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5-Carboxy-2-azabicyclo[2.1.1]hexanes as Precursors of 5-Halo, Amino, Phenyl, and 2-Methoxycarbonylethyl Methanopyrrolidines

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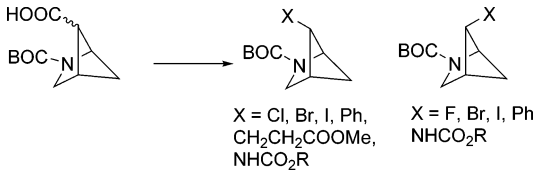
Received December 5, 2005



Novel 5-X-substituted-2-azabicyclo[2.1.1]hexanes (X = 5-*syn*-Cl, -Br, -I, -Ph, -NHCOOR (R = Me, Bn, *t*-Bu), -CH_2CH_2COOMe and X = 5-*anti*-Br, -I, -Ph) were synthesized from the X = 5-*syn*-carboxy derivative. New 5-*anti*-X-2-azabicyclo[2.1.1]hexanes, X = NHCOOR (R = Me, Bn), were prepared stereoselectively from the X = 5-*anti*-carboxy substrate.

Introduction

Pyrrolidines **1** with amino,[1−6] aryl,[7] alkyl,[8,9] fluoro,[10] or thio[6,9,11] substituents at the 3-position, β to the nitrogen atom, are found in a number of biologically significant molecules. The rigid 2-azabicyclo[2.1.1]hexanes **2** can be viewed as pyrrolidines in which conformation is constrained by a 2,4-

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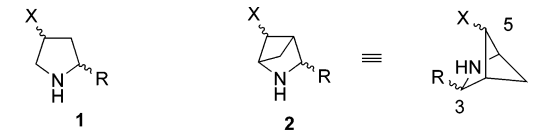
10.1021/jo052506b CCC: $33.50
Published on Web 02/09/2006

methylene bridge. As part of a strategy of incorporation of key pharmacophoric units into inflexible structures,[12−14] azabicycles such as **2**, which display functionality in defined spatial orientations, are of interest. Such molecules may prove to be valuable scaffolds for incorporation into proteins[15] or for drug discovery. However, there is a need for practical methods to introduce a diverse array of substituents onto the 2-azabicyclo-[2.1.1]hexanes. Our focus in this contribution is upon the C_5 methylene bridge position and the substituent X.



R = H, COOH, CH_2OH;
X = amino, alkylamino,
aryl, alkyl, F, SH

Functional groups at C_5 on 2-azabicyclo[2.1.1]hexanes **2** are known.[16] Heteroatoms at C_5 have been introduced by rearrangement routes (X = halogen, hydroxyl),[17] nucleophilic ring closure of cyclobutanes (X = SePh),[13a] or a thermal 2+2 cycloaddition (X/H = difluoride).[18] Aryl X = *syn*-Ph has been introduced via a rearrangement route.[17e] For alkyl groups there are rearrangement (X = *syn*- or *anti*-methyl),[17e] ring closure (X = *syn*-CH_2NH_2, CH_2OH),[13a] and photochemical cycloaddition routes (X/H = Me_2 or X = *syn*- or *anti*-oriented cyclohexane rings fused from C_5 to C_4 or cyclohexanone rings fused from C_5 to C_1).[19] For 5-*syn/anti*-carbonyl substitution several photochemical syntheses are reported,[20] but except for one case of a 5-acetyl group,[20a] these examples are for 1,5-fused cyclohexanone ring systems. Two routes to 5-carboxy azabicycles have been described. One somewhat lengthy route to a 5-syn acid involves ring closure[13a] and subsequent modification of substituents. Recently, we described[21] a shorter approach to the preparation of 5-*syn*- and 5-*anti*-carboxy-2-azabicyclo[2.1.1]-hexanes in multigram quantities from readily prepared and separable 5-acetyl-2-azabicyclo[2.1.1]hexanes first described by Winkler.[20a]

There is a paucity of examples that describe the synthesis of *N*-protected C_5-monosubstituted 2-azabicyclo[2.1.1]hexanes. The reported examples with various *N*-alkoxycarbonyl groups are 5-*anti*-hydroxy **3a**,[17c,d] 5-*anti*-acetyl **4c**,[20a,21] 5-*anti*-carboxy **5c**,[21] 5-*anti*-2-pyridylthioether **6c**,[21] 5-*syn*-hydroxylmethyl **7b** and 5-*syn*-aminomethyl **8b**,[13a] 5-*syn*-acetyl[20a,21] **9c**, 5-*syn*-carboxylic acid[13a,21] **10c**, and 5-*syn*-2-pyridylthioether **11c**.[21] In this paper we describe replacements of 5-carboxy substituents of **5c** or **9c** for the preparation of 5-substituted 2-azabicyclo[2.1.1]hexanes with halo, amino, phenyl, and 2-carboxyethyl substituents X. Since preparation of 5-acids with compatible substituents at other ring positions is feasible, the functional group modifications described for these acids should prove useful in the preparation of more highly functionalized 5-substituted 2-azabicyclo[2.1.1]-hexanes.[22]

3 X = OH
4 X = $COCH_3$
5 X = COOH
6 X = S-2-Pyridyl

a R' = Et
b R' = Bn
c R' = *t*-Bu

7 X = CH_2OH
8 X = CH_2NH_2
9 X = $COCH_3$
10 X = COOH
11 X = S-2-Pyridyl

Results and Discussion

Baeyer−Villiger Attempts with Ketone 9c. We attempted to convert the 5-*syn*-ketone[20a,21] **9c** to the 5-*syn*-acetate **12** under Baeyer−Villiger conditions using MCPBA, buffered MCPBA,

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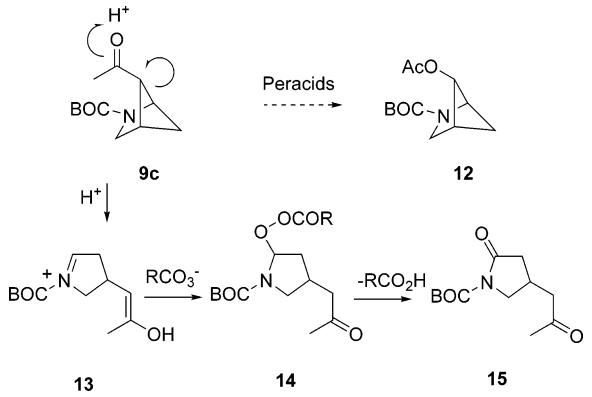
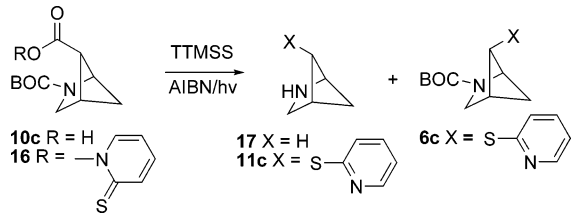
SCHEME 1. Synthesis and Peracid Ring Cleavage of Ketone 9c

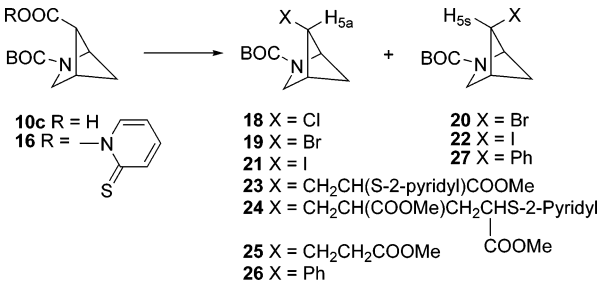


or buffered PAA (Scheme 1). Only ketolactam **15** was isolated. Significant in the ^{13}C NMR spectrum of ketone **15** are its three methylene groups at δ 38.9, 47.4 and 51.6 and the single upfield methine group at δ 30.2, not adjacent to carbonyl or nitrogen. The formation of **15** is rationalized by acid-catalyzed fragmentation of the ketone to give iminium ion **13**, addition of peracid to give **14**, and acid elimination.

Reactions of the Barton Esters of the 5-Acids. Despite their sensitivity to acid, we were successful in oxidizing both the *anti*-**4c** and *syn*-**9c** ketones to the corresponding carboxylic acids **5c**/**10c** with basic sodium hypochlorite. The acid **10c** was earlier converted to its Barton ester **16** and this was reduced to the parent azabicycle **17** by means of radical reducing agents.[21] During the trapping of the bridge radical formed upon irradiation of the Barton ester with tris(trimethylsilyl)silane a mixture of aryl thioethers **6c** (4%) and **11c** (11%) was formed in minor amounts (Table 1, entry 1).[21] These products were also formed as a 3:9 mixture (12%) if the Barton ester **16** was allowed to sit at room temperature in toluene for 48 h. Irradiation with a 250-W tungsten lamp for 1 h or microwave irradiation did not improve this process. In light of the ability of radicals formed from the Barton ester to be trapped by heteroatoms, we decided to first explore using the Barton ester **16** as a precursor of other 5-substituents.[23] The results are shown in Table 1.



It has been found that irradiation of the Barton ester **16** in halogenated solvents (entries 2 and 3), or mixed solvents (entries 4 and 5), affords azabicycles with halogen substituents.[23] The syn halides were formed exclusively (entries 2 and 4 for Cl and Br) or preferentially over the anti isomers (entries 3 and 5 for Br and I). The stereochemistry of these products was readily assigned by using ^1H NMR couplings. The 5-syn isomers are characterized by a singlet peak for H_{5a}, adjacent to the heteroatom substituent. In the 5-anti isomers the H_{5s} hydrogen appears as a doublet (J = 8−9 Hz) by virtue of long-range coupling with H_{6s}. The preference for the syn isomers can be contrasted with the stereoselective formation of *anti*-bromo isomers in a rearrangement route to 5,6-disubstituted 2-azabicyclo-[2.1.1]hexanes.[17b−d]



It also was possible to trap the bridge radical derived from Barton ester **16** with methyl acrylate to form a mixture of separable diastereomeric 5-*syn*-alkylthioethers **23a/23b** and a mixture of four diastereomeric diester products in principle, represented by **24**, derived from the addition of two molecules of methyl acrylate.[24] Raney nickel reduction of the diastereomeric thioethers **23** afforded the 5-*syn*-2-methoxycarbonylethyl azabicycle **25**.[24a] As expected for the syn isomer, decoupling experiments indicate the H_{6s} proton at δ 1.28 does not couple long range with H_{5a}.

Reaction of the 5-*syn*-Acid 10c with Oxidants. Substitutions of other groups for carboxy without the intermediacy of the Barton ester **16** are shown in Table 2. The 5-acid **10c** with lead tetraacetate/LiCl in refluxing toluene affords only the 5-*syn*-chloride **18** (entry 1).[25] With mercuric oxide in the presence of bromine,[26] acid **10c** affords a mixture of bromides in which the syn isomer **19** was favored over the *anti*-bromide **20** if irradiation was performed at ambient temperature (entry 2), but the anti isomer **20** was formed if the irradiation was performed with a refluxing solution of reactants (entry 3). The yields of chloride and bromides in these reactions are lower than those for preparations from the Barton ester **14** (Table 1).

Irradiation of acid **10c** in the presence of phenyliodonium diacetate/iodine affords more useful yields of iodides **21/22**.[27] This reaction was run numerous times with variation of temperature (ambient temperature or reflux), equivalents of reagents (1.1 to 2.2 equiv), time of reaction, and scale. Representative examples from 15 separate trials are shown in Table 2 (entries 4−10). We were unable to optimize the reaction conditions, since seemingly identical experimental conditions led to different outcomes (entries 4/6, 7/9, 8/10). It was shown that a 28:72 mixture of iodides **21** and **22** remains unchanged after 4 h in CCl_4 at 60 °C, or for 2 weeks at ambient temperature while exposed to visible light. Recovery of both iodides from chromatography columns is >90%.

The most reliable route to obtain a mixture of syn and anti iodides is to carry out the reaction with 1.1 equiv of reagents. At ambient temperature upon irradiation for 2 h, two trials (entries 4 and 5) gave mixtures containing 24−50% syn iodide

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TABLE 1. Functional Group Replacements with Use of the 5-*syn*-Barton Ester 16

				products (yield, %)	
entry	conditions	reactant/solvent	X	syn	anti
1	light[a]	TTMSS/cyclohexane[b]	*S*-2-pyridyl and H	**11c** (11) **17** (31)	**6c** (4)
2	light[a]	CCl_4	Cl	**18** (77)	
3	light[a]	$BrCCl_3$	Br	**19** (33)	**20** (4)
4	light[a]	$BrCCl_3$/cyclohexane	Br	**19** (45)	
5	light[a]	CHI_3/cyclohexane	I	**21** (45)	**22** (5)
6	light[c]	CH_2Cl_2/methyl acrylate	CH_2X[d]	**23** (58)	
			CH_2Y[e]	**24** (15)	

[a] 600-W tungsten lamp, AIBN, 30 min. [b] See ref 21. [c] 250-W tungsten lamp, reflux, 4 h. [d] Two diastereomers, X = CH(*S*-2-pyridyl)COOMe. [e] Four diastereomers,Y = CH(COOMe)CH_2CH(*S*-2-pyridyl)COOMe.

TABLE 2. Reactions of 5-*syn*-Acid 10c with Oxidizing Agents

				products (yield, %)[a]	
entry	conditions	reactants/solvent	X	syn	anti
1	85 °C, 6 h	$Pb(OAc)_4$/LiCl/$PhCH_3$	Cl	**18** (15)[b]	–
2	*hν*,[c] 25 °C, 1 h	HgO/bromine/CCl_4	Br	**19** (16)	**20** (2)
3	*hν*,[c] 0.5 h, heat	HgO/bromine/CCl_4[d]	Br	–	**20** (11)
4	*hν*,[c] 25 °C, 2 h[e]	$PhI(OAc)_2$/I_2/CCl_4[f]	I	**21** (50)	**22** (23)
5	*hν*,[c] 25 °C, 1.5 h[e]			**21** (24)	**22** (17)
6	*hν*,[c] 25 °C, 2 h[e,g]			–	**22** (26)
7	*hν*,[c] reflux,10 min[e]	$PhI(OAc)_2$/I_2/CCl_4[h]	I	**21** (23)	**22** (44)
8	*hν*,[c] reflux, 2 h[i]			–	**22** (33)
9	*hν*,[c] reflux, 20 min[j]			–	**22** (26)
10	*hν*,[c] reflux, 1.5 h[k]			**21** (27)	**22** (32)
11	reflux, 16h	$Pb(OAc)_4$/pyridine/cyclohexane	H	**17** (59)[l]	
12	reflux, 3 h	$Pb(OAc)_4$/pyridine/PhH	Ph	**26** (35)	**27** (6)

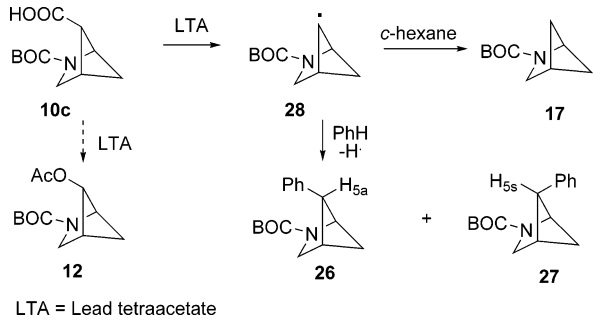
[a] Isolated yields. [b] Corrected for 50% recovered acid. [c] 50-W tungsten lamp. [d] Bromine added at reflux temperature. [e] 1.1 equiv of reagents. [f] Reactions were run on 0.5−4.5 mmol scale. [g] 85:15 syn/anti acid mixture. [h] Reactions were run on 0.5−7.4 mmol scale. [i] 1.4 equiv of reagents. [j] 85:15 syn/anti acid mixture, 2 equiv of reagents. [k] 2.2 equiv of reagents. [l] Corrected for 33% recovery of starting acid.

21 and 17−23% anti iodide **22**; two apparently identical trials represented by entry 6 resulted in only anti iodide **22** (26%). With heating during the irradiation for from 10 min to 2 h three experiments (entries 7−10) gave mixtures ranging from 6% to 23% syn iodide **21** and 18−44% anti iodide **22**; the highest yield for these attempts is shown by entry 7. After seven trials with 2.2 equiv of reagents and heating for 20 min to 2.5 h, for which entries 8−10 are examples, only one trial, 27% syn iodide **21** and 32% anti iodide **22** (entry 10), gave the syn isomer. The remaining trials gave only anti iodide **22** in 12−40% yields.

In a unsuccessful effort to prepare the 5-acetate **12** the 5-*syn*-acid **10c** was reacted with lead tetraacetate/pyridine in refluxing cyclohexane (Scheme 2).[28] Only the parent 2-azabicyclo[2.1.1]-hexane **17** was obtained (entry 11). When the same reaction was attempted in benzene as solvent, an 85:15 mixture largely favoring the 5-*syn*-phenyl **26** over the 5-*anti*-phenyl isomer **27** was obtained (entry 12).[28] The 5-syn isomer **26** could be obtained pure, but the minor 5-anti isomer **27** retained a minor amount of the 5-syn isomer even after extensive chromatography. The 5-*syn*-phenyl isomer **26** was identified by a singlet at δ 3.28 for H_{5a}, while the 5-*anti*-phenyl isomer **27** was identified by the doublet pattern for H_{5s} (J = 8.1 Hz) at δ 3.17.

As shown in Scheme 2, the products in entries 11 and 12 can be obtained from an initially formed radical **28**. Because of the ring strain in this system, it does not lose an electron to afford a planar 5-cation, even in the presence of copper acetate,

SCHEME 2. Reactions of Acid 10c with LTA in Nonhalogenated Solvents



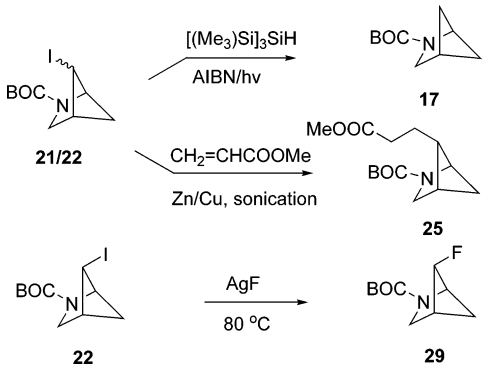
which is reported to facilitate cation formation.[29] Instead the radical **28** either abstracts a hydrogen atom in cyclohexane to give parent **17** or in benzene solvent it adds to the aryl ring and then loses a hydrogen atom to give phenyl isomers **26**/**27**. Arylation reactions have previously been observed for LTA reactions of acids at tertiary bridgehead positions of structures that have unstable bridgehead cations,[28] but arylation at a secondary position is a novel result.

Replacement Reactions of the 5-Iodide. We next attempted to explore further synthetic utility of the iodides **21/22**. Examples of radical and ionic reactions to replace iodide are shown in Scheme 3. The parent azabicycle **17** was obtained in 37% overall yield from the 5-*syn*-acid **10c** when a mixture of iodides was reduced with tris(trimethylsilyl)silane/AIBN in refluxing THF while irradiating with a 250-W tungsten lamp for 30 min. This

(28) (a) Moriarty, R. M.; Khosrowshahi, J. S.; Miller, R. S.; Flippen-Andersen, J.; Gilardi, R. *J. Am. Chem. Soc.* **1989**, *111*, 8943. (b) Davies, D. I.; Waring, C. *J. Chem. Soc., Chem. Commun.* **1965**, 263. (c) Sheldon, R. A.; Kochi, J. K. *Org. React.* **1972**, *19*, 279.

(29) Ogibin, Y. N.; Katzin, M. I.; Nikishin, G. I. *Synthesis* **1974**, *12*, 889.

SCHEME 3. Replacement Reactions with Iodides 21/22



method for the parent from the acid avoids formation of the Barton ester **16** (Table 1, entry 1) and is comparable in yield to the reaction of the acid **10c** with lead tetraacetate (Table 2, entry 11).

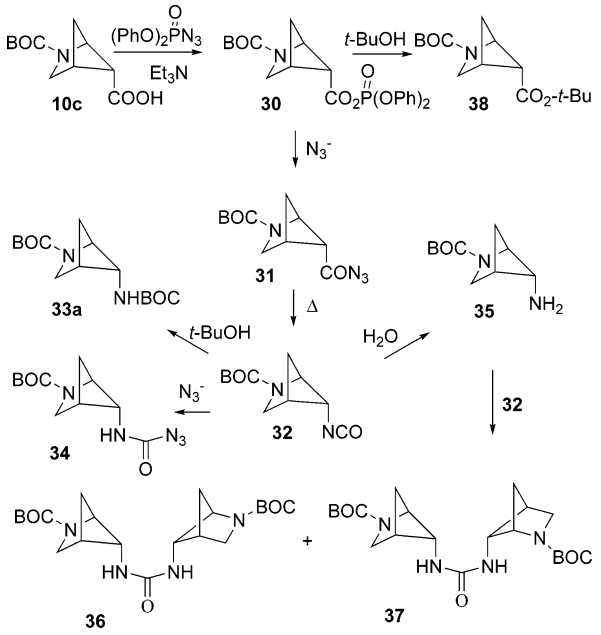
Initial attempts to prepare 5-propanoate ester **25** by irradiation of the 5-*anti*-iodide **22** with a 250-W tungsten lamp in refluxing CCl_4 in the presence of methyl acrylate were unsuccessful and lead to destruction of starting material. However, by adding excess methyl acrylate and the iodide in 1:2 ethanol/water solution to a suspension of zinc powder and copper(I) iodide in water, and then sonicating with an ultrasonic cleaning bath for 1.25 h, the ester **25** was obtained (35%).[30]

The 5-*anti*-iodide **22** fails to react with silver fluoride in nitromethane after 24 h at 60 °C; however, after 4 h at 80 °C the 5-*anti*-fluoride **29** is obtained in 19% yield.[17f] The anti stereochemistry is assigned by the dd pattern for H_5 (J = 62, 7.9 Hz); only the 5-syn proton shows long-range coupling with H_{6syn}. The stereochemical retention in this nucleophilic substitution reaction is consistent with neighboring group participation by the nitrogen bridge.[10b]

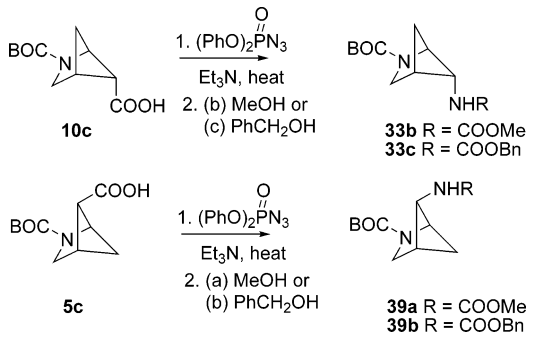
Nonradical Reactions of the 5-Acids 5c/10c: The Curtius Rearrangement. The Curtius rearrangement is a valuable method for replacing a carboxylic acid with an amino group,[31] but could such a rearrangement succeed with azabicyclic acid **10c**? As shown in Scheme 4, when anti acid **10c** was reacted with diphenylphosphoryl azide (DPPA) and triethylamine in refluxing *tert*-butyl alcohol followed by addition of water, only a small amount (8%) of the desired BOC-protected carbamate **33a** was obtained. The other products were the acyl azide **34** (30%), an inseparable mixture of diastereomeric ureas **36**/**37** (26%), and the ester **38** (2%). The stereochemistry of these compounds could be assigned as 5-syn on the basis of the absence of couplings between H_{5anti} and H_{6syn}. The acyl azide **34** was prepared independently in 37% yield by stirring a neat mixture of acid **10c**, DPPA, and triethylamine at room temperature under argon for 3 d; its structure was confirmed by X-ray structural analysis.

To obtain desired protected 5-amines the 5-*syn*-acid **10c** was refluxed in carbon tetrachloride with DPPA and triethylamine for 1.5 h and different alcohols were added. Addition of methanol after 12 h afforded the desired methoxycarbonylamine **33b** in 65% yield. When benzyl alcohol was added in place of methanol, the benzyloxycarbonylamine **33c** was obtained in 82%

SCHEME 4. Curtius Rearrangement of Acid 10c



yield. The same reactions with the 5-*anti*-acid **5c** afforded the 5-*anti*-methoxycarbonylamine **39a** (75%) and 5-*anti*-benzyloxycarbonylamine **39b** (80%). These differentially protected 1,2-amines should be of interest for preparation of quinolone antibiotics.[13g]



Conclusions. In summary, we have described totally stereoselective functional group replacement strategies using readily available 5-carboxy-2-azabicyclo[2.1.1]hexanes **5c**/**10c** to afford new 5-*syn*-chloro, and 5-*syn*-(2-carboxyethyl) derivatives and partially stereoselective syntheses of syn/anti mixtures of mainly 5-*syn*-bromo and 5-*syn*-phenyl isomers. Conditions favoring either 5-*syn*- or 5-*anti*-iodides have been noted. Although there are reproducibility issues for isomer ratios, both of these separable iodides have utility as synthetic intermediates. Conversion of 5-*syn*- and 5-*anti*-carboxylic acids under Curtius rearrangement conditions is stereospecific with retention and affords novel differentially protected conformationally constrained diamines. A simplified route to the parent azabicycle involves decarboxylation of the 5-acid with lead tetraacetate in cyclohexane.

Experimental Section

Preparation of *N*-*tert*-Butoxycarbonyl-4-(2-oxopropyl)pyrrolidin-2-one (15). A solution of 5-*syn*-acetyl **9c** (226 mg, 1.0 mmol), MCPBA (77% purity, 300 mg, 1.34 mmol), and *p*-toluenesulfonic acid monohydrate (56 mg, 0.29 mmol) in CH_2Cl_2 (20 mL) was

(30) Sarandeses, L. A.; Mourino, A.; Luche, J. L. *J. Chem. Soc., Chem. Commun.* **1992**, 798.

(31) (a) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, *30*, 2151. (b) Burgess, K.; Li, S.; Rebenspies, J. *Tetrahedron Lett.* **1997**, *38*, 1681.

stirred in an ice bath for 4 h. Saturated sodium sulfite solution was added to scavenge the unreacted MCPBA. The CH_2Cl_2 layer was separated and washed with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and concentrated. The crude product was purified through a short flash column (cyclohexanes−EtOAc 2:1) to give 140 mg (58%) of pyrrolidinone **15** at R_f 0.38 (cyclohexane/EtOAc 1:2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9H, *tert*-butyl), 2.14 (s, 3H, $COCH_3$), 2.16 (m, 1H, H_3), 2.65 (m, 4H, H_3, H_4, 5-CH_2Ac), 3.27 (m, 1H, H_5), 3.95 (m, 1H, H_5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.9, 28.0, 30.2, 38.9, 47.4, 51.6, 83.0, 149.9, 173.2, 206.3; HRMS *m*/*z* 264.1209, calcd for $C_{12}H_{19}NO_4Na$ (M + Na) 264.1212. Buffered peracids: (a) Ketone **9c** (115 mg, 0.5 mmol), MCPBA (133 mg, 0.77 mmol), and $NaHCO_3$ (75 mg, 0.89 mmol) in CH_2Cl_2 (10 mL) after 72 h at 25 °C afforded after workup 54 mg (44%) of pyrrolidinone **15**. (b) Ketone **9c** (225 mg, 1.0 mmol) and peracetic acid (25%, 1.2 mL) in acetic acid (2.1 mL) containing sodium acetate (120 mg) after 18 h at 25 °C was treated with 10% sodium sulfite until a negative test resulted for peracid with starch-KI paper. Extraction with CH_2Cl_2 (4 × 10 mL), washing of the extracts with water (6 mL) and brine (6 mL), drying over $MgSO_4$ and chromatography afforded 164 mg (68%) of pyrrolidinone **15**.

Preparation of *N*-*tert*-Butoxycarbonyl-5-*syn*-chloro-2-azabicyclo[2.1.1]hexane (18) from Barton Ester 16:[21] **General Procedure.** To a 50 mL flask equipped with cold water condenser was added Barton ester **16** (91 mg crude, 0.27 mmol), AIBN (5 mg), and carbon tetrachloride (2 mL). The reaction solution was irradiated with a 600 W tungsten lamp and refluxed for 30 min. The solvent was removed in vacuo. The residue was extracted with diethyl ether. The ether solution was concentrated and the crude product was purified by a short flash column, eluting with cyclohexanes−EtOAc 30:1 and then CH_2Cl_2−CH_3OH 10:1 to give 41 mg of **18** as a white solid, mp 43 °C (cyclohexane/EtOAc), and 6 mg of 5-*syn*-acid **10c**. The corrected yield from **10c** to **18** was 77%. Chloride **18**: R_f 0.32 (cyclohexane/EtOAc 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 and 1.47 (s and s, 9H), 1.63 (m, 2H, H_6), 2.87 (m, 1H, H_4), 3.24 (d, J = 9.0 Hz, 1H, H_3), 3.43 and 3.50 (d and d, J = 9.0 Hz, 1H, H_3), 3.99 (s, 1H, H_5), 4.32 and 4.43 (d and d, J = 6.3 Hz, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.5, 33.0 and 33.4, 40.0, 45.5 and 46.2, 57.1 and 57.3, 63.7 and 64.7, 79.7 and 79.9, 156.7 and 156.9; HRMS *m*/*z* 240.0760, calcd for $C_{10}H_{16}ClNO_2Na$ (M + Na) 240.0767.

Preparations of *N*-*tert*-Butoxycarbonyl-5-*syn*-bromo-2-azabicyclo[2.1.1]hexane (19) and *N*-*tert*-Butyoxycarbonyl-5-*anti*-bromo-2-azabicyclo[2.1.1]hexane (20) from Barton Ester 16. To a 25 mL reaction flask equipped with a cold water condenser was added Barton ester **16** (91 mg, 0.27 mmol), AIBN (10 mg), and bromotrichloromethane (2 mL). Reaction according to the general procedure gave after chromatography (cyclohexane/EtOAc 40:1) 23 mg of bromide **19** (33% yield) and 3 mg of bromide **20** (4% yield). 5-*syn*-Bromide **19**: R_f 0.46 (cyclohexane/EtOAc 5:1), mp 56 °C (cyclohexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 and 1.48 (s and s, 9H), 1.76−1.88 (m, 2H, H_6), 2.92 (m, 1H, H_4), 3.31 (dd, J = 9.0, 3.6 Hz, 1H, H_3), 3.46 and 3.53 (d and d, J = 9.0 Hz, 1H, H_3), 4.13 (s, 1H, H_5), 4.36 and 4.47 (d and d, J = 6.6 Hz, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.5, 34.3 and 34.8, 40.0, 46.5 and 47.2, 59.1 and 59.3, 63.8 and 64.7, 79.6 and 79.9, 156.6; HRMS *m*/*z* 284.0246, calcd for $C_{10}H_{16}NO_2Na$ (M + Na) 284.0262. 5-*anti*-Bromide **20**: R_f 0.74 (cyclohexane/EtOAc 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9H), 1.64 (t, J = 8.4 Hz, 1H, H_{6s}), 2.90 (dd, J = 7.2, 3.0 Hz, 1H, H_4), 3.00 (m, 1H, H_{6a}), 3.43 (s, 2H, H_3), 3.82 (d, J = 8.4 Hz, 1H, H_5), 4.33 (m, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 38.9, 46.1, 49.0, 55.3, 65.2, 80.2, 155.4; HRMS *m*/*z* 284.0268, calcd for $C_{10}H_{16}NO_2Na$ (M + Na) 284.0262.

Preparation of 5-*syn*-Bromide 19 from Barton Ester 16. To a 25 mL reaction flask equipped with a cold water condenser was added Barton ester **16** (130 mg, 0.39 mmol), AIBN (10 mg), bromotrichloromethane (1 mL), and cyclohexane (2 mL). Reaction according to the general procedure after chromatography (cyclohexane/EtOAc 50:1) gave 46 mg of *syn*-bromide **19** (45% yield).

Preparations of *N*-*tert*-Butoxycarbonyl-5-*syn*-iodo-2-azabicyclo[2.1.1]hexane (21) and *N*-*tert*-Butoxycarbonyl-5-*anti*-iodo-2-azabicyclo[2.1.1]hexane (22) by the Barton Protocol. To a 25 mL reaction flask equipped with a cold water condenser was added Barton ester **16** (109 mg, 0.32 mmol), AIBN (18 mg), iodoform (374 mg, 0.95 mmol), and cyclohexane (10 mL). Reaction according to the general procedure after chromatography with a short flash column in darkness, eluting with cyclohexane/EtOAc gradiently, gave 45 mg of 5-*syn*-iodide **21** (45% yield) and 5 mg of 5-*anti*-iodide **22** (5% yield). 5-*syn*-Iodide **21**: R_f 0.46 (cyclohexane/EtOAc 5:1), mp 44 °C (cyclohexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 and 1.51 (m, 9H), 2.04 (m, 2H, H_6), 2.94 (m, 1H, H_4), 3.38 (m, 1H, H_3), 3.43 and 3.50 (d and d, J = 9.3 Hz, 1H, H_3), 4.21 (s, 1H, H_5), 4.38 and 4.50 (d and d, J = 6.9 Hz, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.7, 28.5, 36.0 and 36.5, 43.9, 48.3 and 49.0, 64.3 and 65.1, 79.6 and 80.0, 156.1; HRMS *m*/*z* 332.0117, calcd for $C_{10}H_{16}INO_2Na$ (M + Na) 332.0123. 5-*anti*-Iodide **22**: R_f 0.71 (cyclohexane/EtOAc 5:1), mp 62 °C (cyclohexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.63 (t, J = 9.0 Hz, 1H, H_{6s}), 2.90 (dd, J = 6.9, 3.0 Hz, 1H, H_4), 3.00 (m, 1H, H_{6a}), 3.37 (d, J = 8.7 Hz, 1H, H_3), 3.47 (d, J = 8.7 Hz, 1H, H_3), 3.65 (d, J = 9.0 Hz, 1H, H_5), 4.34 (br, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.5, 29.5, 40.3, 46.5, 48.4, 65.6, 80.1, 155.2; HRMS *m*/*z* 332.0126, calcd for $C_{10}H_{16}INO_2Na$ (M + Na) 332.0123. Chromatography resulted in isolation of 93% of *syn*-iodide **21** and 98% recovery of *anti*-iodide **22** based upon NMR analysis of a crude reaction mixture.

Preparations of 5-*syn*-[2-Methoxycarbonyl-2-(pyridin-2-ylsulfanyl)ethyl]-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid *tert*-Butyl Ester Diastereomers (23a and 23b) and 2-(*tert*-Butoxycarbonyl-2-azabicyclo[2.1.1]hex-5-*syn*-ylmethyl)-4-(pyridin-2-sulfanyl)pentanedioic Acid Dimethyl Ester (24). Barton ester **16** in CH_2Cl_2 solution was prepared in situ from 5-*syn*-acid **10c** (114 mg, 0.50 mmol) following the general preparation procedure. Without filtration or concentration, methyl acrylate (0.25 mL, 2.8 mmol) and AIBN (10 mg) were added. The reaction mixture was irradiated with a 250 W tungsten lamp while being refluxed for 4 h. The solvent was removed in vacuo. The crude products were purified through a short flash column, eluting with cyclohexane/EtOAc 10:1, then 5:1, to give 110 mg of a mixture of diastereomers **23a** and **23b** (58% yield) and 35 mg of diaddition product **24** (15% yield). The mixture of **23a** and **23b** could be separated by semipreparative HPLC, eluting with 50% acetonitrile aqueous solution to give equal amounts of **23a** and **23b** with the retention time of 21.5 and 23.5 min, respectively. The diastereomers have very similar NMR spectra. The configuration of each diastereomer was not determined. Isomer **23a**: R_f 0.53 (cyclohexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, J = 6.3 Hz, 1H), 1.45 (s, 9H), 1.65 (m, 1H), 1.75 (m, 2H), 2.14 (m, 1H), 2.65 (m, 1H), 3.19 (d, J = 10.8 Hz, 2H), 3.72 (s, 3H), 4.21 and 4.28 (d and d, J = 6.6 Hz, 1H), 4.51 (t, J = 7.2 Hz, 1H), 6.99 (ddd, J = 7.8, 4.8, 0.9 Hz, 1H), 7.17 (d, J = 7.8 Hz, 1H), 7.48 (td, J = 7.8, 1.8 Hz, 1H), 8.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.7 and 27.9, 28.5, 38.0 and 38.1, 40.2, 44.9, 45.3 and 46.1, 46.2 and 46.6, 52.6, 61.6 and 62.7, 79.2 and 79.3, 120.0, 122.3, 136.2, 149.4, 156.2 and 156.5, 157.0, 172.8; HRMS *m*/*z* 401.1531, calcd for $C_{19}H_{26}N_2O_4SNa$ (M + Na) 401.1511. **23b**: R_f 0.53 (cyclohexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, J = 7.5 Hz, 1H), 1.46 (s, 9H), 1.64 (m, 2H), 1.80 (m, 1H), 2.16 (m, 1H), 2.71 (m, 1H), 3.26 (m, 2H), 3.72 (s, 3H), 4.17 and 4.26 (d and d, J = 7.2 Hz, 1H), 4.53 (m, 1H), 7.01 (m, 1H), 7.18 (d, J = 8.1 Hz, 1H), 7.50 (td, J = 7.8, 1.8 Hz, 1H), 8.40 (d, J = 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9 and 28.1, 28.5, 38.0 and 38.1, 40.1, 44.7, 45.4 and 46.2, 46.2 and 46.4, 52.6, 61.5 and 62.5, 79.2 and 79.3, 120.0, 122.3, 136.3, 149.4, 156.3 and 156.5, 156.9, 172.7; HRMS *m*/*z* 401.1511, calcd for $C_{19}H_{26}N_2O_4SNa$ (M + Na) 401.1511. The diester **24** of undetermined stereochemistry: R_f 0.43 (cyclohexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (m, 1H), 1.45 (s, 9H), 1.32 (m, 1H), 1.60 (m, 1H), 1.92 (m, 2H), 2.16 (m, 1H), 2.36−2.65 (m,

3H), 3.15 (m, 2H), 3.64 and 3.69 (s and s, 3H), 3.71 (s, 3H), 4.14 (m, 1H), 4.61 (m, 1H), 6.99 (m, 1H), 7.16 (d, $J = 7.8$ Hz, 1H), 7.48 (td, $J = 7.8$, 1.8 Hz, 1H), 8.37 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0 and 28.2, 28.5, 33.9 (multiple peaks), 37.9 and 38.1, 40.0 and 40.1, 41.1 (multiple peaks), 44.0 and 44.4, 45.3 and 46.1, 46.4 and 46.8, 51.8, 52.6, 61.4 and 62.5, 79.1 and 79.3, 120.1, 122.3, 136.3, 149.3 and 149.4, 156.5 and 156.6, 172.4 and 172.6, 175.2; HRMS *m*/*z* 487.1867, calcd for $C_{23}H_{32}N_2O_6SNa$ (M + Na) 487.1879.

Preparation of 5-*syn*-(2-Methoxycarbonyl)ethyl-2-azabicyclo-[2.1.1]hexane Carboxylic Acid *tert*-Butyl Ester (25). Raney nickel was prepared according to Garner's procedure.[24a] Nickel−aluminum alloy (50/50 by wt %, 1.0 g) in three portions was added to an aqueous NaOH solution (6.0 N, 10 mL) over 30 min with vigorous stirring at 0 °C under argon. The ice bath was removed and the reaction mixture was stirred at room temperature for 3 h. The basic supernatant was decanted. The black solid was washed with water (4 × 50 mL) and MeOH (3 × 20 mL). The resulting Raney nickel was suspended in MeOH (30 mL) under argon. The mixture of thioethers **23a** and **23b** (43 mg, 0.11 mmol) was added. The reaction mixture was stirred under argon at room temperature overnight. TLC indicated the complete consumption of the starting material. The solid in the reaction mixture was removed by filtration. The filtrate was concentrated and purified through a short flash column, eluting with cyclohexane/EtOAc 10:1 to give 25 mg of ester **25** (82% yield): R_f 0.60 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.29 (d, $J = 7.2$ Hz, 1H, H_{6s}, no long-range coupling with H_5), 1.38 (m, 2H), 1.46 (s, 9H), 1.64 (m, 1H, H_{6a}), 1.94 (m, 1H), 2.21 (m, 2H), 2.62 (m, 1H), 3.19 (s, 2H), 3.66 (s, 3H), 4.20 (d, $J = 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.8, 28.5, 31.7, 37.8, 39.7, 45.6, 48.1, 50.6, 61.4, 79.2, 156.5, 173.7; HRMS *m*/*z* 292.1519, calcd for $C_{14}H_{23}NO_4Na$ (M + Na) 292.1525.

One-Step Preparation of 5-*syn*-Chloride 18 from 5-*syn*-Acid 10c. The reaction mixture of 5-*syn*-acid **10c** (60 mg, 0.26 mmol), lead tetraacetate (300 mg, 0.68 mmol), and lithium chloride (80 mg, 1.67 mmol) was dried under high vacuum overnight. Anhydrous toluene (10 mL) was added and the reaction mixture was stirred at 85 °C under argon for 6 h. The solid was removed by filtration. The filtrate was concentrated and purified by a short flash column, eluting with cyclohexanes−EtOAc 30:1 and then CH_2Cl_2−CH_3-OH 10:1 to give 5 mg of chloride **18** and 30 mg of 5-*syn*-acid **10c** (corrected yield 17%).

One-Step Preparation of 5-*syn*-Bromide 19 and 5-*anti*-Bromide 20 from 5-*syn*-Acid 10c (Table 2, entry 2). In a three-neck jacketed reaction flask circulated with running water, the reaction mixture of 5-*syn*-acid **10c** (116 mg, 0.51 mmol), HgO (171 mg, 0.79 mmol), and bromine (0.045 mL, 0.87 mmol) in CCl_4 (20 mL) was irradiated at ambient temperature for 1 h. After the solid had precipitated and settled in the bottom of the reaction flask, the supernatant was decanted to another flask, concentrated, and purified by a short flash column, eluting with cyclohexanes−EtOAc 30:1 to give 21 mg of **19** (16% yield), 2.0 mg of **20** (1.5% yield), and 1.0 mg of unreacted acid **10c** (Table 2, entry 3). The reaction mixture of 5-*syn*-acid **10c** (116 mg, 0.51 mmol) and mercury oxide (171 mg, 0.79 mmol) in carbon tetrachloride (10 mL) was irradiated with a 250-W tungsten lamp. Bromine (0.045 mL, 0.87 mmol) was added by syringe once the reaction mixture started to reflux. The color of the reaction mixture changed from brown to colorless immediately. The mixture was irradiated and refluxed for an additional 15 min. The insoluble solid was removed by filtration. The filtrate was concentrated and purified by a short flash column, eluting with cyclohexanes−EtOAc 30:1 to give 15 mg of 5-*anti*-bromide **20** (11% yield). No 5-*syn*-bromide **19** or starting 5-*syn*-acid **10c** were isolated. Other experiments performed by mixing all reactants before irradiating and refluxing for 30 min, or by irradiating and refluxing the mixture of **10c** and HgO in CCl_4 for 20 min before adding bromine and then irradiating for 30 min, led to the total decomposition of starting material.

Direct Preparations of 5-*syn*-Iodide 21 and 5-*anti*-Iodide 22 from 5-*syn*-Acid 10c (Table 2, entry 4). In a three-necked jacketed reaction flask circulated with running water, the reaction mixture of 5-*syn*-acid **10c** (121 mg, 0.53 mmol), iodobenzene diacetate (IBDA, 189 mg, 0.59 mmol), and iodine (148 mg, 0.59 mmol) in carbon tetrachloride (20 mL) was irradiated with a 250 W tungsten lamp at ambient temperature under argon for 2 h. The reaction solution was concentrated in vacuo and the crude products were purified on a short flash column in darkness, eluting with cyclohexane and then cyclohexane/EtOAc 30:1 to give 83 mg of iodide **21** (50% yield) and 38 mg of iodide **22** (23% yield). For other attempts see the Supporting Information.

Preparation of Parent *N*-*tert*-Butoxycarbonyl-2-azabicyclo-[2.1.1]hexane (17) Directly from 5-*syn*-Acid 10c. The reaction mixture of acid **10c** (0.356 g, 1.57 mmol), lead tetraacetate (1.17 g, 2.64 mmol), and pyridine (0.278 g, 3.52 mmol) in cyclohexane (15 mL) was refluxed under argon for 16 h. The solid in the reaction mixture was removed by filtration. The filtrate was concentrated and purified by a short silica gel column, eluting with cyclohexane/EtOAc 10:1, then 1:1, to give 78 mg of recovered **10c** and 118 mg of parent **17** (51% yield corrected for recovered acid).[21]

Preparations of *N*-*tert*-Butoxycarbonyl-5-*syn*-phenyl-2-azabicyclo[2.1.1]hexane (26) and *N*-*tert*-butoxycarbonyl-5-*anti*-phenyl-2-azabicyclo[2.1.1]hexane (27). The 5-syn acid **10c** (81 mg, 0.36 mmol) in benzene (3 mL) was added to an oven-dried flask purged with argon. Lead tetraacetate (208 mg, 0.47 mmol) was added in one portion followed by the dropwise addition of pyridine (43 mg, 0.57 mmol, 43 μL). The yellow/orange reaction was then heated to 80 °C for 3 h. The reaction was then cooled to room temperature and the crude oil was filtered through Celite, which was washed with ethyl acetate (25 mL). The combined solutions were washed with saturated sodium bicarbonate (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered, and solvent was removed in vacuo. The residue was chromatographed on silica gel, eluting with 30% EtOAc/hexanes to afford 38 mg (41% yield) of an 85:15 mixture of syn and anti phenyl isomers **26**/**27** by comparative NMR integrations of H_6 for each isomer. **Separation of isomers:** See the Supporting Information. When the mixture was analyzed by ^{1}H NMR, the ratio was 87:13 from the integrations of the H_{6a} protons, or 89:11 from the integrations of the H_3 protons. The 5-syn isomer **26**: R_f 0.60 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 and 1.47 (s and s, 9H), 1.50 (m, 1H, H_6), 1.89 (m, 1H, H_6), 2.87 and 2.95 (d and d, $J = 9.0$ Hz, 1H, H_3), 3.10 (m, 1H, H_4), 3.14 and 3.19 (d and d, $J = 9.0$ Hz, 1H, H_3), 3.28 (br, 1H, H_5), 4.66 and 4.77 (d and d, $J = 6.9$ Hz, 1H, H_1), 7.05−7.29 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.5 and 28.7, 37.1 and 37.5, 41.0 and 41.4, 45.2 and 46.2, 52.1, 60.8 and 61.9, 79.0 and 79.2, 116.3 and 116.5, 127.2 and 127.4, 128.4 and 128.5, 138.1, 155.5 and 155.9; HRMS *m*/*z* 282.1464, calcd for $C_{16}H_{21}NO_2Na$ (M + Na) 282.1470. **The 5-anti isomer 27:** R_f 0.60 (cyclohexane/EtOAc 2:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 9H), 1.58 (m, 1H, H_{6s}), 2.27 (m, 1H, H_{6a}), 3.09 (dd, $J = 7.2$, 3.0 Hz, 1H, H_4), 3.17 (d, $J = 8.1$ Hz, 1H, H_5), 3.52 (m, 2H, $2H_3$), 4.54 (br, 1H, H_1), 7.25−7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.7, 38.5, 42.0, 50.7, 57.3, 62.9 and 64.0, 79.5, 116.5, 128.2, 128.6, 138.5, 155.9; HRMS *m*/*z* 282.1473 calcd for $C_{16}H_{21}NO_2Na$ (M + Na) 282.1470.

Preparation of Parent 17 from 5-Iodides 21 and 22. The reaction mixture of 5-*syn*-acid **10c** (0.490 g, 2.16 mmol), IBDA (1.40 g, 4.3 mmol), and iodine (1.09 g, 4.3 mmol) in CCl_4 (70 mL) was irradiated and refluxed under argon for 30 min. The solvent was removed in vacuo. The crude products were passed through a short flash column, rinsed with cyclohexane to removed excessive iodine and reaction byproducts, then eluted with cyclohexane/EtOAc 5:1 solution to give 515 mg of a mixture of iodides **21** and **22**. To this mixture of iodides there was added AIBN (89 mg) and TTMSS (2.0 mL, 6.5 mmol) in THF (15 mL). The reaction mixture was irradiated with a 250 W tungsten lamp while being

refluxed for 4 h under argon. The reaction solution was concentrated and purified by a silica gel short flash column, eluting with cyclohexane/EtOAc 30:1 to give 145 mg of parent compound **17** (37% overall yield).

Preparation of 5-Propanoate 25 from 5-*anti*-Iodide 22. A suspension of zinc powder (65 mg, 1.0 mmol) and copper(I) iodide (63 mg, 0.33 mmol) in water (0.2 mL) was sonicated in an Ultrasonic cleaning bath (Fisher14 Model) for 15 min. Methyl acrylate (0.12 mL, 1.34 mmol), 5-*anti*-iodide **22** (107 mg, 0.35 mmol) in ethanol (0.2 mL) solution, and ethanol in water solution (33%, 3 mL) were introduced. Additional amounts of zinc powder (33 mg) and copper(I) iodide (32 mg) were added. The reaction mixture was sonicated for 1 h. Upon monitoring the reaction at this stage, besides the formation of product **25**, no more iodide **22** remained, but the epimerized stereoisomer 5-*syn*-iodide **21** was detected. Additional methyl acrylate (0.12 mL), zinc powder (65 mg), and copper(I) iodide (61 mg) were added and sonication of the reaction mixture was continued for an additional 1 h. The solid precipitate in the reaction mixture was removed by filtration and washed several times with EtOAc. After removal of solvent in vacuo, the crude products were purified with a short flash column, eluting with cyclohexane/EtOAc 10:1 to give 33 mg of **25** (35% yield) and 6 mg of 5-*syn*-iodide **21** (6%).

Preparation of *N*-*tert*-Butoxycarbonyl-5-*anti*-fluoro-2-azabicyclo[2.1.1]hexane (29). To a solution of *anti*-iodide **22** (22.6 mg, 0.073 mmol) in nitromethane (0.5 mL) there was added silver fluoride (23.2 mg, 0.18 mmol). After heating 1 d at 60 °C showed no reaction by TLC, the solution was stirred at 80 °C for an additional 4 h. The reaction mixture was then diluted with ether (6 mL) and washed with water (2 × 3 mL). The ether layer was dried over $MgSO_4$ and filtered. Solvent was removed in vacuo to give 2.8 mg (19%) of fluoride **29** at R_f 0.39 (1:1 hexane/ether); ^{1}H NMR δ 1.45 (s, 9H), 1.70 (ddd, J = 7.9, 7.3, 2.7 Hz, H_{6s}), 2.83 (m, 2H, H_4/H_{6a}), 3.35 (d, J = 9.7 Hz, 1H, H_3), 3.38 (d, J = 9.7 Hz, 1H, H_3), 4.30 (br, 1H, H_1), 4.80 (dd, J = 62, 7.9 Hz, 1H, H_5); ^{13}C NMR δ 155.4, 98.5 (d, J = 210 Hz), 79.9, 62.2, 47.2, 43.4 and 43.2, 36.7, 28.4; HRMS *m*/*z* 224.1052, calcd for $C_{10}H_{16}FNO_2Na$ (M + Na) 224.1063.

Preparations of 5-*syn*-*tert*-Butoxycarbonylamino-2-azabicyclo-[2.1.1]hexane-2-carboxylic Acid *tert*-Butyl Ester (33a), 5-*syn*-Azidocarbonylamino-2-azabicyclo[2.1.1]hexane-2-carboxylic Acid *tert*-Butyl Ester (34), 1,3-Bis(2-*tert*-butoxycarbonyl-2-azabicyclo-[2.1.1]hex-5-*syn*-yl)ureas (36/37), and 2-Azabicyclo[2.1.1]hexane-2,5-*syn*-dicarboxylic Acid Di-*tert*-butyl Ester (38). Triethylamine (84 mg, 0.12 mL, 0.83 mmol) was added to the solution of 5-*syn*-acid **10c** (105 mg, 0.46 mmol) in *tert*-butyl alcohol (5 mL). Diphenylphosphoryl azide (DPPA, 190 mg, 0.15 mL, 0.69 mmol) was added to the reaction solution after it was heated to reflux under argon. After an additional 4 h at reflux temperature, the reaction solution was concentrated in vacuo. EtOAc (20 mL) was added to the concentrated residue and the EtOAc solution was washed with water, concentrated, and purified by flash column, eluting with gradient cyclohexane/EtOAc, then EtOAc/MeOH 20:1 to give 11 mg of carbamate **33a** (8% yield), 37 mg of azide **34** (30% yield), 50 mg of ureas **36/37** (26% yield), and 3 mg of ester **38** (2% yield). The 5-*syn*-amino derivative **33a**: R_f 0.33 (cyclohexane/EtOAc 5:1), mp 105 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (d, J = 8.1 Hz, 1H, H_6), 1.43 (s, 9H), 1.48 (s, 9H, *tert*-butyl), 1.53 (m, 1H, H_6), 2.83 (m, 1H, H_4), 3.14 (d, J = 9.3 Hz, 1H, H_3), 3.25 (d, J = 9.3 Hz, 1H, H_3), 3.79 (d, J = 7.8 Hz, 1H, H_5), 4.25 (d, J = 6.3 Hz, 1H, H_1), 4.70 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.3, 28.5, 32.8, 41.7, 45.3, 52.7, 62.6, 79.9, 155.0, 156.8; HRMS *m*/*z* 321.1790, calcd for $C_{15}H_{26}N_2O_4Na$ (M + Na) 321.1785. The acyl azide **34**: R_f 0.50 (CH_2Cl_2/EtOAc 5:1), mp 107 °C (ethyl ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.22 (d, J = 8.4 Hz, 1H, H_6), 1.46 (s, 9H), 1.58 (m, 1H, H_6), 2.88 (m, 1H, H_4), 3.11 (d, J = 9.3 Hz, 1H, H_3), 3.27 (d, J = 9.3 Hz, 1H, H_3), 3.88 (dt, J = 7.8, 2.4 Hz, 1H, H_5), 4.28 (dt, J = 6.6, 1.5 Hz, 1H, H_1), 5.25 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 33.0, 41.8, 45.3, 52.7, 62.4, 80.3, 156.0, 156.7; HRMS *m*/*z* 290.1225, calcd for $C_{11}H_{17}N_5O_3Na$ (M + Na) 290.1229; see also, X-ray data. The mixture of ureas **36/37**: R_f 0.25 (CH_2Cl_2/EtOAc 5:1), mp 214 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.12 (d, J = 8.1 Hz, 2H, H_6), 1.44 (s, 18H), 1.52 (m, 2H, H_6), 2.76 (m, 2H, H_4), 3.09 (d, J = 9.0 Hz, 2H, H_3), 3.22 (d, J = 9.0 Hz, 2H, H_3), 3.94 (br, 2H, H_5), 4.20 (d, J = 6.6 Hz, 2H, H_1), 5.52 (br, 2H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.6, 33.0, 41.8, 45.6, 52.4, 63.3, 79.9, 156.8, 157.2; HRMS *m*/*z* 445.2387, calcd for $C_{21}H_{34}N_4O_5Na$ (M + Na) 445.2427. The ester **38**: R_f 0.43 (cyclohexane/EtOAc 5:1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (d, J = 7.5 Hz, 1H, H_6), 1.42 (s, 9H), 1.47 (s, 9H), 1.72 (m, 1H, H_6), 2.70 (s, 1H, H_5), 2.99 (m, 1H, H_4), 3.22 (d, J = 8.7 Hz, 1H, H_3), 3.53 (d, J = 8.7 Hz, 1H, H_3), 4.53 (br, 1H, H_1); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.0 and 28.5 and 29.5, 37.4, 40.7, 46.0 and 46.7, 50.2 and 51.2, 61.6 and 62.5, 79.3 and 80.8, 155.3 and 155.4, 168.7 and 168.9; HRMS *m*/*z* 306.1671, calcd for $C_{15}H_{25}NO_4Na$ (M + Na) 306.1681.

Preparation of 5-*syn*-Azidocarbonylamine 34 from 5-*syn*-Acid 10c (Neat DPPA and Triethylamine). Triethylamine (0.15 mL) was added to 5-*syn*-acid **10c** (107 mg, 0.47 mmol). Over 30 min DPPA (0.25 mL) was added and the neat reaction solution was stirred under argon for 3 d. All volatile components were removed under high vacuum. The crude product was purified by a short flash column, eluting with cyclohexane/EtOAc 10:1, to give 46 mg of azide **34** (37% yield). No other product was detected by ^{1}H NMR or isolated.

Preparation of *N*-*tert*-Butoxycarbonyl-5-*syn*-methoxycarbonylamino-2-azabicyclo[2.1.1]hexane (33b). The reaction mixture of acid **10c** (122 mg, 0.54 mmol) and triethylamine (TEA, 60 mg, 0.085 mL, 0.60 mmol) in carbon tetrachloride (6.0 mL) was heated to reflux. Diphenylphosphoryl azide (DPPA, 163 mg, 0.13 mL, 0.59 mmol) was added with a syringe. The reaction solution was refluxed under argon for 1.5 h. Methanol (0.8 mL) was added and the oil bath was removed. The reaction solution was cooled to room temperature and stirred under argon overnight. It was then concentrated and purified by a short flash column (cyclohexane/EtOAc 10:1) to give 89 mg of protected amine **33b** (65% yield): R_f 0.30 (cyclohexane/EtOAc 2:1), mp 84 °C (cyclohexane/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 8.1 Hz, 1H, H_6), 1.46 (s, 9H), 1.54 (m, 1H, H_6), 2.83 (m, 1H, H_4), 3.13 (d, J = 9.3 Hz, 1H, H_3), 3.25 (d, J = 9.3 Hz, 1H, H_3), 3.64 (s, 3H), 3.81 (m, 1H, H_5), 4.26 (m, 1H, H_1), 4.90 (m, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 32.8, 41.7, 45.3, 52.2, 53.0, 62.2, 79.9, 156.2, 156.7; HRMS *m*/*z* 279.1312, calcd for $C_{12}H_{20}N_2O_4Na$ (M + Na) 279.1321. See the Supporting Information for X-ray data.

Preparation of 5-*syn*-Benzyloxycarbonylamino-*N*-*tert*-butoxycarbonyl-2-azabicyclo[2.1.1]hexane (33c). The reaction mixture of acid **10c** (122 mg, 0.54 mmol) and triethylamine (60 mg, 0.085 mL, 0.60 mmol) in carbon tetrachloride (6.0 mL) was heated to reflux. Diphenylphosphoryl azide (DPPA, 163 mg, 0.13 mL, 0.59 mmol) was added with a syringe. The reaction solution was refluxed under argon for 1.5 h. Benzyl alcohol (0.8 mL) was added and the reaction solution was cooled to room temperature and stirred under argon overnight. The excessive benzyl alcohol was removed by Kugelrohr distillation and the remaining residue was purified on a short flash column (cyclohexane/Et_2O 5:1) to give 146 mg of protected amine **33c** (82% yield): R_f 0.33 (cyclohexane/Et_2O 1:1), mp 121 °C (EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 8.4 Hz, 1H, H_6), 1.45 (s, 9H), 1.54 (m, 1H, H_6), 2.83 (m, 1H, H_4), 3.13 (d, J = 9.3 Hz, 1H, H_3), 3.25 (d, J = 9.3 Hz, 1H, H_3), 3.84 (m, 1H, H_5), 4.27 (m, 1H, H_1), 4.99 (m, 1H, NH), 5.07 (s, 2H), 7.29−7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 32.8, 41.7, 45.3, 53.1, 62.2, 66.9, 79.9, 128.1, 128.2, 128.5, 136.4, 155.4, 156.6; HRMS *m*/*z* 355.1633, calcd for $C_{18}H_{24}N_2O_4Na$ (M + Na) 355.1634. See the Supporting Information for an X-ray structure.

Preparation of *N*-*tert*-Butoxycarbonyl-5-*anti*-methoxycarbonylamino-2-azabicyclo[2.1.1]hexane (39a). The reaction mixture of *anti*-acid **5c** (122 mg, 0.54 mmol) and triethylamine (TEA, 60 mg, 0.085 mL, 0.60 mmol) in carbon tetrachloride (6.0 mL) was

heated to reflux. Diphenylphosphoryl azide (DPPA, 163 mg, 0.13 mL, 0.59 mmol) was added with a syringe. The reaction solution was refluxed under argon for 1.5 h. Methanol (0.8 mL) was added and the oil bath removed. The reaction solution was cooled to room temperature and stirred under argon overnight. It was then concentrated and purified on a short flash column, eluted with cyclohexane/EtOAc 5:1 to give 104 mg of protected amine **39a (**75% yield): R_f 0.23 (cyclohexane/EtOAc 2:1), mp 105 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.56 (m, 1H, H_{6s}), 2.51 (m, 1H, H_{6a}), 2.82 (m, 1H, H_4), 3.37 (m, 2H, H_3), 3.52 (m, 1H, H_5), 3.68 (s, 3H), 4.28 (d, J = 6.3 Hz, 1H, H_1), 5.32 (m, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.4, 37.2, 42.3, 48.7, 52.2, 62.4, 62.6, 79.6, 155.7, 157.0; HRMS *m*/*z* 279.1310, calcd for $C_{12}H_{20}N_2O_4Na$ (M + Na) 279.1321.

Preparation of 5-*anti*-Benzyloxycarbonylamino-*N*-*tert*-butoxycarbonyl-2-azabicyclo[2.1.1]hexane (39b). According to the general procedure, *anti*-acid **5c** (70 mg, 0.31 mmol) and triethylamine (TEA, 35 mg, 0.050 mL, 0.35 mmol) in carbon tetrachloride (6.0 mL) were heated to reflux. Diphenylphosphoryl azide (DPPA, 94 mg, 0.075 mL, 0.34 mmol) was added with a syringe. The reaction solution was refluxed under argon for 1.5 h, benzyl alcohol (0.5 mL) was added, and the oil bath was removed to allow cooling to room temperature. After 12 h under argon and workup as for **33c**, eluting with cyclohexane/Et_2O 5:1, then 2:1, gave 82 mg of **39b** (80% yield): R_f 0.27 (cyclohexane/Et_2O 1:1), mp 84 °C ($CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.46 (s, 9H), 1.56 (m, 1H, H_{6s}), 2.51 (m, 1H, H_{6a}), 2.83 (m, 1H, H_4), 3.41 (d, J = 9 Hz, 1H, H_3), 3.63 (d, J = 9 Hz, 1H, H_3), 3.57 (m, 1H, H_5), 4.30 (d, J = 6.9 Hz, 1H, H_1), 5.11 (s, 2H), 5.27 (m, 1H, NH), 7.30−7.41 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 28.5, 37.2, 42.4, 48.7, 62.6, 66.9, 79.6, 128.1, 128.2, 128.5, 136.3, 155.7, 156.3; HRMS *m*/*z* 355.1624, calcd for $C_{18}H_{24}N_2O_4Na$ (M + Na) 355.1634.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE 0111208 and CHE 0515635).

Supporting Information Available: General experimental, procedures for iodide **21/22 (**entries 5−10 in Table 2), parent **17** from iodide **21**, copies of ^{1}H NMR and ^{13}C NMR for new compounds, and X-ray data for amine derivatives **33b** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO052506B