesters **22a** and **22b** (out of four possible ones) in 36% and 25% yield, respectively (Scheme 10). Reduction of **22a** with BH_3 in THF provided amino ester **23** in 54% yield along with 11% recovered **22a**. Protection of **23** and oxidation afforded **24** in 99% and 75% yield, respectively. The NMR spectra of **24** were complicated by the presence of two rotamers of approximately equal populations, even at moderately elevated temperatures.

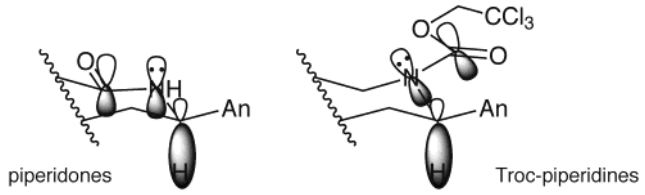
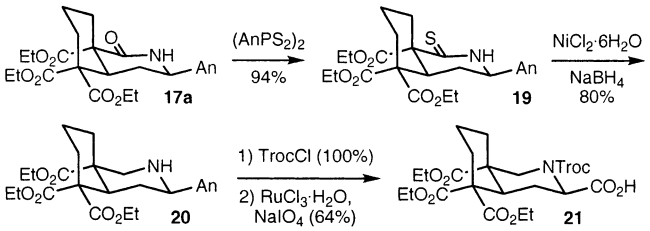
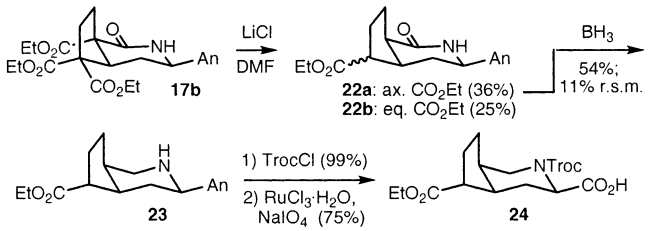


FIGURE 2. Hyperconjugation of the N lone pair with the axial, benzylic C−H bonds is greater in piperidones than in Troc-piperidines, making the benzylic C−H bonds in the former more prone to oxidation by $RuCl_3 \cdot H_2O$.

SCHEME 9



SCHEME 10



Conclusion

We have established that double annulation provides a versatile and generally stereoselective, albeit not enantioselective, route to cis- and trans-fused bicyclic α-amino acids of diverse ring sizes and substitution patterns. The dequaternization reactions described here illustrate a general and desirable feature of these reactions: they often provide more congested, higher energy stereoisomers by delivering H to the less hindered face of a fully substituted reactive intermediate. The poor stereoselectivity of the Krapcho decarboxylation is a clear limitation, and future work will need to address this problem. Compounds **5**, **7a**, **7b**, **12**, **18**, **21**, and **24** are rigidified analogues of pipecolic acid, but they also have a 1,6-disposition of CO_2R groups, and as a result they may also be regarded as rigidified analogues of 2-aminoadipic acid, the homologue of glutamic acid. The methods described in this paper may be useful for the preparation of these and other bicyclic α-amino acids of biological significance.

Experimental Section

Standard Procedure for Addition of a Troc Group. A suspension of a secondary amine and Na_2CO_3 (1.2−2.0 equiv) in THF (2−10 mL) was treated with 2,2,2-trichloroethyl

(18) Yu, J.; Spencer, J. B. *J. Am. Chem. Soc.* **1997**, *119*, 5257. Yu, J.; Spencer, J. B. *J. Org. Chem.* **1997**, *62*, 8618.

chloroformate (1.2−2.0 equiv). The reaction mixture was allowed to stir at rt for 5 h. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated.

Standard Procedure for Oxidation of the An Group. The amide or carbamate was dissolved in a mixture of EtOAc (2 mL), CH_3CN (1 mL), and H_2O (8 mL), and $NaIO_4$ (14.5 equiv) and 30% $RuCl_3 \cdot H_2O$ (3 mol %) were added. The reaction mixture was allowed to stir vigorously at rt for 4 h. The reaction mixture was extracted with EtOAc. Magnesium sulfate was added to the combined organic layers until the dark color of Ru disappeared. The resulting mixture was filtered and evaporated. The residue was dissolved in EtOAc and extracted with diluted $NaHCO_3$ solution. The aqueous layer was carefully acidified with 1 N HCl and then extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and evaporated.

Diethyl 3,3-Dicyano-2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,1-cyclohexanedicarboxylate (3a). A solution of **2** (1.65 g, 6.20 mmol)[8] in THF (10 mL) was added to a stirring solution of 60% NaH (50 mg, 1.24 mmol) in THF (20 mL) under N_2. The flask was cooled to −78 °C. A solution of *p*-anisyl ethynyl ketone[5] (1.05 g, 6.50 mmol) in THF (10 mL) was added slowly to the reaction mixture. The reaction mixture was allowed to stir at rt for 4 h. The reaction was quenched with saturated NH_4Cl solution and diluted with ether. The resulting mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography (15% EtOAc in petroleum ether) gave **3a** (1.93 g, 4.52 mmol, 73% yield) as a white solid, mp 84 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, 8.9 Hz, 2H), 6.96 (d, 8.9 Hz, 2H), 4.33 (∼q, 7.2 Hz, 2H), 4.10 (m, 2H), 3.88 (s, 3H), 3.82 (dd, 2.6 Hz, 6.4 Hz, 1H), 3.78 (dd, 2.6 Hz, 19.0 Hz, 1H), 3.44 (dd, 6.4 Hz, 19.0 Hz, 1H), 2.59 (dm, 13.3 Hz, 1H), 2.51 (dm, 13.2 Hz, 1H), 2.20 (dt, J_d = 4.1 Hz, J_t = 13.2 Hz, 1H), 2.04 (m, 1H), 1.94 (m, 1H), 1.77 (dt, J_d = 3.8 Hz, J_t = 13.3 Hz, 1H), 1.39 (t, 7.2 Hz, 3H), 1.14 (t, 7.2 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 193.2, 169.6, 168.3, 163.7, 130.4 (×2), 129.0, 115.1, 114.2, 113.8 (×2), 62.4, 62.2, 56.7, 55.5, 39.7 (×2), 37.7, 35.6, 31.8, 19.0, 13.8, 13.7. IR (KBr): 2246, 1731, 1683 cm^{-1}. Anal. Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.15. Found: C, 64.76; H, 6.50.

Diethyl (1*R,6*R*,9*R*)-6-Cyano-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2,2-dicarboxylate (4).** Compound **3a** (1.88 g, 4.41 mmol) was dissolved in acetic acid (15 mL), and 5% Pd/C (94 mg, 5 wt %) was added. The mixture was hydrogenated in a Parr shaker at 56 psi for 55 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The crude product was purified by flash chromatography (15−30% EtOAc in petroleum ether) to give **4** (1.39 g, 3.35 mmol, 76% yield) as a white solid, mp 106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 8.6 Hz, 2H), 6.86 (d, 8.6 Hz, 2H), 4.29 (m, 2H), 4.16 (m, 2H), 3.79 (s, 3H), 3.66 (dd, 2.3 Hz, 10.9 Hz, 1H), 3.34 (d, 12.3 Hz, 1H), 2.76 (d, 12.3 Hz, 1H), 2.54 (dm, 13.2 Hz, 1H), 2.27 (m, 2H), 2.15 (m, 1H), 1.98 (m, 2H), 1.79 (m, 2H), 1.47 (dt, J_d = 3.8 Hz, J_t = 13.3 Hz, 1H), 1.36 (dt, J_d = 3.8 Hz, J_t = 13.5 Hz, 1H), 1.31 (t, 7.0 Hz, 3H), 1.20 (t, 7.0 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 171.0, 168.5, 158.6, 135.6, 127.4 (×2), 120.9, 113.4 (×2), 61.1 (×2), 60.8, 57.5, 56.0, 54.7, 46.1, 39.0, 35.1, 33.3, 32.9, 19.1, 13.4, 13.3. IR (KBr): 3335, 2233, 1723 cm^{-1}. Anal. Calcd for $C_{23}H_{30}N_2O_5$: C, 66.65; H, 7.30. Found: C, 66.88; H, 7.70.

Diethyl (1*R,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-9-(4-methoxyphenyl)- 8-azabicyclo[4.4.0]decane-2,2-dicarboxylate.** Compound **4** (1.41 g, 3.40 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (15% EtOAc in petroleum ether) gave the title compound (2.00 g, 3.39 mmol, 100% yield) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 7.25 (d, 8.8 Hz, 2H), 6.86 (d, 8.8 Hz, 2H), 5.03 (t, 9.0 Hz, 1H), 4.75 (d, 11.9 Hz, 1H), 4.68 (d, 11.9 Hz, 1H), 4.27 (m, 2H), 4.20 (m, 2H), 4.02 (d, 14.5 Hz, 1H), 3.85 (d, 14.5 Hz, 1H), 3.79 (s, 3H), 2.58 (dm, 13.6 Hz, 1H), 2.42 (m, 1H), 2.21 (tq, J_t = 3.6 Hz, J_q = 14.5 Hz, 1H), 2.16 (m, 2H), 2.07 (dm, 13.2 Hz, 1H), 1.84 (d quintet, J_d = 14.5 Hz, $J_{quintet}$ = 2.7 Hz, 1H), 1.72 (dt, J_d = 3.8 Hz, J_t = 13.4 Hz, 1H), 1.47 (dt, J_d = 4.2 Hz, J_t = 13.4 Hz, 1H), 1.29 (t, 7.1 Hz, 3H), 1.24 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 170.7, 168.2, 158.8, 154.0, 132.3, 127.0 (×2), 120.6, 113.7 (×2), 95.1, 74.7, 61.4, 61.1, 58.9, 56.0, 54.8, 50.8, 43.2, 40.2, 34.8, 32.7, 31.7, 20.3, 13.5, 13.3. IR (neat): 2232, 1728 cm^{-1}. Anal. Calcd for $C_{26}H_{31}Cl_3N_2O_7$: C, 52.94; H, 5.30. Found: C, 52.64; H, 5.41.

(1*R,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-8-azabicyclo[4.4.0]decane-2,2,9-tricarboxylic Acid, 2,2-Diethyl Ester (5).** The previous compound (540 mg, 0.92 mmol) was subjected to the standard procedure for oxidation of the An group, except 4 times as much solvent and twice as much reagent were used. The residue was crystallized from ether to give **5** (383 mg, 0.73 mmol, 79% yield) as a white solid, mp 175 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 9.90 (br, 1H), 4.88 (d, 12.0 Hz, 1H), 4.65 (d, 12.0 Hz, 1H), 4.25 (m, 5H), 4.10 (d, 14.3 Hz, 1H), 3.54 (br, 1H), 2.59 (dm, 12.8 Hz, 1H), 2.44 (dd, 5.0 Hz, 13.5 Hz, 1H), 2.26 (m, 2H), 2.15 (dd, 1.8 Hz, 12.1 Hz, 1H), 2.05 (dm, 14.1 Hz, 1H), 1.82 (dm, 15.0 Hz, 1H), 1.53 (dt, J_d = 3.8 Hz, J_t = 13.6 Hz, 1H), 1.44 (dt, J_d = 4.0 Hz, J_t = 13.4 Hz, 1H), 1.32 (t, 7.1 Hz, 3H), 1.25 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$, 60 °C): δ 174.3, 171.0, 168.2, 154.0, 119.9, 95.0, 75.7, 62.1, 61.8, 58.5, 56.4, 52.8, 43.9, 39.7, 34.8, 33.4, 27.9, 20.2, 13.9, 13.8. IR (KBr): 3437, 2225, 1728 cm^{-1}. Anal. Calcd for $C_{20}H_{25}Cl_3N_2O_8$: C, 45.51; H, 4.77. Found: C, 45.86; H, 4.74.

Ethyl (1*R,2*S*,6*R*,9*R*)- and (1*R**,2*R*,6*R*,9*R*)-6-Cyano-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2-carboxylate (6a and 6b).** A solution of **4** (414 mg, 1.00 mmol), lithium chloride (64 mg, 1.50 μmol), and water (27 μL, 1.50 mmol) in DMF (10 mL) was refluxed for 48 h. The reaction mixture was cooled and poured into ice−water. The resulting mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography (15−50% EtOAc in petroleum ether) gave **6a** (140 mg, 0.41 mmol, 41% yield) as a white solid, mp 102 °C, and **6b** (100 mg, 0.29 mmol, 29% yield) as a white solid, mp 67 °C. The following are data for compound **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 (d, 8.5 Hz, 2H), 6.87 (d, 8.5 Hz, 2H), 4.26 (dq, J_d = 10.7 Hz, J_q = 7.1 Hz, 1H), 4.17 (dq, J_d = 10.7 Hz, J_q = 7.1 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, 2.6 Hz, 11.1 Hz, 1H), 3.32 (d, 12.5 Hz, 1H), 2.68 (d, 12.5 Hz, 1H), 2.64 (dt, J_d = 1.3 Hz, J_t = 3.5 Hz, 1H), 2.29 (m, 2H), 2.18 (ddd, 11.2 Hz, 12.6 Hz, 13.8 Hz, 1H), 2.00 (dm, J_d = 13.6, 1H), 1.90 (dt, J_d = 13.9 Hz, J_t = 2.7 Hz, 1H), 1.82 (ddd, 3.0 Hz, 5.3 Hz, 12.6 Hz, 1H), 1.72 (m, 2H), 1.44 (tt, J_t = 4.6 Hz, 13.9 Hz, 1H), 1.30 (m, 1H), 1.29 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 172.2, 158.9, 135.7, 127.7 (×2), 121.7, 113.8 (×2), 61.5, 60.5, 57.9, 55.2, 45.0, 42.4, 39.9, 37.3, 33.6, 27.7, 19.3, 14.1. IR (KBr): 3332, 2227, 1714 cm^{-1}. Anal. Calcd for $C_{20}H_{26}N_2O_3$: C, 70.15; H, 7.65. Found: C, 70.24; H, 7.92. The following are data for compound **6b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 8.8 Hz, 2H), 6.85 (d, 8.8 Hz, 2H), 4.11 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.07 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 3.79 (s, 3H), 3.68 (dd, 2.9 Hz, 11.0 Hz, 1H), 3.32 (d, 12.1 Hz, 1H), 2.74 (d, 12.1 Hz, 1H), 2.51 (dt, J_d = 3.7 Hz, J_t = 11.7 Hz, 1H), 2.03 (m, 1H), 1.86 (m, 4H), 1.72 (dt, J_d = 13.2 Hz, J_t = 2.9 Hz, 1H), 1.58 (m, 2H), 1.54 (m, 1H), 1.38 (m, 1H), 1.21 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 174.4, 158.9, 135.6, 127.8 (×2), 121.6, 113.8 (×2), 60.7, 60.5, 55.7, 55.2, 46.1, 44.9, 42.0, 36.0, 32.5, 29.5, 21.8, 14.1. IR (KBr): 3341, 2234, 1732 cm^{-1}.

Ethyl (1*R,2*S*,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2-carboxylate.** Compound **6a** (467 mg, 1.36 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (15% EtOAc in petroleum ether) gave the protected amine (618 mg, 1.19 mmol, 88% yield) as a colorless gum. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 7.26 (d, 8.8 Hz, 2H), 6.87 (d, 8.8 Hz, 2H), 4.95 (dd, 8.1 Hz, 9.9 Hz, 1H),

4.76 (d, 12.0 Hz, 1H), 4.64 (d, 12.0 Hz, 1H), 4.23 (dq, J_d = 10.1 Hz, J_q = 7.1 Hz, 1H), 4.17 (dq, J_d = 10.1 Hz, J_q = 7.1 Hz, 1H), 3.89 (d, 14.3 Hz, 1H), 3.83 (d, 14.3 Hz, 1H), 3.79 (s, 3H), 2.77 (tm, J_t = 3.9 Hz, 1H), 2.37 (m, 3H), 2.17 (tq, J_t = 3.7 Hz, J_q = 14.1 Hz, 1H), 2.09 (dm, J_t = 13.2 Hz, 1H), 1.76 (m, 2H), 1.63 (dt, J_d = 3.7 Hz, J_t = 13.4 Hz, 1H), 1.45 (tt, J_t = 4.6 Hz, 13.6 Hz, 1H), 1.28 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 171.2, 158.5, 153.7, 132.4, 126.9 (·2), 120.6, 113.5 (·2), 95.0, 74.5, 60.0, 58.7, 54.6, 51.4, 41.7, 41.2, 39.9, 34.7, 33.3, 26.7, 19.5, 13.4. IR (neat): 2232, 1724 cm^{-1}. Anal. Calcd for $C_{23}H_{27}Cl_3N_2O_5$: C, 53.35; H, 5.26. Found: C, 53.09; H, 5.53.

(1*R,2*S*,6*R*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-6-cyano-8-azabicyclo[4.4.0]decane-2,9-dicarboxylic Acid, 2-Ethyl Ester (7a).** The previous compound (374 mg, 0.72 mmol) was subjected to the standard procedure for oxidation of the An group. The residue was crystallized from ether to give **7a** (285 mg, 0.62 mmol, 87% yield) as a white solid, mp 180 °C. ^1H NMR (400 MHz, $CDCl_3$, 60 °C): δ 6.00 (br, 1H), 4.90 (d, 12.2 Hz, 1H), 4.64 (d, 12.2 Hz, 1H), 4.22 (m, 3H), 4.14 (d, 13.6 Hz, 1H), 3.36 (d, 13.6 Hz, 1H), 2.74 (m, 1H), 2.45 (dt, J_d = 13.4 Hz, J_t = 12.6 Hz, 1H), 2.33 (m, 2H), 2.20 (m, 1H), 2.07 (dm, J_t = 13.2 Hz, 1H), 1.75 (m, 2H), 1.43 (m, 2H), 1.31 (t, 7.1 Hz, 3H). $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$, 60 °C): δ 173.1, 171.3, 154.2, 120.1, 95.0, 75.8, 61.1, 58.4, 53.4, 42.6, 42.0, 39.6, 35.2, 29.8, 27.6, 19.7, 14.0. IR (KBr): 3430, 2234, 1722 cm^{-1}. Anal. Calcd for $C_{17}H_{21}Cl_3N_2O_6$: C, 44.80; H, 4.64. Found: C, 44.82; H, 4.73.

Dimethyl (2*R,3*R*)-3-Cyano-2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,1-cyclohexanedicarboxylate (8).** Tributyltin hydride (269 μL, 1.00 mmol) was added to a solution of **3b** (398 mg, 1.00 mmol) and AIBN (16 mg, 0.10 mmol) in benzene (10 mL, 0.1 M). The mixture was refluxed for 1.5 h, and then additional tributyltin hydride (269 mL, 1.00 mmol) and AIBN (16 mg, 0.10 mmol) were added. After 5 h, the mixture was cooled to rt, and DBU (359 μL, 2.40 mmol) was added. The mixture was diluted with wet ether, filtered through a short column of silica gel with ether, and concentrated. The crude product was purified by flash chromatography (20% EtOAc in petroleum ether) to give a 5:1 mixture of diastereomers (220 mg, 0.59 mmol, 59% yield). Crystallization from ether gave **8** as a white solid, mp 114 °C. ^1H NMR (400 MHz, C_6D_6, 60 °C): δ 7.98 (d, 9.0 Hz, 2H), 6.63 (d, 9.0 Hz, 2H), 3.59 (s, 3H), 3.52 (m, 2H), 3.46 (m, 1H), 3.26 (s, 3H), 3.25 (s, 3H), 3.13 (q, 4.4 Hz, 1H), 2.32 (dt, J_d = 4.4 Hz, J_t = 13.0 Hz, 1H), 1.90 (m, 1H), 1.48 (m, 2H), 1.20 (m, 2H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 195.7, 171.4, 170.0, 163.7, 130.3 (×2), 129.5, 120.3, 113.7 (×2), 56.5, 55.4, 52.9, 52.6, 38.5, 36.0, 31.3, 30.1, 27.3, 19.8. IR (KBr): 2240, 1730, 1685 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21. Found: C, 64.13; H, 6.17.

Dimethyl (1*R,6*S*)-9-(4-Methoxyphenyl)-8-azabicyclo-[4.4.0]dec-9-en-7-one-2,2-dicarboxylate (9).** Concentrated sulfuric acid (4 mL) was slowly added to a solution of **8** (189 mg, 0.51 mmol) in absolute EtOH (1 mL) with constant stirring at 0 °C. The reaction mixture was then allowed to warm to rt. After 17 h, the mixture was neutralized with saturated $NaHCO_3$ 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 (30% EtOAc in petroleum ether) gave **9** (165 mg, 0.44 mmol, 87% yield) as a white solid, mp 183 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30 (d, 9.0 Hz, 2H), 7.18 (br, 1H), 6.90 (d, 9.0 Hz, 2H), 4.80 (dt, J_d = 2.4 Hz, J_t = 1.6 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 3.69 (d, 4.9 Hz, 1H), 2.96 (dt, J_d = 12.6 Hz, J_t = 4.6 Hz, 1H), 2.25 (dm, 14.1 Hz, 1H), 1.90 (dt, J_d = 3.5 Hz, J_t = 13.7 Hz, 1H), 1.74 (m, 2H), 1.56 (dq, J_d = 4.6 Hz, J_q = 13.5 Hz, 1H), 1.20 (tq, J_t = 3.5 Hz, J_q = 13.5 Hz, 1H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 173.9, 171.0, 170.4, 160.3, 136.9, 127.1, 126.3 (×2), 114.3 (×2), 99.6, 56.9, 55.4, 52.8 (×2), 40.3, 36.6, 27.1, 23.2, 20.9. IR (KBr): 3210, 1733, 1668 cm^{-1}. Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21. Found: C, 64.32; H, 6.46.

Dimethyl (1*R,6*S*,9*R*)-9-(4-Methoxyphenyl)-8-azabicyclo[4.4.0]decan-7-one-2,2-dicarboxylate (10).** A suspension of 10% Pd/C (12 mg, 10 wt %) and **9** (118 mg, 0.32 mmol) in MeOH (2 mL) was allowed to stir at rt under H_2 (balloon) for 20 h. The reaction mixture was filtered through Celite, and the solvent was evaporated to give **10** (122 mg, 0.32 mmol, 100% yield) as a white solid, mp 214 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, 8.7 Hz, 2H), 6.89 (d, 8.7 Hz, 2H), 5.63 (br, 1H), 4.45 (dd, 4.4 Hz, 11.4 Hz, 1H), 3.81 (s, 3H), 3.77 (s, 3H), 3.71 (s, 3H), 3.04 (dm, 12.8 Hz, 1H), 2.95 (dt, J_d = 13.2 Hz, J_t = 4.7 Hz, 1H), 2.24 (dm, 14.5 Hz, 1H), 2.10 (dm, 12.3 Hz, 1H), 1.82 (m, 3H), 1.58 (dq, J_d = 3.8 Hz, J_q = 13.6 Hz, 1H), 1.41 (dm, 13.4 Hz, 1H), 1.21 (tq, J_t = 3.7 Hz, J_q = 13.6 Hz, 1H). $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$): δ 174.5, 170.7, 170.6, 159.5, 133.8, 127.3 (×2), 114.2 (×2), 57.8, 56.8, 55.3, 52.9, 52.7, 34.0, 35.6, 30.4, 25.9, 25.7, 21.9. IR (KBr): 3424, 3185, 1741, 1725, 1666 cm^{-1}. Anal. Calcd for $C_{20}H_{25}NO_6$: C, 63.99; H, 6.71. Found: C, 64.53; H, 6.82.

Dimethyl (1*R,6*S*,9*R*)-9-(4-Methoxyphenyl)-8-azabicyclo[4.4.0]decane-2,2-dicarboxylate (11).** A solution of borane in THF (1 M, 2.1 mL) was added to a suspension of **10** (241 mg, 0.64 mmol) in THF (1 mL) at 0 °C under N_2. The mixture was allowed to stir at rt for 18 h. The solution was cooled in ice−water, and the reaction was quenched by 6 M HCl (1 mL). After the mixture was stirred for 2 h at 0 °C, 1 N NaOH was added until the pH was 10. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product. Flash chromatography (2% MeOH in CH_2Cl_2) gave **11** (169 mg, 0.47 mmol, 73% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, 8.8 Hz, 2H), 6.84 (d, 8.8 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 3.64 (s, 3H), 3.60 (dd, 2.4 Hz, 11.2 Hz, 1H), 3.07 (dd, 3.1 Hz, 11.9 Hz, 1H), 2.97 (dd, 1.8 Hz, 11.9 Hz, 1H), 2.71 (dt, J_d = 13.0 Hz, J_t = 3.9 Hz, 1H), 2.18 (dm, 14.1 Hz, 1H), 2.04 (dm, 12.8 Hz, 1H), 1.95 (m, 2H), 1.79 (dt, J_d = 13.9 Hz, J_t = 3.0 Hz, 1H), 1.65 (dt, J_d = 11.4 Hz, J_t = 12.8 Hz, 1H), 1.56 (br, 1H), 1.38 (m, 1H), 1.15 (m, 2H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 171.6, 171.2, 158.8, 136.9, 127.8 (×2), 113.7 (×2), 61.6, 59.1, 55.3, 52.5, 52.5, 52.4, 39.1, 32.6, 31.7, 26.0, 24.3, 22.7. IR (neat): 3335, 1733 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53. Found: C, 66.71; H, 7.64.

Dimethyl (1*R,6*S*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2,2-dicarboxylate.** Compound **11** (160 mg, 0.44 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (12% EtOAc in petroleum ether) gave the protected amine (232 mg, 0.43 mmol, 98% yield) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.17 (d, 8.7 Hz, 2H), 6.84 (d, 8.7 Hz, 2H), 4.98 (dd, 7.1 Hz, 11.2 Hz, 1H), 4.78 (d, 12.1 Hz, 1H), 4.70 (d, 12.1 Hz, 1H), 4.28 (dd, 7.3 Hz, 14.0 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 6H), 2.85 (dd, 7.9 Hz, 14.0 Hz, 1H), 2.64 (m, 2H), 2.21 (dm, 15.0 Hz, 1H), 1.69 (m, 4H), 1.48 (tq, J_t = 1.7 Hz, J_q = 6.4 Hz, 1H), 1.10 (m, 2H). $^{13}C\{H\}$ NMR (50 MHz, $CDCl_3$): δ 171.4, 171.2, 158.9, 154.4, 133.7, 126.9 (×2), 113.9 (×2), 95.7, 75.0, 58.3, 58.2, 55.2, 52.6, 52.5, 47.1, 35.1, 31.1, 28.4, 26.7, 26.5, 20.7. IR (neat): 1733 cm^{-1}. Anal. Calcd for $C_{23}H_{28}Cl_3NO_7$: C, 51.46; H, 5.26. Found: C, 51.27; H, 5.38.

(1*R,6*S*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-8-azabicyclo[4.4.0]decane-2,2,9-tricarboxylic Acid, 2,2-Dimethyl Ester (12).** The previous compound (230 mg, 0.43 mmol) was subjected to the standard procedure for oxidation of the An group. The residue was crystallized from ether to give **12** (153 mg, 0.32 mmol, 75% yield) as a white solid, mp 135 °C. ^1H NMR (400 MHz, $CDCl_3$, 60 °C): δ 6.50 (br, 1H), 4.78 (d, 11.9 Hz, 1H), 4.70 (d, 11.9 Hz, 1H), 4.24 (br, 1H), 3.82 (br, 1H), 3.73 (s, 6H), 3.30 (br, 1H), 2.60 (dm, 13.4 Hz, 1H), 2.41 (m, 1H), 2.21 (dm, 13.6 Hz, 1H), 1.79 (m, 3H), 1.54 (m, 2H), 1.29 (m, 1H), 1.10 (tq, J_t = 3.5 Hz, J_q = 13.6 Hz, 1H). $^{13}C\{H\}$ NMR (100 MHz, $CDCl_3$, 60 °C): δ 175.4, 171.2, 171.1, 154.9, 95.5, 75.8, 58.7, 57.8, 52.9, 48.7, 35.8, 31.8, 29.9, 26.5, 25.8, 24.2, 21.7. IR (KBr): 3278, 1733 cm^{-1}. $C_{17}H_{22}Cl_3NO_8$.

Triethyl (2*R,3*S*)-3-Cyano-2-[2-(4-methoxyphenyl)-2-oxoethyl]-1,1,3-cyclohexanetricarboxylate (14a).** Cyano triester **13a**[8] (5.50 g, 17.52 mmol) was added to a stirring solution of potassium *tert*-butoxide (393 mg, 3.50 mmol) in CH_2Cl_2 (30 mL) under N_2. The flask was cooled to −78 °C. A solution of *p*-anisyl ethynyl ketone[5] (3.36 g, 21.02 mmol) in THF (15 mL) was added slowly to the reaction mixture. The reaction mixture was allowed to stir at rt for 22 h. The reaction was quenched with saturated aq NH_4Cl and diluted with ether. The resulting mixture was extracted with ether, washed with water and brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography (10−12% EtOAc in petroleum ether) gave **14a** (5.78 g, 12.20 mmol, 70% yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, 9.0 Hz, 2H), 6.94 (d, 9.0 Hz, 2H), 4.36 (q, 7.1 Hz, 2H), 4.11 (m, 2H), 4.00 (dq, J_d = 10.7 Hz, J_q = 7.1 Hz, 1H), 3.87 (s, 3H), 3.79 (dq, J_d = 10.7 Hz, J_q = 7.1 Hz, 1H), 3.65 (dd, 7.7 Hz, 6.4 Hz, 1H), 3.63 (d, 1.8 Hz, 1H), 3.47 (d, 17.4 Hz, 1H), 2.60 (dm, 13.4 Hz, 1H), 2.27 (dt, J_d = 13.9 Hz, J_t = 4.0 Hz, 1H), 2.10 (m, 2H), 1.88 (dt, J_d = 14.5 Hz, J_t = 3.3 Hz, 1H), 1.73 (dt, J_d = 3.8 Hz, J_t = 13.4 Hz, 1H), 1.42 (t, 7.1 Hz, 3H), 1.14 (t, 7.1 Hz, 3H), 1.00 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 194.0, 170.4, 168.6, 167.1, 163.3, 129.9 (×2), 129.0, 117.6, 113.5 (×2), 62.9, 61.7, 61.4, 57.3, 55.1, 49.2, 39.5, 39.1, 33.0, 32.4, 18.8, 13.6, 13.5, 13.0. IR (neat): 2255, 1730, 1601 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60. Found: C, 63.20; H, 6.92.

Triethyl (1*R,6*S*)-9-(4-Methoxyphenyl)-8-azabicyclo-[4.4.0]dec-9-en-7-one-2,2,6-tricarboxylate (15a).** Concentrated H_2SO_4 (4 mL) was slowly added to a stirred solution of **14a** (683 mg, 1.44 mmol) in absolute EtOH (1 mL) at 0 °C. The reaction mixture was then allowed to warm to rt. After 17 h, the mixture was neutralized with saturated aq $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product. Flash chromatography (25% EtOAc in petroleum ether) gave **15a** (619 mg, 1.31 mmol, 91% yield) as a white solid, mp 112 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (d, 8.8 Hz, 2H), 7.09 (br, 1H), 6.88 (d, 8.8 Hz, 2H), 5.45 (dd, 5.9 Hz, 1.5 Hz, 1H), 4.23 (m, 3H), 4.12 (m, 2H), 3.96 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 3.81 (s, 3H), 3.74 (d, 5.9 Hz, 1H), 2.52 (m, 1H), 2.32 (m, 1H), 2.18 (m, 1H), 1.68 (m, 3H), 1.27 (t, 7.1 Hz, 3H), 1.20 (t, 7.1 Hz, 3H), 1.14 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 172.2, 171.0, 170.2, 170.0, 160.2, 137.2, 127.2, 126.5 (×2), 114.0 (×2), 102.0, 61.5, 61.2, 61.2, 56.4, 55.1, 53.0, 39.1, 31.1, 28.0, 18.3, 13.8 (×2), 13.6. IR (KBr): 3220, 1726, 1686 cm^{-1}. Anal. Calcd for $C_{25}H_{31}NO_8$: C, 63.41; H, 6.60. Found: C, 63.40; H, 6.77.

Triethyl (1*R,6*S*,9*S*)- and (1*R**,6*S*,9*R*)-9-(4-Methoxyphenyl)-8-azabicyclo[4.4.0]decan-7-one-2,2,6-tricarboxylate (16a and 17a).** A suspension of 10% Pd/C (380 mg, 10 wt %) and **15a** (3.80 g, 8.03 mmol) in MeOH (40 mL) was allowed to stir at rt under 1 atm of H_2 for 18 h. The reaction mixture was filtered through Celite, and the solvent was evaporated to give the crude product. Flash chromatography (25−50% EtOAc in petroleum ether) gave **16a** (1.69 g, 3.56 mmol, 44% yield) as a white solid, mp 193 °C, and **17a** (1.89 g, 3.97 mmol, 49% yield) as a white solid, mp 199 °C. The following are data for compound **16a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 8.7 Hz, 2H), 6.89 (d, 8.7 Hz, 2H), 6.10 (br, 1H), 4.72 (m, 1H), 4.34 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.22 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.07 (m, 2H), 3.89 (q, 7.1 Hz, 1H), 3.88 (q, 7.1 Hz, 1H), 3.82 (s, 3H), 3.38 (dm, 11.5 Hz, 1H), 2.51 (dm, 14.3 Hz, 1H), 2.34 (dt, J_d = 5.5 Hz, J_t = 13.6 Hz, 1H), 2.23 (dm, 13.7 Hz, 1H), 1.77 (m, 3H), 1.56 (m, 1H), 1.43 (t, 7.1 Hz, 3H), 1.41 (m, 1H), 1.15 (t, 7.1 Hz, 3H), 0.85 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 172.7, 171.8, 170.0, 169.5, 159.1, 133.4, 127.6 (×2), 113.8 (×2), 61.5, 61.4 (×2), 58.0, 55.3, 53.8, 53.7, 32.5, 30.1, 28.0, 25.8, 19.2, 13.9 (×2), 13.6. IR (KBr): 3439, 1734, 1666 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_8$: C, 63.14; H, 6.99. Found: C, 63.17; H, 7.04. The following are data for compound **17a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, 8.7 Hz, 2H), 6.89 (d, 8.7 Hz, 2H), 5.76 (br, 1H), 4.58 (dd, 3.7 Hz, 11.4 Hz, 1H), 4.33 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.16 (m, 5H), 3.81 (s, 3H), 3.58 (dm, 13.4 Hz, 1H), 2.54 (dm, 12.8 Hz, 1H), 2.30 (dm, 7.7 Hz, 1H), 1.79 (m, 4H), 1.61 (m, 2H), 1.34 (t, 7.1 Hz, 3H), 1.22 (t, 7.1 Hz, 3H), 1.22 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 172.4, 172.1, 170.2, 169.6, 159.9, 133.4, 127.4 (×2), 114.6 (×2), 61.7, 61.6, 61.4, 58.4, 56.3, 55.3, 53.4, 38.6, 32.8, 28.4, 25.7, 19.3, 14.0, 13.8 (×2). IR (KBr): 3448, 3183, 1740, 1728, 1657 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_8$: C, 63.14; H, 6.99. Found: C, 62.80; H, 7.26.

Triethyl (1*R,4*S*,6*S*)-4-(4-Methoxyphenyl)-3-azabicyclo-[4.3.0]nonan-2-one-1,7,7-tricarboxylate (17b).** A suspension of 10% Pd/C (230 mg, 10 wt %) and **15b** (2.30 g, 5.01 mmol) in MeOH (40 mL) was allowed to stir at rt under 1 atm of H_2 for 23 h. The reaction mixture was filtered through Celite, and the solvent was evaporated to give **17b** (2.22 g, 4.80 mmol, 96% yield) as a white solid, mp 121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, 8.8 Hz, 2H), 6.90 (d, 8.8 Hz, 2H), 5.88 (br, 1H), 4.57 (dd, 2.1 Hz, 11.5 Hz, 1H), 4.21 (m, 5H), 4.04 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 3.81 (s, 3H), 3.74 (dd, 5.3 Hz, 13.2 Hz, 1H), 2.66 (ddd, 3.1 Hz, 7.7 Hz, 10.3 Hz, 1H), 2.54 (ddd, 3.1 Hz, 8.6 Hz, 10.3 Hz, 1H), 2.32 (m, 2H), 1.88 (ddd, 2.1 Hz, 5.3 Hz, 13.2 Hz, 1H), 1.51 (dt, J_d = 11.5 Hz, J_t = 13.2 Hz, 1H), 1.33 (t, 7.1 Hz, 3H), 1.24 (t, 7.1 Hz, 3H), 1.18 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 171.2, 171.0, 170.8, 169.3, 159.8, 132.7, 127.6 (×2), 114.5 (×2), 64.6, 62.1, 61.8, 61.6, 60.6, 55.7, 55.3, 46.9, 34.6, 31.4, 30.9, 14.0 (×2), 13.9. IR (neat): 3185, 1734, 1664 cm^{-1}. Anal. Calcd for $C_{24}H_{31}NO_8$: C, 62.46; H, 6.77. Found: C, 62.41; H, 6.93.

(1*R,6*S*,9*S*)-8-Azabicyclo[4.4.0]decan-7-one-2,2,6,9-tetracarboxylic Acid, 2,2,6-Triethyl Ester (18).** A solution of **16a** (85 mg, 0.18 mmol) was subjected to the standard procedure for oxidation of the An group. The residue was crystallized from ether to give **18** (55 mg, 0.13 mmol, 72% yield) as a white solid, mp 228 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.07 (br, 1H), 4.33 (dq, J_d = 10.6 Hz, J_q = 7.1 Hz, 1H), 4.14 (m, 6H), 3.31 (dm, 12.8 Hz, 1H), 2.38 (dm, 14.1 Hz, 1H), 2.27 (dm, 13.9 Hz, 1H), 2.12 (dt, J_d = 6.1 Hz, J_t = 14.1 Hz, 1H), 1.96 (dm, 13.2 Hz, 1H), 1.85 (m, 1H), 1.73 (m, 2H), 1.54 (m, 1H), 1.34 (t, 7.1 Hz, 3H), 1.21 (t, 7.1 Hz, 3H), 1.20 (t, 7.1 Hz, 3H) (CO_2H too broad to be seen). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 175.3, 174.6, 171.4, 169.9, 169.7, 62.2, 61.7, 61.6, 58.0, 53.3, 52.8, 35.1, 27.9, 25.7, 24.1, 19.1, 13.8, 13.7, 13.7. IR (KBr): 3283, 1734, 1635 cm^{-1}. Anal. Calcd for $C_{19}H_{27}NO_9$: C, 55.20; H, 6.58. Found: C, 55.23; H, 6.57.

Triethyl (1*R,6*S*,9*S*)-9-(4-Methoxyphenyl)-8-azabicyclo-[4.4.0]decane-7-thione-2,2,6-tricarboxylate (19).** A solution of **17a** (638 mg, 1.34 mmol) and Lawesson's reagent (434 mg, 1.07 mmol) in toluene (15 mL) was allowed to reflux for 48 h. The solvent was evaporated. Flash chromatography (10−25% EtOAc in petroleum ether) gave **19** (622 mg, 1.27 mmol, 94% yield) as a white solid, mp 199 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (br, 1H), 7.18 (d, 8.7 Hz, 2H), 6.91 (d, 8.7 Hz, 2H), 4.57 (dd, 3.9 Hz, 11.5 Hz, 1H), 4.33 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.16 (m, 5H), 3.82 (s, 3H), 3.61 (dm, 11.2 Hz, 1H), 2.88 (dm, 13.9 Hz, 1H), 2.52 (dm, 15.0 Hz, 1H), 1.75 (m, 6H), 1.33 (t, 7.1 Hz, 3H), 1.23 (t, 7.1 Hz, 3H), 1.22 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 205.7, 171.9, 170.4, 169.5, 160.5, 132.0, 127.9 (×2), 115.0 (×2), 62.0, 61.9, 61.8, 59.8, 59.2, 58.0, 55.6, 38.9, 33.2, 31.6, 25.7, 19.9, 14.2, 14.0, 13.7. IR (KBr): 3133, 1727, 1249 cm^{-1}. Anal. Calcd for $C_{25}H_{33}NO_7S$: C, 61.08; H, 6.77. Found: C, 60.94; H, 6.71.

Triethyl (1*R,6*S*,9*R*)-9-(4-Methoxyphenyl)-8-azabicyclo-[4.4.0]decane-2,2,6-tricarboxylate (20).** A solution of **19** (405 mg, 0.82 mmol) and nickel chloride hexahydrate (1.63 g, 6.84 mmol) in MeOH (8 mL) and THF (8 mL) was treated with $NaBH_4$ (776 mg, 20.5 mmol) at 0 °C. After being stirred at rt for 3 h, the reaction mixture was filtered through Celite, rinsing with CH_2Cl_2. The resulting solution was washed with diluted aq $NaHCO_3$. The organic layer was dried over $MgSO_4$ and evaporated. Flash chromatography (20% EtOAc in petro-

leum ether) gave **20** (304 mg, 0.66 mmol, 80% yield) as a white solid, mp 105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, 8.7 Hz, 2H), 6.85 (d, 8.7 Hz, 2H), 4.24 (dq, J_d = 10.8 Hz, J_q = 7.1 Hz, 1H), 4.11 (m, 5H), 3.80 (s, 3H), 3.72 (dd, 3.3 Hz, 11.1 Hz, 1H), 3.33 (d, 12.3 Hz, 1H), 3.25 (dd, 5.0 Hz, 12.5 Hz, 1H), 2.83 (d, 12.3 Hz, 1H), 2.19 (m, 1H), 2.03 (m, 1H), 1.91 (m, 2H), 1.80 (m, 1H), 1.70 (m, 1H), 1.54 (m, 2H), 1.31 (t, 7.1 Hz, 3H), 1.26 (br, 1H),1.22 (t, 7.1 Hz, 3H), 1.19 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 176.0, 170.5, 170.2, 158.8, 136.5, 127.5 (×2), 113.8 (×2), 61.3, 60.6, 60.5, 58.8, 56.7, 55.3, 45.4, 39.5, 32.4, 29.7, 25.3, 25.2, 19.6, 14.1, 14.0, 13.9. IR (neat): 3331, 1733, 1514 cm^{-1}. Anal. Calcd for $C_{25}H_{35}NO_7$: C, 65.06; H, 7.64. Found: C, 65.30; H, 7.87.

Triethyl (1*R,6*S*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-9-(4-methoxyphenyl)-8-azabicyclo[4.4.0]decane-2,2,6-tricarboxylate.** Compound **20** (29 mg, 0.063 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (15% EtOAc in petroleum ether) gave the protected amine (40 mg, 0.063 mmol, 100% yield) as a white solid, mp 87 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 7.10 (d, 8.7 Hz, 2H), 6.82 (d, 8.7 Hz, 2H), 4.98 (dd, 6.4 Hz, 11.7 Hz, 1H), 4.75 (d, 11.0 Hz, 1H), 4.52 (d, 12.3 Hz, 1H), 4.34 (d, 14.5 Hz, 1H), 4.19 (m, 6H), 3.77 (s, 3H), 3.25 (dm, 10.4 Hz, 1H), 3.11 (d, 14.5 Hz, 1H), 2.19 (m, 2H), 1.76 (m, 2H), 1.60 (m, 4H), 1.29 (t, 7.1 Hz, 3H), 1.27 (t, 7.1 Hz, 3H), 1.20 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$, 60 °C): δ 175.5, 170.7, 170.6, 159.1, 153.9, 134.8, 126.4 (×2), 114.2 (×2), 95.5, 75.4, 61.5, 61.4, 61.1, 58.8 and 58.8, 58.0, 55.4 and 55.3, 50.9, 45.5, 37.7, 31.6, 28.7, 26.6, 18.3, 14.1, 14.0, 13.9 (a resonance at δ 29.7 is attributed to grease[19]). IR (neat): 1729, 1514 cm^{-1}. $C_{28}H_{36}Cl_3NO_9$.

(1*R,6*S*,9*R*)-8-(2,2,2-Trichloroethoxycarbonyl)-8-azabicyclo[4.4.0]decane-2,2,6,9-tetracarboxylic Acid, 2,2,6-Triethyl Ester (21).** The previous compound (392 mg, 0.62 mmol) was subjected to the standard procedure for oxidation of the An group to give **21** (227 mg, 0.40 mmol, 64% yield) as a white solid, mp 151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.20 (br, 1H), 5.00 (d, 11.9 Hz, 0.5H), 4.85 (d, 11.9 Hz, 0.5H), 4.64 (d, 11.9 Hz, 0.5H), 4.56 (dd, 10.0 Hz, 19.0 Hz, 1H), 4.50 (d, 11.9 Hz, 0.5H), 4.18 (m, 7H), 3.12 (dd, 7.8 Hz, 15.1 Hz, 1H), 3.03 (d, 11.9 Hz, 0.5H), 2.94 (d, 14.7 Hz, 0.5H), 2.21 (m, 1H), 2.13 (dm, 14.1 Hz, 1H), 1.79 (m, 3H), 1.63 (dt, J_d = 14.1 Hz, J_t = 4.2 Hz, 1H), 1.48 (m, 1H), 1.27 (t, 7.1 Hz, 6H), 1.26 (m, 1H), 1.21 (t, 7.0 Hz, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 176.3, 175.5, 175.3, 170.5 and 170.3, 153.2, 95.1, 75.5 and 75.2, 61.8, 61.2, 57.8, 56.7 and 56.6, 50.1 and 49.8, 44.9 and 44.7, 37.0 and 36.7, 29.7, 28.5, 26.4, 25.3, 24.8, 18.1, 14.0, 13.9. IR (neat): 3209, 1733 cm^{-1}. Anal. Calcd for $C_{22}H_{30}Cl_3NO_{10}$: C, 45.97; H, 5.26. Found: C, 46.24; H, 5.60.

Ethyl (1*R,4*R*,6*R*,7*R*)- and (1*R**,4*R*,6*R*,7*S*)-4-(4-Methoxyphenyl)-3-azabicyclo[4.3.0]nonan-2-one-7-carboxylate (22a and 22b).** A solution of **17b** (2.58 g, 5.59 mmol), LiCl (711 mg, 16.77 mmol), and H_2O (302 μL, 16.77 mmol) in DMF (50 mL) was allowed to reflux for 18 h. The reaction mixture was cooled and poured into ice−water. The resulting mixture was extracted with EtOAc, washed with water and brine, dried over $MgSO_4$, and evaporated to give the crude product. Flash chromatography (50−65% EtOAc in petroleum ether) gave **22a** (645 mg, 2.03 mmol, 36% yield) as a white solid, mp 124 °C, and **22b** (440 mg, 1.39 mmol, 25% yield) as a white solid, mp 199 °C. The following are data for compound **22a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, 8.7 Hz, 2H), 6.89 (d, 8.7 Hz, 2H), 5.77 (br, 1H), 4.42 (dd, 2.6 Hz, 11.4 Hz, 1H), 4.14 (~q, 7.1 Hz, 2H), 3.81 (s, 3H), 2.92 (dt, J_d = 8.4 Hz, J_t = 9.5 Hz, 1H), 2.78 (ddd, 5.2 Hz, 10.2 Hz, 14.6 Hz, 1H), 2.58 (dt, J_d = 5.1 Hz, J_t = 7.9 Hz, 1H), 2.36 (m, 1H), 2.10 (m, 2H), 1.82 (m, 2H), 1.48 (dt, J_d = 11.7 Hz, J_t = 12.8 Hz, 1H), 1.26 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 175.2, 174.7, 160.0, 133.7, 127.6 (•2), 114.7 (×2), 60.8, 56.8, 55.5, 51.6, 43.9, 40.4, 38.5, 29.8, 29.0, 14.4. IR (neat): 3185, 1720, 1648 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30. Found: C, 67.87; H, 7.00. The following are data for compound **22b**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, 8.7 Hz, 2H), 6.89 (d, 8.7 Hz, 2H), 5.71 (br, 1H), 4.40 (dd, 3.2 Hz, 11.4 Hz, 1H), 4.11 (m, 2H), 3.81 (s, 3H), 3.01 (dt, J_d = 6.8 Hz, J_t = 9.5 Hz, 1H), 2.82 (m, 2H), 2.31 (m, 1H), 2.08 (m, 2H), 1.91 (m, 1H), 1.72 (dt, J_d = 13.2 Hz, J_t = 3.3 Hz, 1H), 1.46 (dt, J_d = 11.7 Hz, J_t = 13.1 Hz, 1H), 1.23 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (50 MHz, $CDCl_3$): δ 174.5, 173.2, 160.0, 133.9, 127.7 (×2), 114.7 (×2), 60.7, 57.1, 55.6, 48.7, 44.3, 40.4, 32.1, 28.4, 24.5, 14.4. IR (neat): 3179, 1729, 1653 cm^{-1}. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30. Found: C, 68.12; H, 7.08.

Ethyl (1*R,4*R*,6*R*,7*R*)-4-(4-Methoxyphenyl)-3-azabicyclo-[4.3.0]nonane-7-carboxylate (23).** A solution of BH_3 in THF (1 M, 1.1 mL) was added to a suspension of **22a** (159 mg, 0.50 mmol) in THF (1 mL) at 0 °C under N_2. The mixture was allowed to stir at rt for 24 h. The solution was cooled in ice−water, and the reaction was quenched by 6 M HCl (1 mL). After the mixture was stirred for for 2 h at 0 °C, 1 N NaOH was added until the pH was 10. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated to give the crude product. Flash chromatography (3% MeOH in CH_2Cl_2) gave **23** (82 mg, 0.27 mmol, 54% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (d, 8.8 Hz, 2H), 6.85 (d, 8.8 Hz, 2H), 4.12 (q, 7.1 Hz, 2H), 3.79 (s, 3H), 3.51 (dd, 2.4 Hz, 11.5 Hz, 1H), 3.14 (dd, 2.3 Hz, 12.5 Hz, 1H), 3.10 (dd, 3.6 Hz, 12.3 Hz, 1H), 2.50 (m, 1H), 2.38 (dt, J_d = 12.5 Hz, J_t = 6.0 Hz, 1H), 2.07 (m, 4H), 1.73 (m, 3H), 1.35 (q, 12.4 Hz, 1H), 1.26 (t, 7.1 Hz, 3H). ^{13}C-{H} NMR (50 MHz, $CDCl_3$): δ 176.8, 158.9, 137.4, 127.8 (×2), 114.0 (×2), 60.6, 60.5, 55.5, 50.2, 47.4, 42.9, 37.8, 37.7, 27.1, 26.4, 14.5. IR (neat): 3333, 1729, 1648 cm^{-1}. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31. Found: C, 71.23; H, 8.58.

Ethyl (1*R,4*R*,6*R*,7*R*)-3-(2,2,2-Trichloroethoxycarbonyl)-4-(4-methoxyphenyl)-3-azabicyclo[4.3.0]nonane-7-carboxylate.** Compound **23** (58 mg, 0.19 mmol) was subjected to the standard procedure for addition of a Troc group. Flash chromatography (10% EtOAc in petroleum ether) gave the protected amine (90 mg, 0.19 mmol, 99% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ 7.18 (d, 8.7 Hz, 2H), 6.83 (d, 8.7 Hz, 2H), 4.78 (dd, 5.5 Hz, 11.9 Hz, 1H), 4.69 (d, 11.9 Hz, 2H), 4.61 (br, 1H), 4.33 (dd, 6.1 Hz, 13.6 Hz, 1H), 4.14 (q, 7.1 Hz, 2H), 3.77 (s, 3H), 2.98 (dd, 11.4 Hz, 13.4 Hz, 1H), 2.44 (m, 3H), 2.16 (dt, J_d = 13.6 Hz, J_t = 5.0 Hz, 1H), 1.99 (m, 2H), 1.79 (m, 1H), 1.65 (dt, J_d = 13.9 Hz, J_t = 12.0 Hz, 1H), 1.25 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$, 60 °C): δ 175.1, 159.1, 154.3, 136.1, 126.6 (×2), 114.3 (×2), 96.0, 75.4, 60.6, 57.1, 55.5, 51.6, 44.4, 40.0, 38.7, 36.4, 30.2, 30.0, 14.5. IR (neat): 1717 cm^{-1}. Anal. Calcd for $C_{21}H_{26}Cl_3NO_5$: C, 52.68; H, 5.47. Found: C, 52.75; H, 5.71.

(1*R,4*R*,6*R*,7*R*)-3-(2,2,2-Trichloroethoxycarbonyl)-3-azabicyclo[4.3.0]nonane-4,7-dicarboxylic Acid, 7-Ethyl Ester (24).** The previous compound (74 mg, 0.15 mmol) was subjected to the standard procedure for oxidation of the An group to give **24** (47 mg, 0.11 mmol, 75% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (br, 1H), 4.82 (d, 11.9 Hz, 0.5H), 4.82 (d, 11.9 Hz, 0.5H), 4.75 (d, 11.9 Hz, 0.5H), 4.68 (d, 11.9 Hz, 0.5H), 4.41 (dd, 5.4 Hz, 11.3 Hz, 0.5H), 4.39 (dd, 5.4 Hz, 11.3 Hz, 0.5H), 4.18 (m, 1H), 4.16 (q, 7.1 Hz, 2H), 2.92 (dd, 11.6 Hz, 13.6 Hz, 0.5H), 2.88 (dd, 11.6 Hz, 13.6 Hz, 0.5H), 2.40 (m, 4H), 2.01 (m, 2H), 1.79 (m, 2H), 1.28 (m, 1H), 1.27 (t, 7.1 Hz, 3H). ^{13}C{H} NMR (100 MHz, $CDCl_3$): δ 178.0 and 177.3, 175.0 and 175.0, 154.4 and 153.8, 95.6 and 95.4, 75.4 and 75.4, 60.9, 55.1, 50.8 and 50.2, 43.4 and 43.3, 39.2 and 39.1, 38.4 and 38.2, 29.9 and 29.8, 29.7 and 29.6, 29.6 and 28.9, 14.5. IR (neat): 3230, 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{20}Cl_3NO_6$: C, 43.24; H, 4.84. Found: C, 43.42; H, 5.18.

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Supporting Information Available: 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. This material is available free of charge via the Internet at http://pubs.acs.org.

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