Synthesis of (+)- and (−)-*N*-BOC-7-Azabicyclo[2.2.1]heptan-2-ones, Versatile Intermediates for the Enantiospecific Synthesis of (+)- and (−)-Epibatidine and Analogues

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(+)- and (−)-Epibatidine, nonopiate antinociceptive alkaloids, have been prepared from (−)- and (+)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one which were produced by resolution of the racemic mixture of the corresponding alcohols obtained in the previous racemic synthesis. In the present work, we report the enantiospecific synthesis of (−)- and (+)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one from L-glutamic acid and levulinic acid. Also, this report describes the selective formation of *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes from *N*-benzyl-5-(1′-methoxycarbonyl-3′-oxobutyl)proline *via* a decarbonylation/iminium ion cyclization process. These functionalized intermediates are of potential value for the enantiospecific synthesis of epibatidine analogues.

Introduction

The alkaloid epibatidine (**5**) exhibits remarkable nonopiate antinociceptive properties[1] and the uncommon structure of a 5-(2′-chloropyridinyl) substituent attached in an *exo*-orientation to a 7-azabicyclo[2.2.1]heptane. Recently the absolute configuration of the natural product has been determined to be 1*R*,2*R*,4*S*, corresponding to the (+)-enantiomer.[2]

The synthesis of (±)-epibatidine has been accomplished by using three different and distinct synthetic approaches: (a) the carbon skeleton, including the single nitrogen atom bridge, was generated by Diels–Alder reaction of *N*-(methoxycarbonyl)pyrrole and (phenylsulfonyl)(6-chloro-3-pyridyl)acetylene;[3] (b) the carbon skeleton was assembled in the early steps, and the single nitrogen atom bridge was constructed in the last steps of the synthesis;[4] and (c) a 7-azabicyclo[2.2.1]heptane system was synthesized and condensed with a pyridine derivative.[2,5] The [2.2.1]heptane systems mentioned above are represented by structures (±)-**1**, (±)-**2**, and **3**, respectively.

(+)- and (−)-Epibatidine were obtained by resolution from the racemic mixture through their di-*p*-toluoyltartaric acid salts.[3] They also have been prepared from enantiomerically pure synthetic intermediates, in turn obtained from earlier enantiomeric mixtures which were resolved by chiral-HPLC[4b] or by separation of the diastereomeric esters of the racemic alcohols **4**.[2] None of the previous reports provides an enantiospecific synthesis of (+)- and (−)-epibatidine (**5**).

In planning an enantiospecific synthesis of (+)- and (−)-epibatidine (**5**), we chose a synthetic route based on approach c, above, because it allows all the asymmetric elements to be controlled in a simple structure, an *N*-R-7-azabicyclo[2.2.1]heptan-2-one, as present in bicycles **1** and **2**. Bicycle **3** was excluded as an intermediate since it is symmetrical. Considering the deprotection protocols for the respective *N*-protecting functions, (+)- and (−)-*N*-BOC-azabicycles **1** were chosen as the most versatile chiro-intermediates for the enantiospecific synthesis of (+)- and (−)-epibatidine (**5**).

The preparation of (+)- and (−)-epibatidine (**5**), from (+) and (−)-azabicycles **1**, has been reported by Fletcher *et al.*[2] Also, the problems encountered in that synthesis relating to the stereoselective removal of the residual hydroxyl function could be avoided by following the procedure employed by Nakai *et al.*[5b] to carry out the same kind of transformation. Our synthetic goal, therefore, was the enantiospecific synthesis of (+)- and (−)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one (**1**).

Results and Discussion

(+)- and (−)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one (**1**) could be conceptionalized as deriving from a suitable 2,3-disubstituted-7-azabicyclo[2.2.1]heptane by selective manipulation of the side chains at C-2 and C-3. To synthesize such a 2,3-disubstituted-7-azabicyclo[2.2.1]heptane system, we planned to use the synthetic methodology developed in the anatoxin field.[6] Thus, the bicyclic ring system was to originate from keto acids **16** *via* decarbonylation/ intramolecular iminium ion cyclization (Scheme 1). The skeleton of keto acids **16** was to result from condensing (*S*)-1-benzyl-5-thioxoproline *tert*-butyl ester (**13**)[6a] with triflate **12** by the alkylation/sulfur-extrusion sequence.[7]

The parent hydroxy ester of triflate **12** is just two carbons shorter than its related component in the ana-

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Scheme 1. Synthesis of *trans*-2,3-Disubstituted-7-azabicyclo[2.2.1]heptanes

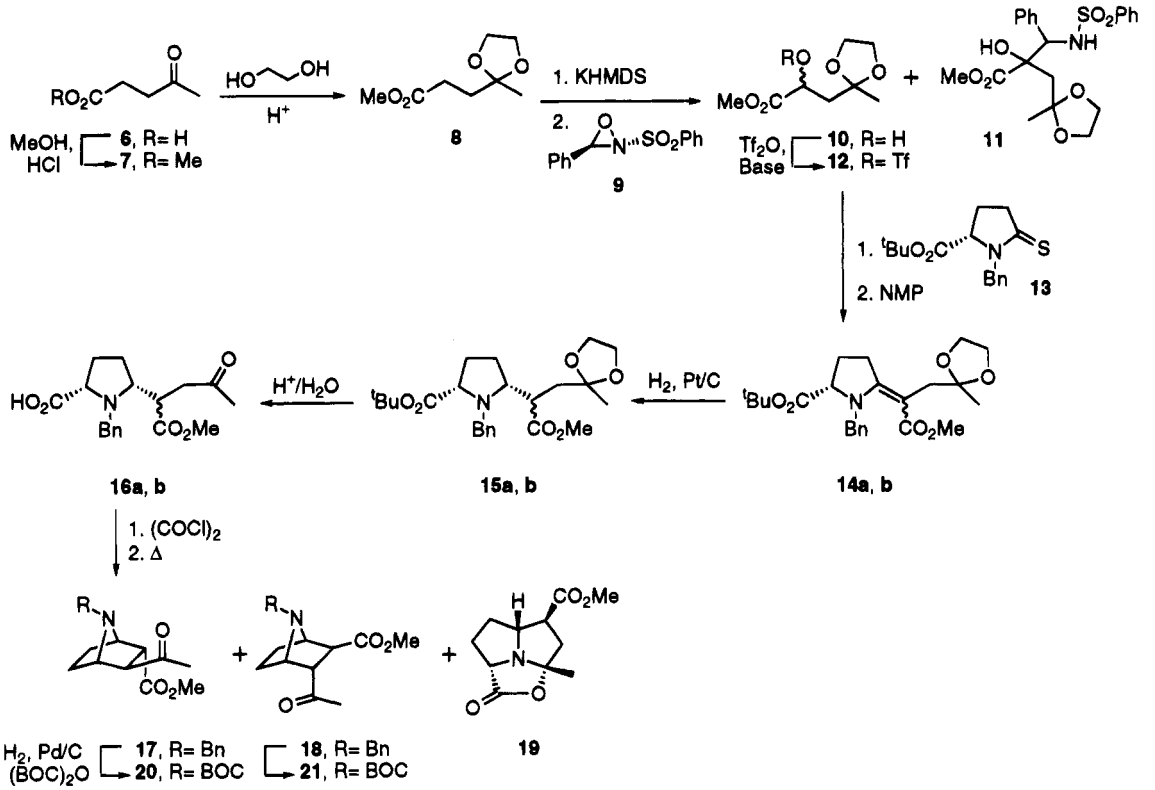
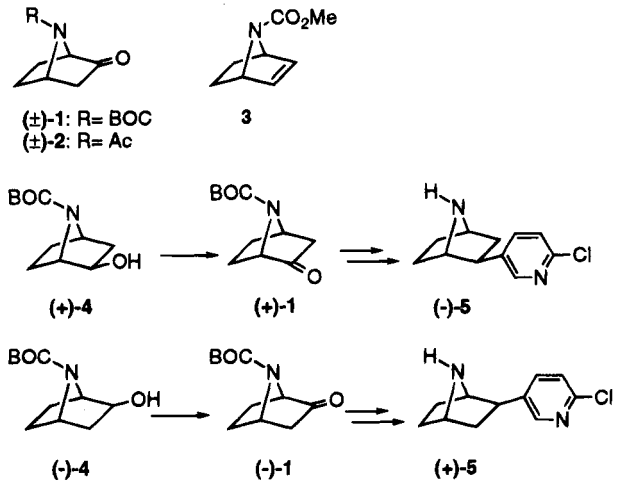


Chart 1



toxin group[6b] and it was readily synthesized from levulinic acid (**6**) in three straightforward steps. Esterification (HCl/MeOH) of levulinic acid (**6**) provided methyl ester **7** in 81% yield, and its keto function was protected as its ethylene ketal (ethylene glycol/*p*-TsOH) to produce the ketal methyl ester **8** in 79% yield. Introduction of the hydroxyl function at C-2 was achieved by generation of the potassium enolate of ketal methyl ester **8** and electrophilic addition of oxaziridine **9**.[8] This procedure afforded the 2-hydroxy ester **10** in 73% yield and the adduct **11**, mainly as one diastereomer, in 17% yield. The latter compound could originate from several consecutive rearrangements of the intermediate adduct, tending to produce the most stable anion. No compounds related to adduct **11** have been reported; however, the byproduct described as resulting from this reagent presents the same carbon structure but lacks the 2-hydroxyl function.[8a,9] Triflate **12** was obtained from the corresponding 2-hydroxy ester **10** by treatment with Tf_2O/2,6-di-*tert*-butyl-4-methylpyridine;[10] replacement of the base by 2,6-lutidine led to the formation of considerable α,β-unsaturated esters.

Alkylation of *S*-thiolactam **13**, prepared from L-glutamic acid,[6b] with triflate **12**, followed by sulfide contraction (PPh_3/*N*-methylpiperidine) provided the vinylogous carbamate **14** in 68% yield as a 6/5 mixture of geometrical isomers. Hydrogenation (5% Pt/C, EtOAc) of vinylogous carbamates **14** gave the *cis*-pyrrolidines **15**,[6a] in 91% yield, as a 1/1 diastereomeric mixture at C-1′. Acid hydrolysis (5/5/1, *i*-PrOH/H_2O/AcOH) of the ketal esters **15** produced the diastereomeric mixture of keto acids **16** (same ratio as their precursors). The last transformation is quantitative for crude product. Further purification by column chromatography afforded an 85% yield of keto acids **16** and also allowed isolation of pure diastereomers **16a** and **16b** which were employed to investigate the stereochemical course of the intramolecular cyclization of the iminium ions **22a** and **22b**. The stereochemistry of these keto acids **16a** and **16b** was established by NMR spectroscopy and will be discussed subsequently.

For the synthetic sequence, the diastereomeric mixture of crude keto acids **16** was decarbonylated [$(COCl)_2$] and the resulting iminium ions were subjected to intramolecular cyclization (Δ; 1,2-DCE/*tert*-BuOH)[6c] to give the 2,3-disubstituted-7-azabicyclo[2.2.1]heptanes **17** and **18** in 51% yield, as a 3/1 mixture of diastereomers (ratio established by ^1H NMR). This diastereomeric mixture

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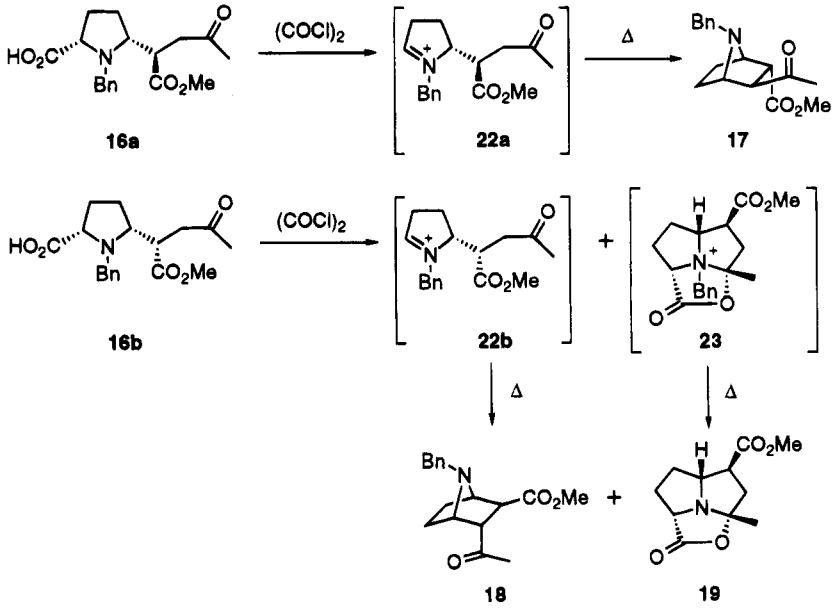
Scheme 2. Stereochemical Course of Intramolecular Cyclization of Iminium Ions 22a and 22b



was separated into the single diastereomers **17**, 34% yield, and **18**, 13% yield, but for the continuing synthesis the diastereomeric mixture was submitted to the next step. The other cyclization product, which is not derived from the decarbonylation/ iminium cyclization pathway, is the pyrrolizidine **19**, and it was isolated in 11% yield as a single diastereomer. Removal of the *N*-benzyl group and reprotection as the *tert*-butyl carbamate of the 3/1 mixture of bicycles **17** and **18** afforded the *N*-BOC-bicycles **20** and **21**, 82% yield, as a 3/1 mixture also (based on ^{1}H NMR).

The stereochemical course of the intramolecular cyclization of the iminium ions **22a** and **22b** (Scheme 2) was determined by subjecting the single diastereomers **16a** and **16b** to the decarbonylation/cyclization protocol. Under these conditions, the keto acid **16a** provided exclusively the *trans*-2,3-disubstituted bicycle **17**, 70% yield, and the keto acid **16b** gave the other *trans*-2,3-disubstituted bicycle **18**, 15% yield, and the pyrrolizidine **19**, 38% yield. Thus, intramolecular cyclization of iminium ions **22a** and **22b** produces *trans*-spatial relationships of the side chains. Each keto acid **16a** and **16b** gives only one 2,3-disubstituted bicycle, **17** and **18**, respectively.

The observed yield (70%) for bicycle **17** from pure diasteromer **16a** agrees with the one expected (34% from the 1/1 diastereomeric mixture); however, the yields from pure diasteromer **16b** of bicycle **18** and pyrrolizidine **19** were lower and higher than expected (25 and 22%, respectively). The explanation resides in the decarbonylation reaction times, which were set twice as long in experiments involving the single diastereomers. This extended reaction time does not affect the yield of bicycle **17** but it does change the ratio of bicycle **18**/pyrrolizidine**19**. Iminium ion **22b** and ammonium ion **23** originate from the initially formed acid chloride. While iminium ion **22b** is fully generated upon warming at the end of acid chloride formation,[11] ammonium ion **23** is generated continuously during the formation. The formation of the intermediate **23** can be explained by intramolecular attack of the nitrogen on the ketone carbonyl moiety, followed by lactonization. Ammonium ion **23** then is transformed into the tertiary amine **19** during the cyclization by nucleophilic displacement by chloride anion. This competitive reaction explains the low yield of bicycle **18** in comparison with that found for bicycle **17**, keeping in mind that intramolecular iminium ion cyclization is a reversible process.[6a]

Removal of the *N*-benzyl group and reprotection as the *tert*-butyl carbamate (BOC) of each bicycle **17** and **18** gave the *N*-BOC-bicycles **20**, 82% yield, and **21**, 83% yield, respectively. The *trans*-spatial relationships of the side chains was determined at this stage by observing the coupling patterns of the signals corresponding to H-2 and H-3.[12] The ^{1}H NMR spectra of both diastereomers **20** and **21** show a double triplet (exo-H) and a doublet (endo-H) assigned to H-2 and H-3 in diastereomer **20** and to H-3 and H-2 in diastereomer **21**.[13] The chemical shifts exhibited for H-2 (3.73 and 3.11) and H-3 (3.06 and 3.70)[14] in both diastereomers **20** and **21** agree with the exo- and endo-position assignments.[11] The absolute configuration at the C-2 and C-3 centers was determined by 2D-NMR experiments which will be discussed in a later section.

Enolization (500 mol % NaH, 10% MeOH/THF)[6c] of the 3/1 mixture of keto esters **20/21** and subsequent trapping (250 mol % TBDMSCl) gave a 3/7 mixture of 1-silyloxy alkenes **24a/24b**, 70% yield, and recovered starting keto esters **20/21**, 11% (Scheme 3). Assignment of *Z*-geometry to the double bond was done on the basis of the configuration found for similar compounds described in our related work.[11] The assignment of the C-3 configuration was made on the basis of the coupling pattern observed for H-3, which appears as a multiplet (exo position) in 1-silyloxy alkene **24a** and as a singlet (endo position)[12] in 1-silyloxy alkene **24b**. Ozonolysis (MeOH/Pyd)[6b] of the mixture of 1-silyloxy alkenes **24a/24b** followed by reductive isolation (PPh_3) afforded the 1,3-keto esters **25**, 81% yield, as a 1/1 mixture of C-3 epimers. The last keto

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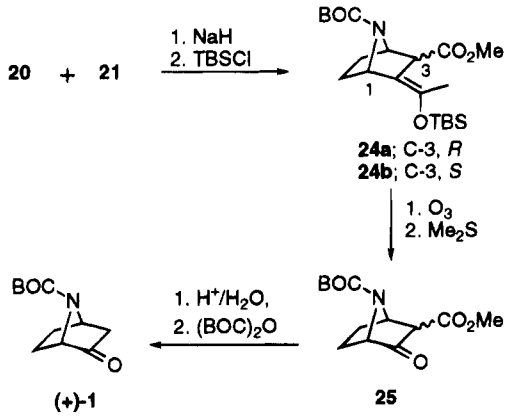
(13) The signal and coupling pattern of H-3 in bicycle **21** was hidden beneath the methoxy peak in $CDCl_3$; therefore, the spectrum was recorded in C_6H_6.

(14) The reported chemical shifts are referred to $CDCl_3$, as solvent, for both diastereomers.

Scheme 3. Synthesis of (+)-N-BOC-7-azabicyclo[2.2.1]heptan-2-one (1) from 2,3-Disubstituted Bicycles 20 and 21



esters **25** were hydrolyzed and decarboxylated (HCl/H_2O) to give a crude free amine which was reprotected as its BOC-carbamate [$(BOC)_2O$, Et_3N] to afford the ketone (+)-**1** in 85% yield ($[\alpha]^{22}_D$ +73.5°).

The more straightforward procedure to obtain ketone (−)-**1**, from 2,3-disubstituted bicycles **20** and **21** is to make their bis-TMS enol ethers **26**, ozonize them to form the β-keto esters **28**, and decarboxylate the corresponding acids. But enolization (LDA/TMSCl)[15] of the mixture of bicycles **20/21**, followed by ozonolysis and then decarboxylation (toluene, Δ_x) yielded ketone (−)-**1** ($[\alpha]^{22}_D$ −72.6°) in only 17% yield. The low yield was the result of a different reaction pathway for the ozonolysis of the ketene acetal moiety[16] leading to formation of the 2-TMSO ester acid **27a**. When the final toluene solution was extracted (1.8 M KOH), the 2-hydroxy diacid **27b** was formed; however, when **27b** was submitted to oxidative decarboxylation conditions,[17] no ketone (−)-**1** was obtained.

Much better overall yields of ketone (−)-**1** from bicycles **20/21**, were afforded by a longer procedure which consists in the stepwise removal of the acetyl group and oxidative cleavage of the methyl ester function. Selective enolization (160 mol % KHMDS) of the acetyl group of bicycles **20** and **21**, followed by trapping (310 mol % TMSCl) of the generated kinetic enolates gave the crude 1-silyloxy alkenes **29** and **32** (Scheme 4). These enol ethers, when treated with ozone then Me_2S,[16,18] provided the *trans*-1,4-ester acids **30** and **33** and DMSO as the only products. Radical decarboxylation[19] of acids **30** and **33** afforded the methyl esters **31** and **34** in 40 and 15% overall isolated yields from γ-keto esters **20** and **21**, respectively. The experimental procedure employed involved activation of the acids, as mixed anhydrides (i-BuO_2CCl/Et_3N), formation of the thioxamate ester, and its photolytic cleavage in the presence of 1,1-dimethylethanethiol. The configurations at C-2 in epimers **31** and **34** were assigned on the basis of the coupling pattern/chemical shift observed for H-2: the ^1H NMR spectrum of methyl ester **34** displays a dd (J = 8.9 and 5.1 Hz) at 2.55 ppm for H-2, while the methyl ester **31** shows a multiplet at 3.46 ppm for the same hydrogen. These data allow assignment of an endo H-2 in the epimer **34** and an exo H-2 in epimer **31**. When single diastereomers **20** and **21** were subjected to the sequence enolization/ozonolysis/decarboxylation, single diastereomers **31** and **34** were obtained in 51 and 57%, respectively.

The lithium enolates of methyl esters **31** and **34** were generated (LDA) and trapped (TMSCl)[15] separately to give the TMS-ketene acetals **35**, in quantitative yields, but in different *E*/*Z* diastereomeric ratios, 8/3 and 1/9, respectively. Ozonolysis (CH_2Cl_2/*tert*-BuOH) of the respective ketene acetals mixtures, followed by reduction (Me_2S) provided 1/2 mixtures of ketone (−)-1/2-TMSO-methyl esters **36** in both cases. Treatment of the latter mixtures with HCl/MeOH or TBAF afforded 25%/59% and 27%/58% yield of ketone (−)-**1**/2-hydroxy esters **37**, respectively.

The 2-hydroxy methyl esters **37** were excellent sources of ketone (−)- **1**: reduction [$Ca(BH_4)_2$][20] of the 2-hydroxy esters **37** gave diols **38** (82% yield of crude, 4/1 mixture, C-2 epimers) which were easily oxidized ($NaIO_4$)[21] to afford ketone (−)-**1** in 71% from methyl esters **37**. Thus, ketone (−)-**1** ($[\alpha]^{22}_D$ −73.6°) was obtained in 68% overall yield from each of the methyl esters **31** and **34**. The methodology employed to prepare ketone (−)-**1** from these methyl esters were more effective than alternate procedures which produce either ketone (−)-**1**[22] or 2-hydroxy methyl ester **37**.[8a] Alkylation of the lithium and potassium enolates, proceeding from methyl esters **31** and **34**, with dimethyl sulfide provided low yields (40%) of the related 2- methylsulfenyl esters.[22] The subsequent methyl ester hydrolysis required drastic conditions (KOH, ethylene glycol, Δ_x) which diminished even more the overall yield. Also, other procedures successfully employed in the early stages of our synthesis for α-hydroxylation of esters[8a] provided 2-hydroxy esters **37** in only 43% yield.

Stereochemical Outcome of the Iminium Ion Cyclization

The determination of the absolute configuration at C-2 and C-3, in disubstituted bicycles **17** and **18**, is not essential to development of our synthetic route. Both stereocenters disappear in latter stages of the synthesis to generate the carbonyl function which is present in ketones (+)-**1** and (−)-**1**.

We decided to determine the absolute configurations, however, at C-2 and C-3, in bicycle **17**, because of the differences and surprising selectivity shown by the iminium cyclization reaction, and because of the potential of these intermediates for analogue synthesis. The ^1H NMR spectrum of bicycle **17** shows a δ (J = 4.5 Hz) at 2.88 ppm, assigned to either the α-H of the ester or keto function. This hydrogen occupies an endo position[12] and is attached to the carbon at 58.7 ppm (Figure 1, H−C correlation) which displays a cross peak with the carbon at 206 ppm (C−C correlation, J = 41 Hz). Thus, the methyl ketone must occupy the exo position at C-3, and the configuration of this carbon is *R*. Previously, we

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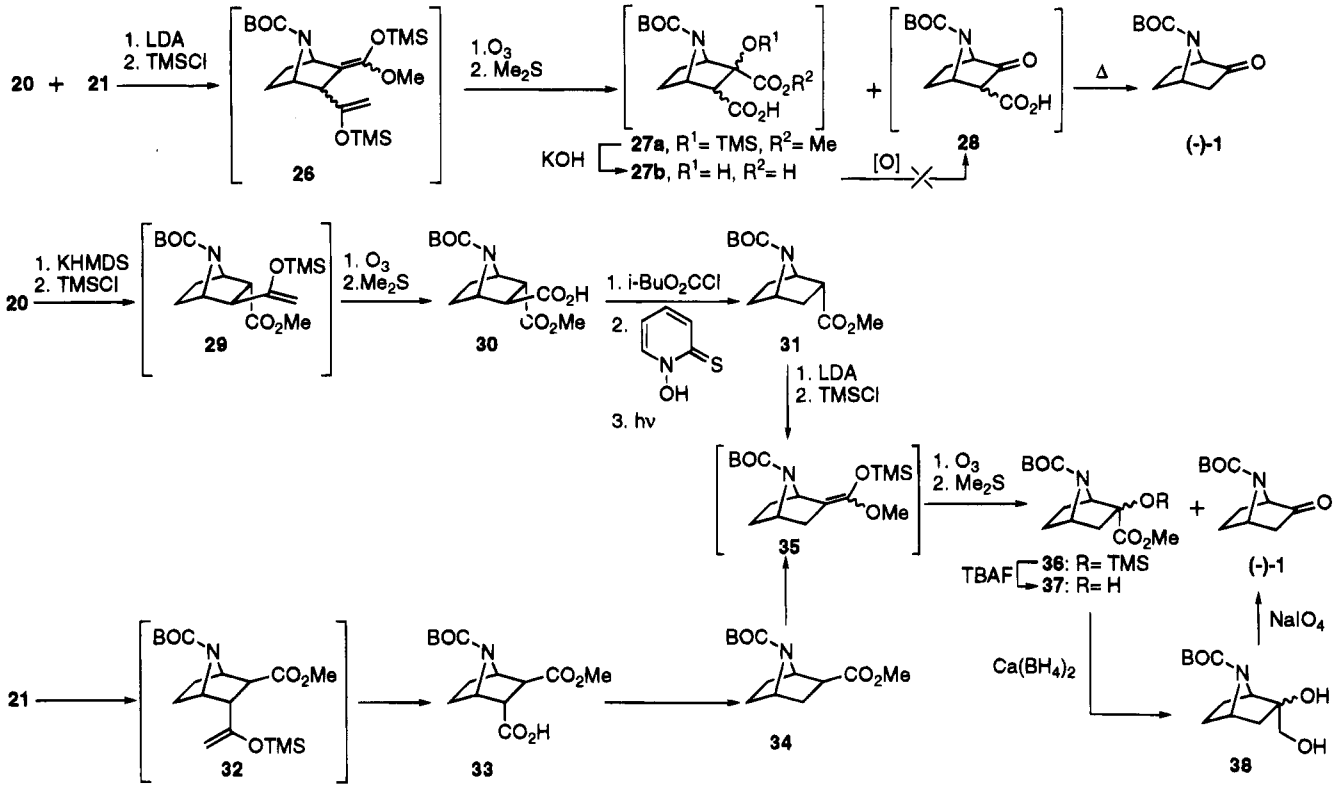
Scheme 4. Synthesis of (−)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one (1) from 2,3-Disubstituted Bicycles 20 and 21



stated that the pair of bicycles **17** and **18** exhibit trans-relationships for their respective side chains; therefore, the configuration of C-2 in bicycle **17** also must be *R*. Carbon C-2 (47.9 ppm) shows a correlation with the carbon at 173 (J = 61 Hz) and is attached to the hydrogen at 3.58 ppm (exo-H) which is overlapped by the bridge hydrogens. Since bicycles **17** and **18** show opposite configurations at C-2 and C-3, both configurations must be *S* in bicycle **18**. These conclusions also allowed assignment of configuration to their respective precursors, keto acids **16a** and **16b**.

The 2D-NMR data are supported further by the fact that 2,3-disubstituted bicycles **17** and **18** were selectively transformed to the monosubstituted bicycles **31** and **34**, respectively, in which the C-2 configurations are established by a simple study of the H-2 coupling patterns, exhibited in the ^{1}H NMR spectrum, of both compounds.

Conclusion

(−)- and (+)-*N*-BOC-7-azabicyclo[2.2.1]heptan-2-one (**1**) have been enantioselectively synthesized from L-glutamic acid and levulinic acid. They are versatile intermediates for the enantiospecific synthesis of (+)- and (−)-epibatidine. While mixtures of diastereomers are formed at several stages of the synthesis, all reactions can be carried out using the mixtures since the diastereomers converged to a single product, (−)- or (+)-(**1**). Diastereomeric separation was carried out at different stages in order to determine the stereochemical course of key steps and the stereochemistry of the intermediates and/or products.

We also report the selective formation of *trans*-2,3-disubstituted-7-azabicyclo[2.2.1]heptanes from *N*-benzyl-5-[1′-(methoxycarbonyl)-3′-oxobutyl]proline *via* decarbonylation/iminium ion cyclization. These bicyclic systems are of potential value for the enantiospecific synthesis of epibatidine analogues.

Experimental Section

General. Glassware was oven dried before use and cooled to room temperature under a nitrogen atmosphere. THF was distilled from sodium/benzophenone; CH_3CN, CH_2Cl_2, 1,2-DCE, *tert*-BuOH, and TMSCl were distilled from CaH_2; MeOH was distilled from Mg. *N*-Methylpiperidine and oxalyl chloride were distilled prior to use. Final solutions before rotary evaporation were dried over Na_2SO_4 and chromatography was carried out using (a) 70−230 or (b) 230−400 mesh silica gel, unless otherwise noted. IR spectra were taken in $CHCl_3$ and NMR spectra were taken in $CDCl_3$, unless otherwise noted. ^{1}H-Coupling constants, J, are reported in hertz. Where DEPT experiments were carried out with ^{13}C NMR acquisitions, the carbon multiplicities are listed as (0) quaternary, (1) methine, (2) methylene, (3) methyl.

Methyl levulinate (7)[23] was prepared from levulinic acid (**6**) using an improved general procedure.[24] bp 40−45 °C, 0.2 mm Torr (81%); ^{13}C NMR δ 206.6, 173.1, 51.7, 37.8, 29.8, 27.6.

Methyl 3-(2-Methyl-1,3-dioxolan-2-yl)propanoate (8). To a solution of methyl levulinate (**7**, 71.0 g, 0.54 mol) in benzene (1.62 L) were added ethylene glycol (75.3 mL, 83.8 g, 1.35 mol) and *p*-toluenesulfonic acid hydrate (1.28 g, 6.73 mmol), and the mixture was refluxed under Ar for 20 h, using a Dean−Stark apparatus. After H_2O collection ceased, the reaction mixture was allowed to cool to rt and washed with saturated $NaHCO_3$ (2 × 1 L), water (1 L), and saturated NaCl (1 L). Drying and evaporating the solvent and distilling the residue (82−86 °C, 3 Torr) yielded the ketal **8** (74.8 g, 79%): ^{1}H NMR δ 3.94 (m, 4H), 3.67 (s, 3H), 2.40 (t, J =7.6, 2H), 2.03

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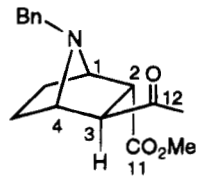

17

H-C CORRELATIONS

ppm, C-x \ ppm, H-x	2.88, H-3	3.57, H-1	3.58, H-2	3.59, H-4
47.9, C-2			√	
58.7, C-3	√			
62.0, C-1		√		
62.3, C-4				√

A √ in the intersection square indicates the observation of a crosspeak.

C-C CORRELATIONS

ppm, C-x \ ppm, C-x	47.9, C-2	58.7, C-3	62.0, C-1	62.3, C-4	173, C-11	206, C-12
47.9, C-2		37	33		61	
58.7, C-3				34		41

The number in the intersection square means that a crosspeak is observed and its magnitude represents the *J*(C-x/C-x, hertz) between those two carbons.

Figure 1. Determination of the absolute configuration at C-2 and C-3 in bicycle **17** by 2D-NMR experiments.

(t, J =7.6, 2H), 1.33 (s, 3H); ^{13}C NMR δ 173.5, 108.7, 64.4, 51.1, 33.7, 28.4, 23.6. Anal. Calcd for $C_8H_{14}O_4$: C, 55.1; H, 8.1. Found: C, 54.7; H, 8.2.

Methyl (±)-2-Hydroxy-3-(2-Methyl-1,3-dioxolan-2-yl)-propanoate (10) and Methyl (±)-2-Hydroxy-2-[phenyl(*N*-(phenylsulfonyl)amino)methyl]-3-(2-methyl-1,3-dioxolan-2-yl)propanoate (11). A solution of ketal methyl ester **8** (14.45 g, 83.05 mmol) in THF (200 mL) was added to a 0.94 M solution of KHMDS in THF (123.7 mL, 116.3 mmol) and diluted with additional THF (200 mL), at −78 °C over a period of 15 min, and the resulting yellow solution was stirred for an additional 25 min. At that time, a solution of oxaziridine **9**[8] (30.35 g, 116.3 mmol) in THF (200 mL) was added over 25 min and the reaction mixture was stirred for another 30 min and then quenched with saturated NH_4Cl (150 mL), maintaining the temp at −78 °C. The mixture was allowed to reach rt (1 h) and most of the THF was evaporated. Ether (1.00 L) was added to produce a suspension which was filtered to separate a white solid (13.34 g) from the two liquid layers. The layers of the filtrate were separated, and the aqueous phase was extracted with ether (500 mL). The combined organic phase was washed with saturated NaCl (500 mL), dried, and evaporated to leave a yellow gummy solid which was chromatographed (b, 1/1 hex/EtOAc) to provide 2-hydroxy ester **10** (13.90 g), contaminated with $PhSO_2NH_2$ and the adduct **11**, as a 4/3 mixture of two diastereomers (650 mg, 2% yield). The 2-hydroxy ester **10** was further purified, by removal of the $PhSO_2NH_2$ (crystallization from ether), to afford pure 2-hydroxy ester **10** (11.54 g, 73%). The white solid (13.34 g), separated by filtration at the beginning of the isolation, was treated with saturated $NaHCO_3$ (100 mL) and the resulting suspension extracted with CH_2Cl_2 (4 × 50 mL) to provide more of adduct **11** (5.41 g, 15%) as a single diastereomer.

2-Hydroxy ester 10: ^{1}H NMR δ 4.40 (m, 1H), 3.99 (m, 4H), 3.76 (s, 3H), 3.69 (d, J = 5.4, 1H, OH), 2.28 (dd, J =14.8, 3.2, 1H), 2.15 (dd, J =14.8, 7.5, 1H), 1.38 (s, 3H); ^{13}C NMR δ 174.0 (0), 109.2 (0), 67.7 (1), 64.1 (2), 64.0 (2), 51.8 (3), 41.4, (2) 24.0 (3). Anal. Calcd for $C_8H_{14}O_5$: C, 50.5; H, 7.4. Found: C, 50.6; H, 7.6.

Adduct 11 (one diastereomer): mp 174−175 °C; IR 3480, 3380, 1745 cm^{-1}; ^{1}H NMR δ 7.49 (d, J =7.3, 2H), 7.21 (m, 8H), 5.73 (d, J =10.2, 1H, NH), 4.66 (d, J =10.2, 1H), 4.64 (s, 1H, OH), 3.88 (m, 4H), 3.67 (s, 3H), 2.22 (d, J =14.9, 1H), 1.53 (d, J =14.9, 1H), 1.14 (s, 3H); ^{13}C NMR δ 174.1 (0), 140.6 (0), 135.7 (0), 131.8 (1), 128.6 (1, 2C), 128.3 (1, 2C), 128.0 (1, 2C), 127.8 (1), 126.7 (1, 2C), 109.4 (0), 78.00 (0), 64.1 (2), 63.8 (2), 63.3 (1), 52.6 (3), 43.6 (2), 24.6 (3). Anal. Calcd for $C_{21}H_{25}NO_7S$: C, 57.9; H, 5.8; N 3.2. Found: C, 57.6; H, 5.8; N, 3.2.

(*E* and *Z*),(2*S*)-*N*-Benzyl-5-[1′-(methoxycarbonyl)-2′-(2″-methyl-1″,3″-dioxolan-2-yl)ethylidene]proline *tert*-Butyl Ester (14). 2-Hydroxy ester **10** (12.1 g, 64.0 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (16.4 g, 80.0 mmol)[10] were dissolved in CH_2Cl_2 (190 mL) and the solution was cooled at −15 °C. Freshly distilled (from P_2O_5) Tf_2O (11.8 mL, 19.9 g, 70.4 mmol) was added at 0.84 mL/min, and the resulting white suspension was stirred, keeping the temperature below −5 °C, for 2 h. Cold hexanes (200 mL) were added, the reaction mixture was filtered, the white solid was washed with additional hexanes (100 mL), and the combined filtrates were evaporated at rt. The residue was diluted with hexanes and filtered, and the filtrate was evaporated and dried (in vacuo, 30 min). The resulting crude triflate **12** was submitted to the next reaction step.

The crude triflate **12** was dissolved in CH_3CN (36 mL), thiolactam **13** (16.8 g, 57.6 mmol)[6a] was added, and the solution was stirred overnight at rt. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (207 mL), PPh_3 (18.5 g, 70.4 mmol) was added, and the resulting solution was allowed to warm to rt over 1 h. After cooling to −15 °C, *N*-methylpiperidine (9.72 mL, 7.93 g, 80.0 mmol) was added at 0.57 mL/min and the mixture was allowed to warm to −5 °C (NaCl/ice/H_2O bath) and stirred for 26.5 h during which time the temperature increased to −2 °C. The reaction mixture was washed with 0.5 M KH_2PO_4 (2 × 350 mL) and saturated $NaHCO_3$ (350 mL). The aqueous washes were extracted separately with CH_2Cl_2 (100 mL each), and the combined organic phase was dried, filtered, and evaporated to give a yellow gummy solid which was triturated with 4/1 hex/EtOAc (100 mL), the mixture filtered, and the filter cake rinsed with additional 4/1, hex/EtOAc solution. The combined filtrates were evaporated and chromatographed (a, 7/3 hex/EtOAc) to afford the vinylogous carbamate **14** (16.93 g, 68%), as a 6/5 mixture of diastereomers (^{1}H NMR ratio): ^{1}H NMR δ 7.28 (m, 3H), 7.15 (m, 2H), 5.55 (d, J = 17.3, 0.57 H), 4.56 (d, J = 15.1, 0.43H), 4.30 and 4.29 (2d, J = 17.4 and 14.9, 1H), 3.89 (m, 5H), 3.65 (s, 3 × 0.57H), 3.57 (s, 3 × 0.43H), 3.11, 2.89, and 2.68 (3m, 4H), 2.03 (m, 2H), 1.44 (2s, 9H), 1.29 and 1.23 (2s, 3H); ^{13}C NMR δ 172.1, 171.6, 171.3 and 169.0 (0, 2C), 159.7 and 159.0 (0, 1C), 138.4 and 136.8 (0, 1C), 128.6, 128.3, 127.2, 127.0 and 126.3 (1, 5C), 111.4 and 110.3 (0, 1C), 90.5 and 89.6 (0, 1C), 81.5 and 81.4 (0, 1C), 67.1 and 65.9 (1, 1C), 65.1, 65.0, 64.8 and 64.7 (2, 2C), 53.9 and 51.4 (2, 2C), 50.7 and 50.5 (3, 1C), 40.2, 36.0, 34.0 and 32.5 (2, 2C), 27.9 (3, 3C), 26.6 and 24.9 (2, 1C), 25.2 and 24.2 (3, 1C). Anal. Calcd for $C_{24}H_{33}NO_6$: C, 66.8; H, 7.7; N, 3.3. Found: C, 66.6; H, 7.8; N, 3.3.

(2*S*,5*R*,1′*R* and *S*)-*N*-Benzyl-5-[1′-(methoxycarbonyl)-2′-(2′-methyl-1″,3″-dioxolan-2-yl)ethyl]proline *tert*-Butyl Ester (15a and 15b). To a degassed solution of vinylogous carbamate **14** (13.0 g, 30.1 mmol) in dry EtOAc (147 mL) was added 5% Pt/C (1.47 g), and the resulting suspension was hydrogenated (50 psi), for 20 h. The solution was filtered (Celite), the filter cake was rinsed with MeOH and CH_2Cl_2,

and the combined filtrate was evaporated to provide 12.12 g of crude. Purification by column chromatography (b, 3/2, hex/EtOAc) afforded saturated esters **15** (11.83 g, 91%) as a 1/1 mixture of diastereomers: ^{1}H NMR δ 7.28 (m, 5H), 4.01 and 3.97 (2d, J = 13.5 and 13.4, 1H), 3.89 (m, 4H), 3.71 (s, 3 × 0.5 H), 3.68 (d, J = 13.6, 0.5H), 3.66 (s,3 × 0.5 H), 3.60 (d, J = 13.6, 0.5 H), 3.27 (m, 1H), 3.11 (m, 0.5 H), 2.98 (q, J = 6.5, 0.5 H), 2.81 (m, 1H), 2.25 and 1.92 (2m, 6H), 1.32, 1.31 and 1.29 (3s, 12H); ^{13}C NMR δ 175.7, 175.1, 173.6 and 173.3 (0, 2C), 138.5 and 138.4 (0, 1C), 129.4, 129.3, 128.0, 127.9, 126.9 and 126.8 (1, 5C), 109.5 and 109.1 (0, 1C), 79.9 and 79.7 (0, 1C), 67.1, 67.0, 66.6 and 65.7 (1, 2C), 64.5 (2, 2C), 58.8 and 57.9 (2, 1C), 51.4 and 51.2 (3, 1C), 44.0, 43.7 (1, 1C), 38.7 and 34.9 (2, 1C), 28.7 and 28.4 (2, 1C), 27.7 (3, 3C), 26.91 and 26.89 (2, 1C), 24.3 and 24.1 (3, 1C); Anal. Calcd for $C_{24}H_{35}NO_6$: C, 66.5; H, 8.1; N, 3.2. Found: C, 66.5; H, 8.2; N, 3.2.

(2*S*,5*R*,1′*R* and *S*)-*N*-Benzyl-5-[1′-(methoxycarbonyl)-3′-oxobutyl]proline (16a and 16b). A solution of ester ketals **15** (11.8 g, 27.3 mmol) in *i*-PrOH (116 mL), H_2O (116 mL), and glacial acetic acid (23.2 mL) was refluxed for 9 h, cooled, poured into 1.5 M KH_2PO_4 (477 mL) and extracted with 4/1, $CHCl_3$/*i*-PrOH (3 × 235 mL). The combined organic phase was dried, filtered, and evaporated, and the remaining AcOH was removed by azeotropic distillation with toluene to provide crude acids **16** (9.25 g, quantitative), as a 1/1 mixture of diastereomers. This material is suitable for use in the next reaction step without further purification. Purification by column chromatography (b, 92/8, CH_2Cl_2/MeOH) decrease the yield to 85% and allowed isolation of separate pure diastereomers **16a** and **16b**. Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.8; H, 7.0; N, 4.2. Found: C, 64.5; H, 7.1; N, 4.2.

Keto acid 16a: mp 103−104 °C; $[\alpha]^{22}_D$ −12.1° (c 1.40, $CHCl_3$); IR 1755, 1725 cm^{-1}; ^{1}H NMR δ 7.29 (m, 3H), 7.24 (m, 2H), 3.97 (d, J = 13.1, 1H), 3.75 (s, 3H), 3.66 (d, J = 13.1, 1H), 3.58 (dd, J = 7.8, 5.5, 1H), 3.38 (q, J = 7.1, 1H), 3.17 (m, 1H), 3.02 (dd, J = 17.8, 9.9, 1H), 2.61 (dd, J = 17.8, 3.3, 1H), 2.20 (s, 3H), 2.11 (m, 2H), 1.88 (m, 1H), 1.60 (m, 1H); ^{13}C NMR δ 206.2 (0), 174.2 (0), 173.8 (0), 135.3 (0), 129.5 (1,2C), 128.9 (1, 2C), 128.3 (1), 66.3 (1), 66.1 (1), 58.9 (2), 52.4 (3), 43.4 (1), 41.5 (2), 30.0 (3), 28.54 (2), 28.47 (2).

Keto acid 16b: $[\alpha]^{23}_D$ +84.7 (c 1.25, $CHCl_3$); IR 1750, 1720 cm^{-1}; ^{1}H NMR δ 7.31 (m, 5H), 4.13 (d, J = 12.9, 1H), 3.76 (s, 3H), 3.67 (d, J = 12.9, 1H), 3.56 (dd, J = 8.9, 3.6, 1H), 3.45 (m, 1H), 3.12 (m, 1H, overlap), 3.04 (dd, J = 18.1, 9.5, 1H), 2.45 (dd, J = 18.2, 4.6, 1H), 2.20 (s, 3H), 2.06 (m, 2H), 1.88 (m, 1H), 1.57 (m, 1H); ^{13}C NMR δ (ppm) 205.7 (0), 174.6 (0), 172.8 (0), 135.5 (0), 129.5 (1,2C), 128.9 (1, 2C), 128.3 (1), 66.8 (1), 65.2 (1), 57.4 (2), 52.5 (3), 43.1 (2), 41.2 (1), 29.6 (3), 28.7 (2), 26.8 (2).

(1*R*,2*R*,3*R*,4*S*)- and (1*R*,2*S*,3*S*,4*S*)-3-Acetyl-7-benzyl-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (17 and 18) and (3*S*,4a*R*,5*S*,6a*S*)-5-(methoxycarbonyl)-6a-methyloctahydro-2-oxooxazolo[2,3,4-*cd*]pyrrolizidine (19). A cold (−10 °C) solution of crude keto acids **16a** and **16b** (2.44 g, 7.33 mmol) in 1,2-DCE (13.7 mL) was slowly cannulated into a solution of oxalyl chloride (0.83 mL, 1.21 g, 9.51 mmol) and DMF (0.10 mL, 110 mg, 1.4 mmol) in 1,2-DCE (25.0 mL) cooled at −10 °C. The solution was stirred for 1 h, allowing it to reach −5 °C, and then stirring was continued for 25 min at rt. *tert*-Butyl alcohol (18 mL) and 1,2-DCE (116 mL) were added, and the solution was immersed in a preheated bath (65 °C) and stirred for 16 h under an Ar atmosphere. The mixture was allowed to cool to rt and then washed with saturated $NaHCO_3$ (200 mL), and the aqueous washing was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic phase was dried, filtered, and evaporated to give a brown oil (1.91 g) which was chromatographed (b, 7/3 hex/EtOAc) to afford a mixture of bicyclic ketones **17** and **18** (1.07 g, 51%). Further elution (9/1, $CHCl_3$/MeOH) provided the ring-fused lactone **19** (360 mg, 22%), which was further purified by a second chromatography (b, 9/1 $CHCl_3$/MeOH) to give an 11% yield of pure ring-fused lactone **19**.

The mixture of bicyclic ketones **17** and **18** was separated into pure components by chomatography (b, 7/3, hex/EtOAc), to provide the less polar isomer **17** (381 mg, 34.3%) and the more polar isomer **18** (140 mg, 12.5%). Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.1; H, 7.4; N, 4.8. Found: C, 70.7; H, 7.7; N, 4.9.

17: $[\alpha]^{22}_D$ −5.2° (c 1.04, $CHCl_3$); IR 1735, 1715 cm^{-1}; ^{1}H NMR δ 7.26 (m, 5H), 3.69 (s, 3H), 3.58 (m, 3H), 3.55 (d, J = 13.5, 1H), 3.46 (d, J = 13.5, 1H), 2.88 (d, J = 4.5, 1 endo-H), 2.14 (s, 3H), 1.94 (m, 1H), 1.81 (m, 1H), 1.51 (m, 1H), 1.40 (m, 1H); ^{13}C NMR δ 206.7 (0), 173.2 (0), 139.2 (0), 128.2 (1, 2C), 128.1 (1, 2C), 126.9 (1), 62.3 (1), 62.0 (1), 58.7 (1), 51.9 (3), 51.2 (2), 47.9 (1), 28.3 (3), 27.2 (2), 23.3 (2).

18: $[\alpha]^{23}_D$ +15.8° (c 1.45, $CHCl_3$); IR 1730, 1715 cm^{-1}; ^{1}H NMR δ 7.29 (m, 5H), 3.68 (m, 3H, overlap), 3.67 (s, 3H), 3.58 (d, J = 13.7 , 1H), 3.53 (d, J = 13.7, 1H), 3.03 (d, J = 4.3, 1 endo-H), 2.16 (s, 3H), 1.99 (m, 1H), 1.74 (m, 1H), 1.41 (m, 1H), 1.23 (m, 1H); ^{13}C NMR δ 206.4 (0), 174.0 (0), 139.2 (0), 128.2 (1, 2C), 128.1 (1, 2C), 126.9 (1), 63.5 (1), 61.6 (1), 58.5 (1), 52.0 (3), 51.2 (2), 47.8 (1), 29.6 (3), 26.8 (2), 22.7 (2).

19: $[\alpha]^{23}_D$ −18.2° (c 1.13, $CHCl_3$); IR 1770, 1740 cm^{-1}; H^1 NMR δ 3.97 (q, J = 7.6, 1H, overlap), 3.92 (dd, J = 7.3, 2.1, 1H), 3.72 (s, 3H), 2.85 (dt, J = 11.3, 7.6, 1H), 2.79 (dd, J = 14.1, 11.3, 1H), 2.48 (dd, J =14.1, 11.3, 1H), 2.40 (m, 1H), 2.31 (m, 1H), 2.22 (m, 1H), 1.62 (m, 1H, overlap), 1.58 (s, 3H); ^{13}C NMR δ (ppm) 177.4 (0), 172.8 (0), 107.0 (0), 70.2 (1), 63.6 (1), 52.1 (1), 48.4 (3), 42.1 (2), 31,3 (2), 31.2 (2), 25.7 (3). Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.7; H, 6.7; N, 6.2. Found: C, 58.3; H, 6.8; N, 6.0.

(1*R*,2*R*,3*R*,4*S*)- and (1*R*,2*S*,3*S*,4*S*)-3-Acetyl-7-(*tert*-butoxycarbonyl)-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (20 and 21). $(BOC)_2O$ (4.26 g, 19.5 mmol) was added to a solution of a mixture of benzyl amines **17** and **18** (1.40 g, 4.88 mmol) in MeOH (57.4 mL) followed by 10% Pd/C (280 mg), and the resulting suspension was hydrogenated (50 psi, rt) for 7 h. The reaction mixture was filtered, the insoluble material was thoroughly washed with MeOH and CH_2Cl_2, and the combined filtrates were evaporated. The residue was diluted with ether, washed with saturated $NaHCO_3$ and saturated NaCl, dried, and evaporated leaving an oil which was chromatographed (b, 7/3 hex/EtOAc) to afford carbamates **20** and **21** (1.18 g, 82%), as a white solid.

Using the same procedure, the less polar diastereomer **17** (360 mg, 1,25 mmol) gave the related carbamate **20** (305 mg, 82%), and the more polar diastereomer **18** (110 mg, 0.38 mmol) gave **21** (95 mg, 83%). Anal. Calcd for $C_{15}H_{23}NO_5$: C, 60.6; H, 7.8; N, 4.7. Found: C, 60.4; H, 8.0; N, 4.6.

20 (trans isomer): mp 107−108 °C; $[\alpha]^{22}_D$ −47.1° (c 1.01, $CHCl_3$); IR 1715, 1695 cm^{-1}; ^{1}H NMR δ 4,49 (m, 2H), 3.73 (dt, J = 2.1, 5.1, 1H, overlap), 3.06 (d, J = 4.5, 1H), 2.30 (s, 3H), 1.92 (m, 1H), 1.73 (m, 1H), 1.60 (m, 1H), 1.44 (m, 1H, overlap), 1.41 (s, 9H); ^{13}C NMR δ 204.4 (0), 172.1 (0), 154.3 (0), 80.4 (0), 59.3 (1), 58.7 (1), 58.0 (1), 51.9 (3), 46.9 (1), 29.2 (2), 28.2 (3), 27.9 (3, 3C), 25.1 (2).

21 (the other trans isomer): $[\alpha]^{23}_D$ +31.8° (c 1.73, $CHCl_3$); IR 1730, 1700 cm^{-1}; ^{1}H NMR δ 4.60 (m, 1H), 4.52 (m, 1H), 3.70 (s + m, 3 + 1H), 3.11 (d, J = 5.1, 1 endo-H), 2.22 (s, 3H), 1.85 (m, 1H), 1.68 (m, 1H), 1.50 (m, 1H, overlap), 1.43 (s, 9H), 1.29 (m 1H); ^{1}H NMR δ (C_6D_6) 4.43 (m, 2H), 3.78 (dt, J = 2,0, 5.0, 1H), 3.32 (s, 3H), 3.23 (d, J = 5.0, 1 endo-H), 1.54 (s, 3H), 1.42 (s, 9H), 1.34 (m, 2H), 1.16 (m, 1H, overlap), 1.00 (m 1H); ^{13}C NMR δ 205.0 (0), 172.8 (0), 154.5 (0), 80.3 (0), 60.5 (1), 58.0 (1), 57.9 (1), 52.2 (3), 48.0 (1), 29.7 (3), 29.3 (2), 28.1 (3, 3C), 24.5 (2).

(*Z*,1*S*,3*R*,4*R*)- and (*Z*,1*S*,3*S*,4*R*)-2-(((1-*tert*-Butyldimethylsilyl)oxy)ethylidene)-7- (*tert*-butoxycarbonyl)-3-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (24a and 24b). A suspension of NaH (177 mg, 80% oil dispersion, 5.90 mmol) was washed with hexanes (3 × 1.5 mL) and THF (2 × 1.5 mL). A solution of 1,4-keto ester **20** and **21** (350 mg, 1.18 mmol) and MeOH (5 μL, 4 mg, 0.12 mmol) in THF (5.40 mL) was added to this suspension of washed NaH in THF (8.70 mL) at 0 °C, and the mixture was stirred for 15.5 h at this temperature. Then the supernatant of a centrifuged solution of TBDMSCl (445 mg, 2.95 mmol) and Et_3N (0.14 mL, 102 mg, 1.01 mmol) in THF (1.10 mL) was added and stirring was continued for 7.5 h at rt. The reaction mixture was poured into 1 M KH_2PO_4 (24 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phase was washed with 5%

$NaHCO_3$ (50 mL), dried, filtered, and evaporated to give 610 mg of residue. Purification by column chromatography (b, 4/1, hex/EtOAc) provided 1-silyloxy alkenes **24** (340 mg, 70%), as a mixture of epimers at C-3, and starting material (40 mg, 11%). Before eluting the crude 1-silyloxy alkenes **24**, the SiO_2 column was deactivated with 16/4/1 hex/EtOAc/Et_3N (105 mL) and then rinsed with 4/1 hex/EtOAc (100 mL). Pure diastereomers **24a** and **24b** could be obtained by repeating the chromatography.

24a: ^1H NMR δ (peaks of the major rotamer) 4.53 (m, 1H), 4.40 (m, 1H), 3.66 (s, 3H), 3.59 (m, 1H), 1.91 (m, 1H, overlap), 1.88 (d, J = 1.8, 3H), 1.61 (m, 3H), 1.44 (s, 9H), 0.86 (s, 9H), 0.11 and 0.08 (2s, 6H); ^{13}C NMR δ (rotamers) 171.4, 79.9, 59.9, 51.5, 50.0, 29.1, 28.2 (3 C), 25.5 (3 C), 19.5, 17.9, −3.4, −3.7.

24b: ^1H NMR δ (peaks of the major rotamer) 4.67 (m, 1H), 4.42 (m, 1H), 3.64 (s, 3H), 3.09 (s, 1H), 1.88 (m + d, J = 1.18, 1 + 3 H), 1,46 (m, 3 H, overlap), 1.43 (s, 9 H), 0.86 (s, 9 H), 0.12 and 0.10 (2s, 6H); ^{13}C NMR δ (rotamers) 171.5, 141.1, 117.6, 79.5, 60.6, 57.80 and 57.60, 52.3, 51.7, 30.7, 29.46 and 28.51, 28.2 (3 C), 25.5 (3C), 19.5, 17.9, −3.6.

(1*S*,3*R* and *S*,4*R*)-7-(*tert*-Butoxycarbonyl)-3-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptan-2-one (25). Ozone (1.8 mL/min) was passed through a solution of silyloxy alkenes **24** (490 mg, 1.19 mmol) in MeOH (50.0 mL) and pyridine (1.00 mL) at −78 °C until a light blue color persisted. After sweeping the solution first with O_2 and then with N_2, Ph_3P (700 mg, 2.67 mmol) was added and stirring was continued for 1 h at −78 °C and 1 h at rt. The reaction mixture was evaporated, and the residue was taken up in CH_2Cl_2 and washed with 5% aqueous HCl and saturated $NaHCO_3$. Drying, filtering, and evaporating gave an oil, which was purified by chromatography (b, 7/3 hex/EtOAc) to afford 1,3-keto esters **25** (260 mg, 81%) as a 1/1 mixture of diastereomers: ^1H NMR δ 4.85 (d, J = 4.9, 0.5 H), 4.74 (dd, J = 5.1, 4.1, 0.5 H), 4.37 (d, J = 4.3, 0.5 H), 4.33 (d, J = 5.6, 0.5 H), 3.76 (s, 3 × 0.5 H), 3.74 (s, 3 × 0.5 H), 3.46 (d, J = 5.1 , 0.5 H), 3.01 (s, 0.5 H), 2.00 (m, 2 H), 1.64 (m, 2 H), 1.46 (s, 9H); ^{13}C NMR δ 201.8 (0), 201.7 (0), 166.8 (0), 166.0 (0), 154.2 (0), 153. 7(0), 81.01 (0), 80.6 (0), 64.1 (1), 62.7 (1), 59.4 (1), 58.6 (1), 58.3 (1), 57.6 (1), 52.4 (3), 52.2 (3), 27.9 (3, 3C), 27.1 (2), 24.6 (2), 24.4 (2), 23.7 (2). Anal. Calcd for $C_{13}H_{19}NO_5$: C, 58.0; H, 7.1; N, 5.2. Found: C, 58.0; H, 7.4; N, 5.0.

(1*S*,4*R*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one [(+)-1]. A solution of 1,3-keto ester **25** (110 mg, 0.41 mmol) in 10% HCl (25 mL) was refluxed for 3.5 h under an Ar atmosphere. The solution was allowed to cool to rt and evaporated; the remaining water was removed by azeotropic distillation with EtOH. The crude free amine was dissolved in CH_2Cl_2 (10 mL), and Et_3N (0.2 mL, 729 mg, 7.21 mmol) and $(BOC)_2O$ (131 mg, 0.6 mmol) were added. The solution was stirred for 6 h at rt and then washed with saturated Na_2CO_3. The organic layer was dried, filtered, and evaporated to provide an oily residue, which was chromatographed (b, 4/1, hex/EtOAc) to yield ketone (+)-**1** (73 mg, 85%); $[\alpha]^{22}_D$ +73.5° (*c* 1.00, $CHCl_3$); IR 1760, 1690 cm^{-1}; ^1H NMR δ 4.56 (t, J = 4.5, 1H), 4.25 (d, J = 4.7, 1H), 2.47 (dd, J = 17.4, 5.1, 1H), 1.99 (m + d, J = 17.4, 2 + 1 H), 1.59 (m, 2H), 1.45 (s, 9H); ^{13}C NMR δ 209.4 (0), 155.0 (0), 80.8 (0), 63.9 (1), 56.0 (1) 45.2 (2) 28.1(3, 3C), 27.5 (2), 24.3 (2). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.5; H, 8.1; N, 6.6. Found: C, 62.7; H, 8.2; N, 6.6.

(1*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one [(−)-1]. Bis-Enolization Pathway. Procedure a: A solution of LDA/THF was prepared at 0 °C, from diisopropylamine (0.11 mL, 79.4 mg, 0.78 mmol), 2.16 M BuLi (0.34 mL, 0.73 mmol), and THF (0.70 mL), by stirring for 20 min. This solution was cooled at −78 °C, and a solution of 1,3-keto esters **20** and **21** (87.7 mg, 0.30 mmol) in THF (0.30 mL) was added slowly. The stirred solution was maintained at −78 °C for 30 min, and TMSCl (0.13 mL, 111 mg, 1.02 mmol) was added. After 15 min at this temperature, the mixture is allowed to warm to rt during 1 h and then evaporated in vacuo at rt. The residue was mixed with pentane and filtered and the solvent evaporated to give crude bis-TMS enol ethers **26** (120 mg, 92%). A ^1H NMR (C_6D_6) spectrum of this crude was recorded and showed TMS peaks (diastereomers, rotamers) and no methyl ketone peaks.

Ozone (2.0 mL/min) was passed through a solution of bis-silyl enol ethers **26** (120 mg, 0.27 mmol) in CH_2Cl_2 (10.0 mL) and pyridine (0.25 mL) at −78 °C until a light blue color persisted. After sweeping the solution first with O_2 and then with N_2, Me_2S (0.24 mL, 203 mg, 3.27 mmol) was added and stirring was continued for 20 min at −78 °C and for 1 h at rt. The reaction mixture was evaporated, and the residue was dissolved in toluene (5 mL) and refluxed for 4 h. Evaporation gave a brown oil, which was purified by chromatography (b, 4/1 hex/EtOAc) to afford the ketone (−)-**1** (10.7 mg, 17%).

Procedure b (basic treatment after decarboxylation): Bis-enolization followed by ozonolysis of 1,3-keto esters **20** and **21** (100 mg, 0.34 mmol) was performed as described in procedure a. After sweeping with N_2, MeOH (2 mL) and then Me_2S (0.30 mL, 254 mg, 4.08 mmol) were added to the −78 °C solution and the mixture was allowed to reach rt overnight. The solvents were removed to provide 120 mg of crude. A ^1H NMR spectrum of this crude indicated the presence of a major product containing methyl ester, *tert*-butyl, and TMS groups (compound **27a**). This crude was dissolved in toluene (67.5 mL) and the solution was refluxed for 3.5 h. The reaction mixture was cooled to rt, mixed with 1.84 M KOH/H_2O, and stirred for 5 min, the layers were separated, and the basic treatment was repeated three additional times (10 mL of 1.84 M KOH/H_2O total). The organic phase was diluted with ether, washed with saturated NaCl, dried, and evaporated to provide 40 mg of crude which was chromatographed (b, 4/1, hex/EtOAc) to yield ketone (−)-**1** (14.0 mg, 19%): $[\alpha]^{22}_D$ −72.6° (*c* 1.00, $CHCl_3$); ^1H NMR spectrum is identical the the one shown for its enantiomer (+)-**1a**.

The basic aqueous phase was stirred for 4 h at rt, the pH was adjusted to 2.3 with 1 M H_3PO_4, and it was extracted with 4/1 $CHCl_3$/*i*-PrOH (4 × 20 mL). The combined organic phase was dried and evaporated to give 60 mg of crude. A ^1H NMR spectrum of this crude reflected a single compound containing a *tert*-butyl group and the absence of methyl ester and TMS groups, consistent with the 1,4-diacid **27b** (59% yield). However, treatment with NIS and subsequent refluxing (3 h) in benzene or heating with $NaIO_4$ (H^+, 55 °C, 30 h) produced none of ketone (−)-**1**.

(1*R*,2*R*,3*R*,4*S*)- and (1*R*,2*S*,3*S*,4*S*)-7-(*tert*-Butoxycarbonyl)-3-carboxy-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]-heptane (30 and 33). To a 1 M KHMDS/THF solution (2.02 mL, 2.02 mmol), diluted with additional THF (3.50 mL) and cooled at −78 °C, was added a solution of 1,4-keto esters **20** and **21** (380 mg, 1.28 mmol) in THF (4 mL) at 0.17 mL/min. The resulting solution was stirred at −78 °C for 45 min, and TMSCl (0.51 mL, 437 mg, 4.02 mmol) was added slowly. The mixture was stirred at −78 °C for 10 min and then allowed to warm to 0 °C over 30 min. It was diluted with hexanes (10 mL) and washed with 0.01 M phosphate buffer (pH 7, 2 × 15 mL). The separate aqueous layers were extracted with hexanes (2 × 20 mL), and the combined organic phase was dried, filtered, and evaporated to provide crude TMS-enol ethers **29** and **32** which were submitted to the next reaction step without further purification.

A solution of crude silyloxy alkenes **29** and **32** in CH_2Cl_2 (6.60 mL) and MeOH (8.25 mL) was treated with excess O_3 at −78 °C. After O_2 and N_2 purges, the −78 °C solution was treated with Me_2S (0.40 mL, 338 mg, 5.45 mmol), stirred at this temperature for 10 min, and allowed to warm up to rt over 1 h. Evaporation gave a mixture of DMSO and 1,4-keto acids **30** and **33**, as a mixture of two trans isomers (530 mg). Chromatographic purification led to significant loss; however, chromatography (b, 9/1, CH_2Cl_2/EtOH) did allow isolation of a single 1,4-keto acid **30** (70 mg, 44%): ^1H NMR δ 9.33 (br s, 1H, COOH), 4.61 (br s, 1H), 4.51 (br s, 1H), 3.73 (s, 3H), 3.58 (dt, J = 1.8, 5.1, 1H), 3.05 (d, J = 5.1, 1H), 1.88 (m, 1H), 1.72 (m, 1H), 1.57 (m, 1H), 1.47 (m, 1H, overlap), 1.42 (s, 9H); ^{13}C NMR δ (rotamers) 176.8 (0), 171.7 (0), 154.6 (0), 80.7 (0), 60.4 (1), 58.2 (1), 52.2 (3), 50.2 (1), 49.5 (1) 29.0 (2), 28.2 (3, 3C), 24.9 (2).

Using the procedure described above, 1,4-keto ester **20** (480 mg, 1.75 mmol) produced a single diastereomeric acid ester **30**, 640 mg crude, and 1,4-keto esters **21** (180 mg, 0.64 mmol) gave the acid ester **33**, 230 mg crude. These crudes were

contaminated with DMSO and small amounts of cumene (stabilizing agent in the KHMDS solution) and were submitted to the next reaction step as such.

33: ^{1}H NMR δ 4.56 (m, 2H), 3.74 (s, 3H), 3.67 (dt, J = 2.0, 5.1), 3.00 (d, J = 5.1, 1H), 1.89 (m, 1H), 1.76 (m, 1H), 1,58 (m, 1H), 1.46 (m, 1H, overlap), 1.44 (s, 9H); ^{13}C NMR δ (rotamers) 173.9 (0), 172.6 (0), 80.3 (0), 60.2 (1), 58.0 (1), 52.2 (3), 49.9 (1), 49.5 (1), 29.0 (2), 28.0 (3, 3C), 24.9 (2).

(1*R*,2*R*,4*S*)- and (1*R*,2*S*,4*S*)-7-(*tert*-Butoxycarbonyl)-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (31 and 34). To a solution of crude acid esters **30** and **33** (530 mg) in THF (6.75 mL) at 0 °C were added Et_3N (0.28 mL, 204 mg, 2.02 mmol) and isobutyl chloroformate (0.26 mL, 274 mg, 2.00 mmol). After 15 min, a solution of *N*-hydroxy-2-thiopyridone (345 mg, 2.71 mmol, crystallized from EtOH)[23] and Et_3N (0.38 mL, 277 mg, 2.74 mmol) in THF (7 mL) was added and the mixture was allowed to warm to rt during 1 h, protected from light. The precipitate of $Et_3NH^+Cl^-$ was filtered off and washed with dry THF. The yellow filtrate was irradiated for 1.5 h, in the presence of 1,1-dimethylethanethiol (0.86 mL, 1.22 g, 13.6 mmol), with two tungsten lamps (~100 W) at rt (water bath). The reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ and saturated NaCl. Drying and evaporating gave a residue which was chromatographed (b, 9/1 hex/EtOAc) to provide methyl ester **31** (131 mg) and methyl ester **34** (49 mg), 40 and 15% yield, respectively, from 1,4-keto esters **20** and **21**.

(1*R*,2*R*,4*S*)-Methyl ester 31 (less polar, H-2 exo): mp 91–92 °C; IR 1735, 1695 cm^{-1}; $[\alpha]^{23}_D$ −22.6° (*c* 1.01, $CHCl_3$); ^{1}H NMR δ 4.39 (m, 1H), 4.21 (m, 1H), 3.71 (s, 3H), 3.46 (m, 1H), 1.96 (m, 1H), 1.85 (dd, J = 12.4, 4.8, 1H), 1.78 (m, 1H), 1.72 (m, 1H), 1.48 (m, 2H, overlap), 1.45 (s, 9H); ^{13}C NMR δ (rotamers) 173.1 (0), 155.3 (0), 79.8 (0), 58.3 (1), 57.1 (1), 51.8 (3), 46.3 (1), 32.4 (2), 29.2 (2), 28.2 (3, 3C), 25.4 (2). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5. Found: C, 60.9; H, 8.1; N, 5.5.

(1*R*,2*S*,4*S*)-Methyl ester 34 (more polar, H-2 endo): IR 1740, 1770 cm^{-1}; $[\alpha]^{23}_D$ −10.1° (*c* 1.06, $CHCl_3$); ^{1}H NMR δ 4.50 (m, 1H), 4.30 (m, 1H), 3.70 (s, 3H), 2.55 (dd, J = 8.9, 5.1, 1H), 2.28 (m, 1H), 1.80 (m, 2H), 1.61 (dd, J = 12.4, 8.9, 1H), 1.43 (s, 9H), 1.42 (m, 2H, overlap); ^{13}C NMR δ 173.6 (0), 154.7 (0), 79.5 (0), 59.1 (1), 55.8 (1), 51.9 (3), 47.3 (1), 33.1 (2), 29.3 (2), 28.7 (2), 28.1 (3, 3C). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5. Found: C, 61.1; H, 8.3; N, 5.5.

Using the procedure described above, the crude acid ester **30** (640 mg, single diast) gave methyl ester **31** (210 mg, 51% from bicycle **20**), and crude acid ester **33** (240 mg, single diast) provided methyl ester **34** (88 mg, 57% from bicycle **21**).

(*E* and *Z*,1*R*,4*S*)-2-(1′-Methoxy-1′-((trimethylsilyl)oxy)-methylidene)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptane (35). A solution of LDA/THF was prepared at 0 °C from diisopropylamine (0.15 mL, 108 mg, 1.07 mmol), BuLi (0.43 mL, 2.16 M, 0.93 mmol), and THF (3.7 mL) by stirring for 20 min and then cooled to −78 °C, and a solution of methyl ester **31** (200 mg, 0.78 mmol) in THF (2.0 mL) was added at 0.17 mL/min. The stirred solution was maintained at −78 °C for 40 min, and TMSCl (0.30 mL, 257 mg, 2.36 mmol, distilled from CaH_2) was added. After 10 min at this temperature, the mixture was allowed to warm to rt during 45 min and then evaporated at rt. The residue was mixed with pentane and filtered and the filtrate evaporated to give crude ketene methyl-TMS acetals **35** (249 mg, 97%), as a 8/3 mixture of geometric isomers, which were used in the next reaction step without further purification: ^{1}H NMR δ (C_6D_6, rotamers) 4.89 (m, 1H), 4.30 (m, 1H), 3.30 (s, 3 × 0.27 H), 3.25 (s, 3 × 0.73 H), 2.55 (2m, 1H), 1.89 (m, 2H), 1.69 (m, 1H), 1,51 (m, 1H), 1.42 and 1.41 (2s, 9 H), 1.13 (m, 1H), 0.19 and 0.11 (2s, 6H).

Using the procedure described above, methyl ester **34** (84 mg, 0.33 mmol) was transformed to the crude mixture of geometric isomers **35** (110 mg, quant), in the ratio 1/9.

(1*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one [(−)-1] and (1*R*,2*S* and 1*R*,2*R*)-7-(*tert*-Butoxycarbonyl)-2-hydroxy-2-(methoxycarbonyl)-7-azabicyclo[2.2.1]heptane (37). A suspension of crude ketene methyl-TMS acetals **35** (249 mg, ratio 8/3) in CH_2Cl_2 (15.0 mL) and *tert*-BuOH (0.50 mL) was treated with excess O_3 at −78 °C. After O_2 and N_2 purges, the −78 °C solution was treated with Me_2S (0.30 mL, 254 mg, 4.01 mmol) and stirred at this temperature for 10 min and at rt overnight (10 h). Evaporation gave a mixture of DMSO, ketone (−)-**1**, and 2-TMSO ester **36** (255 mg). This mixture was dissolved in THF (1.4 mL) and treated with TBAF (0.78 mL, 1 M) at rt for 1 h, and then AcOH (0.05 mL, 17.4 M, 0.87 mmol) was added and stirring was continued for 5 min. The solvent was evaporated and the residue was chromatographed (b), eluting with 7/3 hex/EtOAc to afford ketone (−)-**1** (42 mg, 25% yield from methyl ester **31**) and then with 1/1 hex/EtOAc to give the 2-hydroxy ester **37** (125 mg, 59% yield from methyl ester **31**), as a mixture 4/1 of C-2 epimers.

Using the procedure described above, crude ketene methyl-TMS acetals **35** (110 mg, ratio 1/9) provided ketone (−)-**1** (18 mg, 27% yield from methyl ester **34**) and 2-hydroxy ester **37** (51 mg, 58% yield from methyl ester **34**).

Ketone (−)-1: $[\alpha]^{22}_D$ −73.6° (*c* 1.10, $CHCl_3$); ^{1}H NMR spectrum is identical to that of its enantiomer (+)-**1**.

2-Hydroxy ester 37: IR 3560, 1725, 1690 cm^{-1}; ^{1}H NMR δ (rotamers) 4.23 (m, 1H), 4.14 (m, 1H), 3.80 (s, 3 H), 3.38 and 3.04 (s and br s, 1H, OH), 2.54 (ddd, J = 12.7, 5.2, 2.7, 0.2 H), 2.33 (m, 0.2 H, overlap), 2.26 (d, J = 13.2, 0.8 H), 1.96–1.54 (m, ~4 H), 1.46 (s, 9H), 1.45 (m, 1H, overlap); ^{13}C NMR δ (rotamers) 175.9 and 172.8 (0, 1C), 155.8 (0), 83.2 and 79.4 (0, 1C), 80.0 (0), 62.7 (1), 56.3 (1), 53.3 and 52.7 (3, 1C), 42.8 and 42.6 (2, 1C), 28.3 and 28.2 (3, 3C), 27.7 (2), 23.2 (2). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.5; H, 7.8; N, 5.2. Found: C, 57.5; H, 7.7; N, 5.1.

(1*R*,2*R* and 1*R*,2*S*)-7-(*tert*-Butoxycarbonyl)-2-hydroxy-2-(hydroxymethyl)-7-azabicyclo[2.2.1]heptane (38). The 2-hydroxy ester **37** (125 mg, 0.48 mmol) and $CaCl_2$ (107 mg, 0.96 mmol) were dissolved in THF (0.7 mL) and EtOH (1.0 mL), and the solution was cooled at 0 °C. While being stirred, $NaBH_4$ (75 mg, 1.94 mmol) was added, the reaction mixture was stirred for 1.5 h at 0 °C and for 1.5 h while slowly warming to rt, the excess of $NaBH_4$ was quenched by slow addition of 10% tartaric acid (2.0 mL), and the mixture was extracted with ether (3 × 15 mL). The combined organic phase was washed with saturated $NaHCO_3$ (10 mL) and saturated NaCl (10 mL), the aqueous washes were back extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phase was dried, filtered, and evaporated to give crude diols **38** (92 mg, 82% yield), as a mixture of C-2 epimers. This crude material was submited to the next step without further purification: ^{1}H NMR δ 4.24 (m, 0.8 H), 4.13 (m, 0.8 H + 2 × 0.2 H), 3.70 (d, J = 11.7, 0.8 H), 3.58 (d, J = 11.6, 0.8 H), 3.49 and 3.47 (2d, 2 × 0.2 H), 2.25 (m, 0.2 H), 1.86–1.51 (m, ~4H), 1.46 and 1.44 (2s, 9H), 1.35 (m, 2H); ^{13}C NMR δ (rotamers) 156.4 and 155.3 (0, 1C), 81.7, 80.0 and 79.1 (0, 2C), 67.1 and 66.0 (2, 1C), 64.4 (1), 56.0 (1), 43.9 and 41.1 (2, 1C), 29.1 and 27.9 (2, 1C), 28.2 (3, 3C), 23.2 and 22.0 (2, 1C).

(1*R*,4*S*)-7-(*tert*-Butoxycarbonyl)-7-azabicyclo[2.2.1]-heptan-2-one [(−)-1] from Diol 38. A solution (pH = 4) of $NaIO_4$ (205 mg, 0.96 mmol) in H_2O (2.5 mL) was added to a cold (0 °C) stirring solution of crude diol **38** (92 mg, 0.34 mmol) in absolute EtOH (1.0 mL). The mixture was stirred for 30 min at 0 °C and for 30 min while warming to rt. It was partitioned between H_2O (10 mL) and $CHCl_3$ (20 mL), the layers were separated, and the aqueous phase was extracted with $CHCl_3$ (4 × 20 mL). The combined organic phase was washed with H_2O (10 mL), dried, filtered, and evaporated to give 90 mg of crude. Purification by chromatography (b, 4/1, hex/EtOAc) provided pure ketone (−)-**1** (69 mg, 71% from 2-hydroxy ester **37**).

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