# Synthesis of (1*R*,3*R*,5*S*)-1-Amino-3-(hydroxymethyl)bicyclo[3.1.0]hexane as a Precursor for the Synthesis of Carbocyclic Nucleosides

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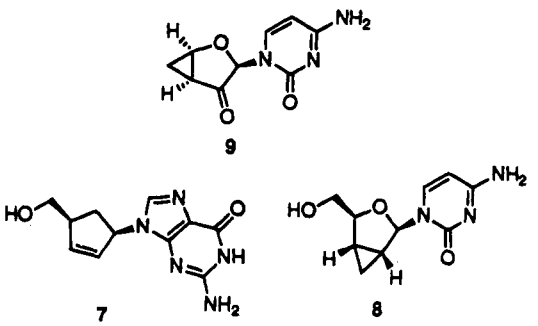
The stereocontrolled synthesis has been achieved of a 1,5-methano-1-amino-5-(hydroxymethyl)-cyclopentane, a potential component for carbocyclic nucleosides. Stereocontrol was manifest by converting (*R*)-2-((benzyloxy)ethyl)oxirane specifically to (2*S*,3*S*)-2-amino-2,3-methanoadipate through a series of lactones. This aminocyclopropanecarboxylate was then cyclized to the corresponding cyclopentanone ester. Reduction of the ketone, elimination, and hydrogenation of the double bond led primarily to the cyclopentane with the amino and ester groups trans (9/1). Enolization followed by an ammonium chloride quench then inverted this to a mixture in which the cis isomer was dominant (4/1). Simple functional group manipulation then gave the target (1*R*,3*R*,5*S*)-1-amino-3-(hydroxymethyl)bicyclo[3.1.0]hexane.

## Introduction

Carbocyclic nucleosides are pharmacologically important isosteres of nucleosides possessing a variety of antineoplastic and antiviral activities. Since carbocyclic nucleosides are enzymatically and hydrolytically more stable than nucleosides, there may be an advantage in the therapeutic use of these compounds. In the synthesis of carbocyclic nucleosides, key intermediates are the substituted 1-amino-3-(hydroxymethyl)cyclopentanes.[1] These aminocyclopentanes can be converted to carbocyclic nucleosides via the Traube synthesis or the method of Shaw and Warrener.[2] While a variety of substituted cyclopentanes have been synthesized and converted to carbocyclic nucleosides, such aminocyclopentanes with carbon substituents at both C-1 and C-5 have not been prepared.

We now report an enantiospecific synthesis of a (1*R*,3*R*,5*S*)-1-amino-3-(hydroxymethyl)bicyclo[3.1.0]hexane (**4**), which could be useful for conversion to the corresponding carbocyclic nucleosides (e.g., **5** and **6**). Having the bridging cyclopropyl ring at this juncture will flatten the five membered ring, analogously to a double bond between C-1 and C-5. Several carbocyclic nucleosides containing a double bond between C-4 and C-5, e.g., **7**, have been found to have significant antiviral activity.[3] Additionally, nucleosides such as **8** and **9** containing a cyclopropane ring fused to the sugar portion have shown antiviral activity.[4] Recently we have presented new routes to (1*S*,3*R*)-1-amino-3-(hydroxymethyl)cyclopentanes.[5] Our plans were to apply this new methodology to the preparation of the cyclopentane-fused carbocyclic nucleoside precursor **4**.




While syntheses of bicyclo[3.1.0] hexanes have been reported,[6] none of the published methods meet our needs for an efficient enantiospecific synthesis with the requisite regiochemistry and functionality. Our synthetic plan is outlined in Scheme 1. We projected that the desired bicyclic amino alcohol **4** could be prepared from the corresponding amino ester **3**. This amino ester, in turn, should be preparable from β-keto ester **2**, the ketone of which would be reduced and the alcohol eliminated followed by hydrogenation to give **3**. Alternatively, the intermediate alcohol could be deoxygenated via radical chemistry to give **3**. The keto ester **2** should be available via a Dieckmann condensation of aminoadipate **1**, following our recently developed protocol.[5a,c] In the present

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(1) Leading references concerning the biological activity of carbocyclic nucleosides are citations 1–4 in ref 5a; leading references concerning the chiral syntheses of carbocyclic nucleosides are citations 7–9, 13, and 14 in ref 5a.

(2) Leading references concerning the conversion of cyclopentylamines to carbocyclic nucleosides are citations 10 and 11 in ref 5a.

(3) (a) Taylor, S. J. C.; Southerland, A. G.; Lee, S.; Wisdom, R.; Thomas, S.; Roberts, S. M.; Evans, C. *J. Chem. Soc., Chem. Commun.* **1990**, 1120. (b) Jones, M. F.; Myers, P. L.; Robertson, C. A.; Storer, R.; Williamson, C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2479. (c) Vince, R.; Brownell, J. *Biochem. Biophys. Res. Commun.* **1990**, *168*, 912. (d) Exall, A. M.; Jones, M. F.; Mo, C. L.; Myers, P. L.; Paternoster, I. L.; Singh, H.; Storer, R.; Weingarten, G. G.; Williamson, C.; Brodie, A. C.; Cook, J.; Lake, D. E.; Meerholz, C. A.; Turnbull, P. J.; Highcock, R. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2467.

(4) Synthesis of **8**: (a) Okabe, M.; Sun, R.-C. *Tetrahedron Lett.* **1989**, *30*, 2203. Syntheses of **9**: (b) Kawana, M.; Kuzuhara, H. *Nucleosides Nucleotides* **1992**, *11*, 551. (c) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1990**, *46*, 2587. (d) Wu, J.-C.; Chattopadhyaya, J. *Tetrahedron* **1989**, *45*, 4507. (e) Adachi, T.; Iwasaki, T.; Miyashi, M.; Inoue, I. *J. Chem. Soc., Chem. Commun.* **1977**, 248. (f) Sasaki, T.; Minamoto, K; Suzuki, H. *J. Org. Chem.* **1973**, *38*, 958.

(5) (a) Bergmeier, S. C.; Cobas, A. A.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 2369. (b) Bergmeier, S. C.; Lee, W. K.; Rapoport, H. *J. Org. Chem.* **1993**, *58*, 5019. (c) Park, K. H.; Rapoport, H. *J. Org. Chem.*, **1994**, *59*, 394.

(6) The synthesis of cyclopropanes has been reviewed by Tsuji, T.; Nishida, S. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 7, p 307. Amino-substituted cyclopropanes are reviewed by Vilsmaier, E. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; Chapter 22, p 1341.

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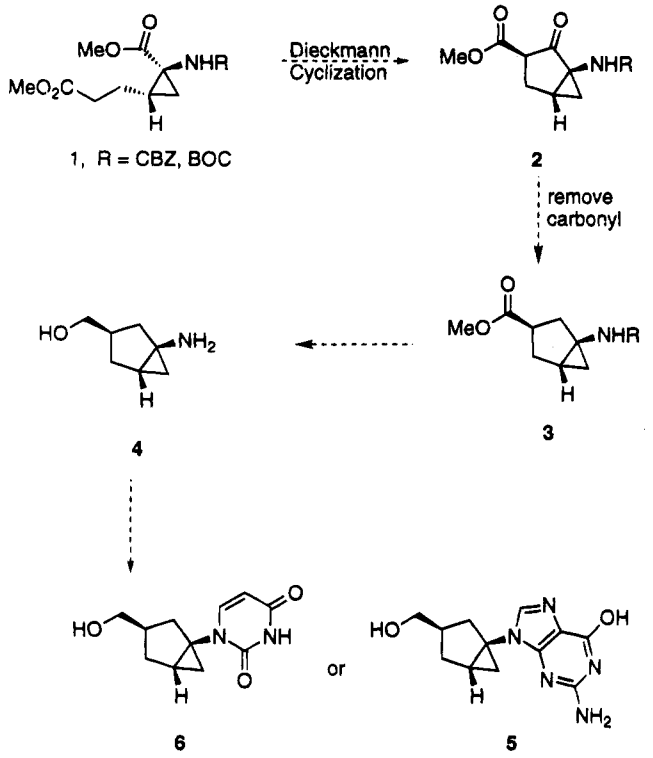
**Scheme 1. Proposed Synthesis of (1*R*,3*R*,5*S*)-1-Amino-3-(hydroxymethyl)bicyclo-[3.1.0]hexane (4) as a Precursor to Carbocyclic Nucleosides**




case, a variety of protecting groups can be used on the nitrogen as there is no α-proton which can lead to racemization. Thus, any readily introduced and removed protecting group such as benzyloxycarbonyl (CBZ) or *tert*-butoxycarbonyl (BOC) would be applicable.

## Results and Discussion

**Synthesis of (2*S*,3*S*)-2-Amino-2,3-methanoadipate.** The key intermediate for our synthesis was *N*-protected-2,3-methanoadipate, a representative of the growing group of 1-aminocyclopropane carboxylic acids (ACCs).

1-Aminocyclopropanecarboxylic acids (ACCs) are an important and interesting class of compounds both from the synthetic viewpoint and for their varied and potentially useful biological applications, including possible use as conformationally constrained amino acid components of peptides. The intense synthetic activity in this area has been reviewed in two recent articles[7] which also cover ACCs isolated from natural sources.

Relative to the numerous protocols available for the construction of ACCs, limited methods lead to the asymmnetric synthesis of these compounds.[8] Methods that allow stereochemical control of the amino and carboxyl moieties as well as other substituents on the cyclopropane are even less common. Most of the latter rely on chiral auxiliaries and chromatographic or other resolution techniques for the separation of frequently complex diastereomeric mixtures.

Our goal was to develop a method by which specific isomeric 1-amino-2-(2-hydroxyethyl)cyclopropanecarboxylic acid derivatives could be diastereo- and enantiospecifically prepared from a simple precursor readily derived from the chiral pool. The 2-hydroxyethyl substituent was chosen as a versatile side chain since a single carbon extension would produce the target 2,3-methanoadipate backbone. To meet these requirements, we chose the enantiomerically pure epoxide **10** (Scheme 2), whose synthesis we recently reported[9] from (*S*)-aspartic acid. It was treated with the dianion of *tert*-butyl hydrogen malonate (**11**) prepared by the monesterification of malonic acid with *t*-BuOH, DCC, and DMAP,[10] followed by treatment with LiHMDS. Rapid nucleophilic opening of the epoxide occurred, accompanied by lactonization to form acid **12**. Conversion to *tert*-butyl ester γ-lactone **13** then proceeded in 77% overall yield from epoxide **10**.

Hydrolysis of the γ-lactone ring of **13** followed by immediate esterification of the intermediate hydroxy acid with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea gave an 80/20 mixture of diester **14** and lactone **13**. The ratio of **14**/**13** was determined by integration of the $^1$H NMR resonances of the methinyl proton α to the hydroxyl oxygen of **14** and the lactone oxygen of **13** which appear at 4.6−4.8 and 3.75−3.95 ppm, respectively. This mixture was used directly in the next step.

Tosylation of alcohol **14** with *p*-toluenesulfonic anhydride[11] in pyridine produced tosylate **15** in 92% yield. At this point, chromatography led to an easy separation of **15** and recovered lactone **13**. To effect cyclopropane formation, tosylate **15** was treated with KHMDS in THF. The cyclopropane diester **16** thus formed in 93% yield was quantitatively hydrogenolyzed to alcohol **17** with hydrogen and a Pd/C catalyst without affecting the cyclopropane ring.

Initial attempts to differentiate between the two carboxylates of **17** were based on the report[12] that the alkaline hydrolysis of 2-substituted cyclopropane 1,1-dicarboxylates was selective at the less hindered ester. Although we were applying acid, rather than alkaline, hydrolysis to the di-*tert*-butyl ester **17**, we considered that selectivity might also be observed during TFA-induced cleavage. Indeed, selective cleavage was observed; however, the ratio was a modest 4/1 in favor of cleavage of the less hindered carboxylate. Alternatively, total differentiation was achieved by using excess TFA and obtaining, quantitatively and specifically, δ-lactone acid **18**.

With the functionality of the two carboxyls thus cleanly and widely distinguished as δ-lactone and carboxylic acid, we proceeded to convert the carboxylic acid into a protected amine. A number of variations of the Curtius reaction, including the popular diphenyl phosphorazidate procedure,[13] were applied but gave poor yields. Best results were obtained by activation as the mixed anhydride with ethyl chloroformate,[14] followed by acyl azide

(7) (a) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231. (b) Williams, R. M.; Fegley, G. J. *J. Am. Chem. Soc.* **1991**, *113*, 8796. These articles provide exhaustive coverage of this area.

(8) (a) Alami, A.; Calmes, M.; Daunis, J.; Excale, F.; Jacquier, R.; Roumestant, M.-L.; Viallefont, P. *Tetrahedron: Asymmetry* **1991**, *2*, 175. (b) Groth, U.; Halfbrodt, W.; Schöllkopf, U. *Liebigs Ann. Chem.* **1992**, 351. (c) Aitken, D.J.; Guillaume, D.; Husson, H.-P. *Tetrahedron* **1993**, *49*, 6375.

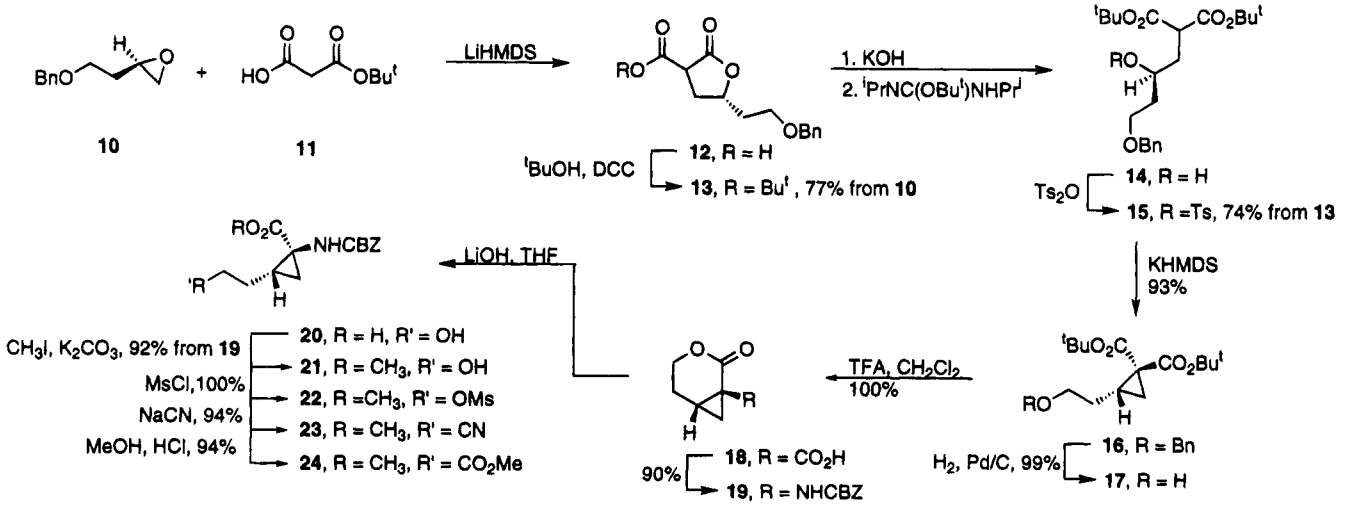
(9) Frick, J. A.; Klassen, J. B.; Bathe, A.; Abramson, J. A.; Rapoport, H. *Synthesis* **1992**, 621. A related process has recently appeared starting with glycidol: Burgess, K.; Ho, K.-K.; Ke, C.-Y. *J. Org. Chem.* **1993**, *58*, 3767. Burgess, K.; Lim, D.; Kwok-Kan, H.; De, C.-Y. *J. Org. Chem.* **1994**, *59*, 2179.

(10) For previous reports of **11** see: (a) Baumgarten, E.; Hauser, C. R. *J. Am. Chem. Soc.* **1944**, *66*, 1037. (b) Hauser, C. R.; Levine, R.; Kibler, R. F. *J. Am. Chem. Soc.* **1946**, *68*, 26.

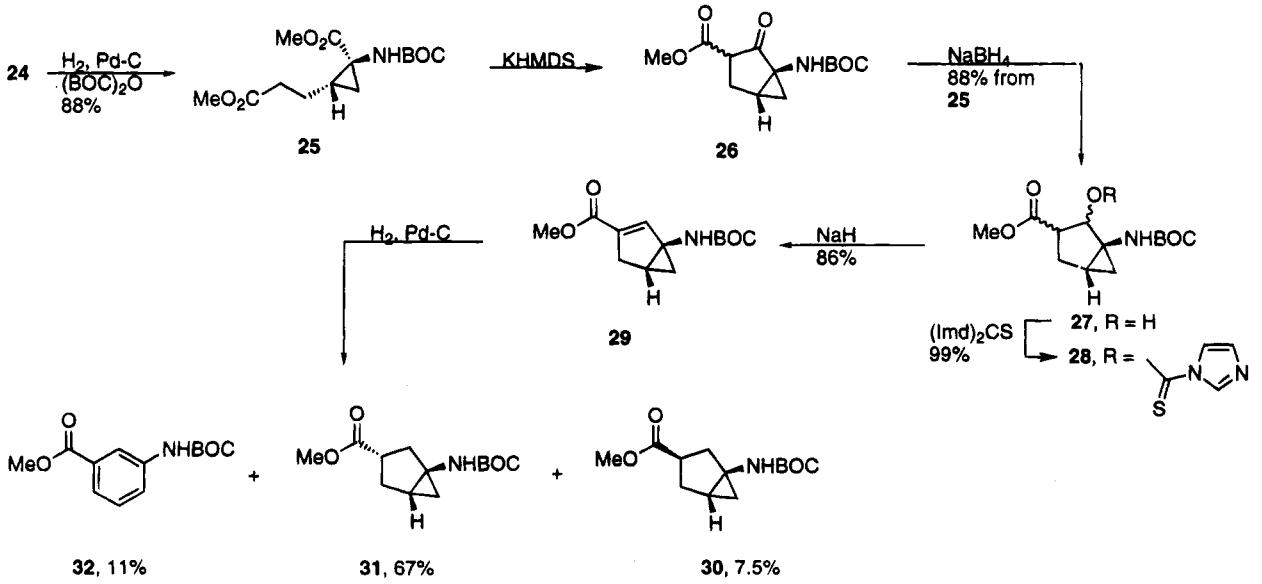
(11) Field, L. *J. Am. Chem. Soc.* **1952**, *74*, 394. Peterli-Roth, P.; Maguire, M. P.; León, E.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 4186. Use of *p*-toluenesulfonyl chloride led to considerable chloride formation.

(12) Baldwin, J. E.; Adlington, R. M.; Rawling, B. J. *Tetrahedron Lett.* **1985**, *26*, 481.

**Scheme 2. Preparation of (2S,3S)-2-Amino-2,3-methanoadipic Acid**




**Scheme 3. Dieckmann Cyclization and Ketone Removal**




formation and capture of the rearranged isocyanate as its benzyl carbamate. In this manner, the *N*-CBZ-cyclopropylamine **19** was obtained in 90% yield from diester **17**.

It remained to extend the ethyl side chain by one carbon, and this was achieved by first hydrolysis (LiOH) of the lactone to hydroxy acid **20** followed by esterification ($CH_3I$) to hydroxy ester **21** in 92% yield. Mesylation to **22** was quantitative.

The additional carbon needed for **23** and **24** was introduced by displacing the mesylate with cyanide and then converting the nitrile to the methyl ester with HCl in MeOH. Initially we planned to use compound **24** in our synthesis, but low yields in the latter stages prompted us to examine other protecting groups on the nitrogen. Thus the BOC derivative **25** was prepared and ultimately used. The key diester **25** was prepared in 71% yield from lactone **19**.

**Cyclization of (2S,3S)-2-Amino-2,3-methanodipate 25 and Conversion to (1R,3R,5S)-1-Amino-3-(hydroxymethyl)bicyclo[3.1.0]hexane (4).** With amino diester **25** in hand, the Dieckmann cyclization was carried out with KHMDS to give **26** in 98% yield as a 3/1 mixture of diastereomers at C-3 (Scheme 3). The $\beta$-keto ester **26** proved to be quite unstable and could not be purified and fully characterized; it was thus immediately reduced to alcohols **27**. These hydroxy esters **27** were obtained as a mixture of all four possible diastereomers in a ratio of 18/3/2/1. The diastereomers were not separated since they converged in the next step, which eliminated two stereocenters. A variety of conditions were examined to convert the hydroxy esters **27** to the olefin **29**. Conversion of the alcohol to the mesylate followed by elimination with a variety of bases (KOBu$^t$, NaH, KHMDS, DBU) gave only a low yield of **29**. Dehydration of the alcohol with dialkylcarbodiimide-(isopropyl or cyclohexyl)/CuCl also gave very low yields (0–23%) of **29**. At this point, reasoning that the bicyclic olefin **29** might be too unstable to survive the basic elimination conditions, it appeared that a radical-based removal of the hydroxyl would be more suitable. Attempting to perform a radical deoxygenation of the

(13) (a) Shiori, T.; Ninomiya, K.; Yamada, S.-I. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Yamada, S.-I.; Ninomiya, K.; Shiori, R. *Tetrahedron Lett.* **1973**, 2343. (c) Ninomiya, K.; Shiori, T.; Yamada, S. *Tetrahedron* **1974**, 30, 2151.

(14) A general procedure for using ethyl chloroformate as an activating agent in a Curtius reaction is given in Kaiser, C.; Weinstock, J. *Organic Syntheses;* Wiley: New York, 1988; Collect. Vol. VI, p 910.

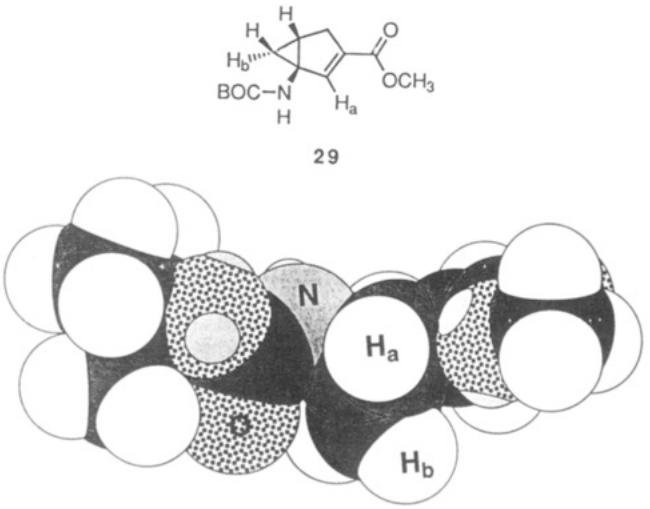



**Figure 1.** Space filling model of **29**.

(thiocarbonyl)imidazolide **28** with *n*-$Bu_3SnH$, we discovered that the major product of the reaction (*n*-$Bu_3SnH$, refluxing toluene) was the elimination product **29**. On the basis of this observation, alcohol **27** was converted to the (thiocarbonyl)imidazolide **28**, followed by elimination with NaH to give an excellent yield of olefin **29**.

We had anticipated that a catalytic reduction of **29** would give the single cis diastereomer **30**. However, the folding of the bicyclic ring system precluded that. Instead, reduction occurred preferentially from the top face of the molecule, giving the trans amino ester **31** in 67% yield as the major product. The desired cis product **30** was obtained in only 7.5% yield. A space-filling model of **29** (Figure 1) shows that the bottom face of the molecule is blocked by the cyclopropane ring. Interestingly, 11% of the *m*-aminobenzoate **32** was produced, presumably from the vinyl cyclopropane by a rearrangement followed by dehydrogenation. This is further indication of the high degree of strain in this bicyclic compound. Attempts to alter the diastereoselectivity of the hydrogenation by varying reaction conditions (catalyst, solvent) as well as the nitrogen protecting group did not significantly alter the product ratio.

Since reduction of the double bond did not give us the desired stereoisomer, a method to epimerize the ester was needed (Scheme 4). In our previous syntheses[5] an epimerization/lactamization strategy was employed to convert a mixture of diastereomers to a single cis diastereomer. The bicyclic **30/31** cannot undergo such a reaction sequence due to the high ring strain of the intermediate tricyclic lactam. However, treatment of a mixture of **30** and **31** with 30 mol % of KHMDS followed by quenching with ammonium chloride converted a 1/9 mixture of **30/31** to a 4/1 mixture of **30/31** in good yield; **30** was easily separated from **31** by column chromatography. NOESY studies (mixing time, 1.1 s) of ester **30** and the final product **4** clearly show the cis nature of the ester group of **30** or the hydroxymethyl group of **4** with the amino group (Figure 2). NOESY spectra of **30** showed an NOE of the cyclopropyl proton with the methine on C-3. NOESY spectra of **4** showed an NOE of the cyclopropyl proton with the methine proton on C-3. Additionally, an NOE of the other cyclopropyl proton with the methine proton on C-5 was observed.

The final conversion of **30** to the target hydroxymethyl **4** was easily done by first reducing the ester to alcohol

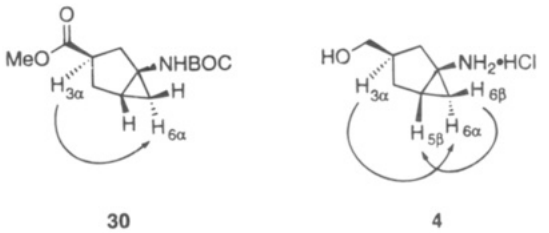
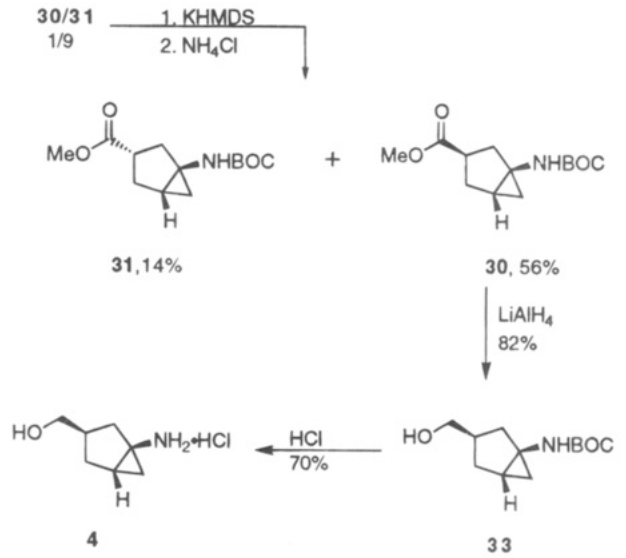



**Figure 2.** Key interactions obtained from NOESY spectra.

**Scheme 4. Epimerization of Amino Ester 30/31 and Conversion to (1*R*,3*R*,5*S*)-1-Amino-3-(hydroxymethyl)bicyclo-[3.1.0]hexane (4)**




**33** with $LiAlH_4$. The BOC group was removed with anhydrous HCl in $CH_2Cl_2$ to give the hydrochloride salt **4**. Thus we have achieved a concise enantiospecific synthesis of (1*R*,3*R*,5*S*)-1-amino-3-(hydroxymethyl)bicyclo-[3.1.0]hexane. This compound can be readily converted to carbocyclic nucleosides via known methods. The synthesis of this type of molecule should allow access to a new class of carbocycles for SAR studies.[15] Additionally, this methodology provides ready access to chiral 1,2,3-trisubstituted bicyclo[3.1.0]hexanes.

## Experimental Section

**General.** All reactions were conducted under an atmosphere of dry nitrogen unless otherwise noted. Final solutions before concentration were dried over $MgSO_4$. THF and $Et_2O$ were distilled from Na/benzophenone, MeOH was distilled from Mg, and $CH_2Cl_2$ was distilled from $CaH_2$. Chromatography was carried out using 230−400-mesh silica gel. NMR spectra were taken in $CDCl_3$ and are referenced to internal TMS unless otherwise noted; coupling constants are reported in hertz; 2D NOESY experiments were conducted using a phase sensitive NOESY pulse program.

***(R)*-γ-(2-(Benzyloxy)ethyl)-(*R,S*)-α-(*tert*-butoxycarbonyl)-γ-butyrolactone (13).** To a solution of HMDS (73 mL, 0.35 mol) in THF (100 mL), cooled in an ice/water bath, was added slowly *n*-BuLi (150 mL, 2.25 M, 0.34 mol). This solution was stirred for 15 min, then cooled to −78 °C, *tert*-butyl hydrogen malonate (**11**, 27 g, 0.17 mol) was added, and the dry ice bath was replaced by an ice/water bath. After 15 min, DMPU (7.0

(15) Recently the synthesis of the analogous 4-amino-2-hydroxy-1-(hydroxymethyl)bicyclo[3.1.0]hexane has been reported: Altmann, K.-H; Kesselring, R.; Francotte, E.; Rihs, G. *Tetrahedron Lett.* **1994**, *35*, 2331.

mL, 56 mmol) was added, the reaction mixture was cooled again to −78 °C, and epoxide **10** (10.0 g, 56 mmol) was added. The dry ice bath was removed, the reaction was allowed to warm to rt, and after 3 h, the solution was poured into brine (100 mL). The pH was lowered to 2.4 with concentrated phosphoric acid and the separated aqueous layer was extracted with diethyl ether (3 × 200 mL). The combined organic extracts were washed with brine (100 mL), dried, filtered, and evaporated to give crude acid **12**, as a yellow oil. This acid was immediately dissolved in $CH_2Cl_2$ (700 mL) and the resulting solution was chilled with an ice/water bath. To this solution were added *t*-BuOH (14.5 g, 168 mmol), DCC (40.5 g in 75 mL $CH_2Cl_2$, 168 mmol), and DMAP (0.37 g, 3 mmol), and the solution was allowed to warm slowly to rt while stirring overnight. The reaction mixture was filtered through Celite which was washed with petroleum ether/$CH_2Cl_2$ (2/1, 200 mL). The combined filtrate was evaporated and the resulting slightly yellow oil was purified by column chromatography (4/1, hexanes/ETOAc); yield 17.9 g, 77%,: $R_f$ 0.23 (4/1 hexanes/EtOAc); $^1$H NMR (/ indicates diastereomeric signals) δ 7.30−7.42 (m, 5H), 4.62−4.82 (m, 1H), 4.47/4.53 (s, 2H), 3.48−3.70 (m, 3H), 2.54−2.66 (m, 1H), 1.91−2.38 (m, 3H), 1.49/1.50 (s, 9H); $^{13}$C NMR δ 172.0/172.1, 166.84/166.86, 137.9, 128.3, 127.64, 127.58, 82.66/82.86, 76.44/77.44, 73.13/73.14, 66.03, 47.87/48.18, 35.61, 32.05/32.17, 27.77/27.80; $[\alpha]^{20}_D$ +31.2° (*c* 6.46, $CH_2Cl_2$). Anal. Calcd for $C_{14}H_{24}O_5$: C, 67.5; H, 7.5. Found: C, 67.6; H, 7.5.

**Di-*tert*-butyl (4-(Benzyloxy)-(*R*)-2-hydroxybutyl)malonate (14).** The lactone **13** (12.2 g, 38.4 mmol) was dissolved in dioxane (25 mL) and cooled in an ice/water bath. To this solution was added KOH (2.4 g, dissolved in 10 mL of water), and the mixture was stirred overnight. It was then evaporated, and the residue was dissolved in dichloromethane (150 mL) and chilled in an ice/water bath. This solution was acidified to pH 3 by the addition of citric acid (1 M, 50 mL, then solid). The mixture was extracted with methylene chloride (3 × 100 mL), and the separated organic phase was dried and evaporated until 150 mL of methylene chloride remained. To this solution was added *O*-*tert*-butyl *N*,*N*'-diisopropylisourea (20 g), the mixture was heated at reflux for 2 h and then filtered through Celite, and the filter cake was washed with methylene chloride (3 × 100 mL). The combined filtrate was concentrated to an oil, and lactone **13** and diester **14** were isolated together by chromatography (4/1 hexane/ethyl acetate). This mixture, 11.6 g, was used directly in the next step. The ratio of lactone to diester was 1/4 as determined by integration of the $^1$H NMR resonance of the methinyl proton of the lactone (δ 4.6−4.8) and that of the alcohol (δ 3.75−3.95).

**Di-*tert*-butyl (4-(Benzyloxy)-(*R*)-2-(tosyloxy)butyl)malonate (15).** The mixture of the hydroxy ester **14** (8.33 g, 21 mmol) and lactone **13** (3.3 g) was dissolved in 50 mL of pyridine and chilled in an ice/water bath. To this solution was added $Ts_2O$ (16 g, 49 mmol), and the solution was allowed to stir overnight. The reaction mixture was diluted with ethyl acetate (200 mL) and extracted with citric acid (1 M, 3 × 100 mL) and saturated sodium bicarbonate (100 mL). The organic layer was then washed with brine, dried, and evaporated. Chromatography (4/1 hexane/EtOAc) of the residue led to isolation of oily tosylate **15** (11.5 g, 74% overall based on consumed lactone **13**) and the recovery of the lactone (**13**, 3.2 g): $R_f$ 0.30 (4/1 hexanes/EtOAc); $^1$H NMR δ 7.76 (d, *J* = 7.3, 2H), 7.28−7.38 (m, 5H), 4.82−4.93 (m, 1H), 4.36 (s, 2H), 3.31−3.45 (m, 4H), 2.41 (s, 3H), 2.19−2.30 (m, 1H), 2.05−2.15 (m, 1H), 1.82−1.95 (m, 2H), 1.46 (s, 9H), 1.43 (s, 9H); $^{13}$C NMR δ 168.2, 167.8, 144.5, 138.1, 129.7, 128.2, 127.7, 127.4, 81.7, 79.0, 72.8, 65.5, 49.6, 33.6, 33.4, 27.8, 27.7, 21.6; $[\alpha]^{20}_D$ +15.1° (*c* 5.1, $CH_2Cl_2$). Anal. Calcd for $C_{29}H_{40}O_8S$: C, 63.5; H, 7.3. Found: C, 63.4; H, 7.2.

**Di-*tert*-butyl (*S*)-2-(2-(Benzyloxy)ethyl)cyclopropane-1,1-dicarboxylate (16).** To a stirred solution of tosylate **15** (10.18 g, 18.6 mmol) in THF (150 mL) was added under nitrogen at −78 °C via syringe KHMDS in THF (37 mL, 1 M, 37 mmol), and the reaction mixture was allowed to warm to 0 °C over 20 min. After being stirred for 20 min, the reaction mixture was diluted with ether (100 mL) and washed with 50 mL portions of 1 M citric acid, sodium bicarbonate, and brine. After drying, the solvent was evaporated and the residue was purified by chromatography (10/1 hexane/EtOAc); yield of **16** as an oil, 6.4 g, 93%; $R_f$ 0.36 (9/1 petroleum ether/EtOAc); $^1$H NMR δ 7.26 (s, 5H), 4.51 (s, 2H), 3.57 (d, *J* = 6.6 Hz, 2H), 1.45−1.95 (m, 3H), 1.47 (s, 9H), 1.45 (s, 9H), 1.23 (d, *J* = 6.8, 2H); $^{13}$C NMR δ 169.6, 167.5, 138.3, 128.3, 127.6, 127.5, 81.3, 81.1, 72.9, 69.3, 35.8, 28.9, 28.0, 27.9, 23.9, 19.9; $[\alpha]^{20}_D$ +28.4° (*c* 7.24, $CH_2Cl_2$). Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.2; H, 8.6. Found: C, 70.1; 8.4.

**Di-*tert*-butyl (*S*)-2-(2-Hydroxyethyl)cyclopropane-1,1-dicarboxylate (17).** To a solu-tion of benzyl ether **16** (6.0 g, 15.8 mmol) in MeOH (30 mL) was added 10% Pd/C (720 mg), and the vessel was evacuated and then purged with $H_2$. After overnight stirring, the reaction mixture was filtered through Celite and evaporated to yield, as an oil, the chromatographically and spectrally pure alcohol **17**; yield, 4.5 g, 99%: $^1$H NMR δ 3.72 (d, *J* = 6.5, 2H), 1.51−1.88 (m, 3H), 1.45 (s, 9H), 1.43 (s, 9H), 1.23 (m, 2H); $^{13}$C NMR δ 169.7, 167.6, 81.5, 81.4, 62.0, 35.7, 31.6, 27.9, 23.8, 19.6; $[\alpha]^{20}_D$ +50° (*c* 2.27, $CHCl_3$). Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.9; H, 9.1. Found: C, 62.7; H, 9.1.

**(1*R*,6*S*)-1-Carboxy-3-oxabicyclo[4.1.0]2-heptanone (18).** The diester **17** (4.5 g) was dissolved in methylene chloride (450 mL), trifluoroacetic acid (12.1 mL, 1000 mol %) was added, and the reaction was refluxed overnight. The solvent was evaporated leaving lactone acid **18** as a white solid; yield, quantitative: mp 90−92 °C; can be recrystallized from ether/hexane, mp unchanged; $^1$H NMR δ 4.41 (dddd, *J* = 12.13, 5.93, 1.33, 1.32 Hz 1H), 4.25 (ddd, *J* = 12.85, 12.81, 3.69 Hz, 1H), 2.68−2.72 (m, 1H), 2.32 (tq, *J* = 14.0, 5.58, 2.97, 1H), 2.16−2.19 (m, 1H), 2.13 (*J* = 5.48, 1H), 1.99 (dd, *J* = 8.38, 5.42, 1H); $^{13}$C NMR δ 174.7, 169.7, 66.3, 26.7, 25.9, 21.7, 20.3; $[\alpha]^{20}_D$ +64° (*c* 2.69, $CHCl_3$). Anal. Calcd for $C_7H_8O_4$: C, 53.8; H, 5.2. Found: C, 53.5; H, 4.8.

**(1*S*,6*S*)-1-[*N*-((Benxyloxy)carbonyl)amino]-3-oxabicyclo[4.1.0]-2-heptanone (19).** Acid **18** (2.7 g, 17.3 mmol) was dissolved in acetone (35 mL) and cooled to 0 °C, and to this solution were added TEA (4.9 mL, 34.7 mmol) and then ethyl chloroformate (2.0 mL, 20.9 mmol). The solution was allowed to stir for 0.5 h, at which time benzene (30 mL) was added, the resulting cloudy mixture was filtered through Celite, the Celite pad was washed with benzene (20 mL), and the combined filtrate was evaporated. The residual oil was dissolved in acetone (35 mL) and cooled to 0 °C, and to this solution was added sodium azide (2.25 g, 34.6 mmol) dissolved in water (10 mL). After stirring for 0.5 h, the reaction mixture was diluted with water (100 mL) and extracted with methylene chloride (3 × 100 mL). The combined methylene chloride extracts were dried and evaporated to an oil which was dissolved in toluene (100 mL) and refluxed for 2 h before benzyl alcohol (3.77 mL, 34.6 mmol) was added and the solution refluxed again overnight. The solvent was evaporated and the residue was purified by chromatography (1/1 hexane/EtOAc); yield, 4.1 g, 90%: $^1$H NMR δ 7.29−7.40 (m, 5H), 5.88 (bs, 1H), 4.22−4.27 (m, 1H), 3.99−4.16 (m, 1H), 2.38−2.45 (m, 1H), 1.91−2.04 (m, 2H), 1.73 (t, *J* = 6.3, 1H), 1.37 (t, *J* = 7.9, 1H), $^{13}$C NMR δ 171.3, 156.5, 136.0, 129.4, 128.0, 127.9, 66.9, 65.1, 35.1, 24.3, 21.2, 16.0. Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4. Found: C, 64.2; H, 5.8; N, 5.2.

**Methyl (1*S*,2*S*)-1-[*N*-((Benzyloxy)carbonyl)amino]-2-(2-hydroxyethyl)cyclopropanecarboxylate (21).** To a solution of carbamate **19** (2.71 g, 10.4 mmol) in THF (80 mL) was added an aqueous LiOH solution (LiOH·$H_2O$, 522 mg, 12.45 mmol in $H_2O$, 10 mL). This mixture was allowed to stir overnight at rt; then the reaction mixture was acidified by the addition of Bio-Rad AG50W-X4 acid cation exchange resin (5.05 g, 26.1 mmol) and allowed to stir for 0.5 h. The mixture was filtered, the resin was washed with chlororform, and the combined filtrate was dried and evaporated to give hydroxy acid **20**. The hydroxy acid was dissolved in a mixture of acetonitrile (110 mL) and DMF (20 mL), to this solution was added potassium carbonate (2.86 g, 21 mmol) and methyl iodide (6.5 mL, 104 mmol), and the mixture was stirred overnight and then partitioned between ethyl acetate (100 mL) and water (100 mL). The aqueous phase was extracted with ethyl acetate (2 × 100 mL), and the combined ethyl acetate extracts were washed with brine, dried, and evaporated. The

residue was purified by chromatography (1/1 hexane/EtOAc); yield 2.8 g, 92% of ester **21**: mp 89–90 °C; $^1$H NMR $\delta$ 7.31–7.39 (m, 5H), 5.46 (s, 1H), 5.15 (AB quartet, $J_{AB}$ = 12.2, 2H), 3.74–3.78 (m, 1H), 3.71 (s, 3H), 3.61–3.65 (m, 1H), 1.98–2.04 (m, 1H), 1.68–1.78 (m, 3H), 1.47 (dd, $J$ = 8.2, 4.9, 1H), 1.25 (dd, $J$ = 9.5, 4.9, 1 H); $^{13}$C NMR $\delta$ 171.6, 157.7, 135.8, 128.5, 128.3, 128.1, 67.3, 61.7, 52.6, 37.9, 30.6, 29.4, 21.8; $[\alpha]^{22}_D$ −26.9° (*c* 0.84, $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.3; H, 6.4; N, 4.6.

**Methyl (1*S*,2*S*)-1-[*N*-((Benzyloxy)carbonyl)amino]-2-(2-(methanesulfonyloxy)ethyl)cyclopropanecarboxylate (22).** To a solution of alcohol **21** (2.74 g, 9.35 mmol) in methylene chloride (120 mL) at 0 °C were added TEA (3.26 mL, 23.4 mmol) and MsCl (1.45 mL, 18.7 mmol). After 0.5 h, saturated bicarbonate (100 mL) was added and the reaction was allowed to stir for another 0.5 h. The reaction mixture was extracted with methylene chloride (2 × 100 mL), and the combined organic phase was dried, filtered, and evaporated. Purification by column chromatography gave mesylate **22**; yield, quantitative: $^1$H NMR $\delta$ 1.37–1.43 (m, 1H), 1.51–1.56 (m, 1H), 1.61–1.75 (m, 1H), 2.01–2.17 (m, 2H), 2.99 (bs, 3H), 3.72 (bs, 3H), 4.20–4.38 (m, 2H), 5.10 (bs, 2H), 5.57 (bs, 1H), 7.30–7.36 (m, 5H). Anal. Calcd for $C_{16}H_{21},NO_9$: C, 51.8; H, 5.7; N, 3.8. Found: C, 51.5; H, 5.5; N, 3.4.

**(1*S*,2*S*)-1-[*N*-((Benzyloxy)carbonyl)amino]-1-(methoxycarbonyl)-2-(2-cyanoethyl)cyclopropane (23).** To a solution of **22** (5.6 g, 15.3 mmol) in DMF (80 mL) were added NaCN (4.5 g, 90 mmol) and NaI (2.3 g, 15.3 mmol). The reaction was heated at 80 °C for 2 h, then poured into water (150 mL) and extracted with EtOAc. The combined organic extracts were washed with water (3 × 100 mL) and brine and dried. Evaporation and chromatography (40% EtOAc/hexane) of the residue gave 4.4 g (94%) of **23** as a white solid: mp 90–92 °C; $[\alpha]^{20}_D$ −14.7° (*c*, 0.3, $CHCl_3$); $^1$H NMR (acetone-$d_6$) $\delta$ 7.36–7.30 (m, 5H), 7.10 (bs, 1H), 5.08 (s, 2H), 3.66 (s, 3H), 2.57–2.46 (m, 2H), 2.04–1.86 (m, 2H), 1.68 (m, 1H), 1.44 (m, 1H), 1.35 (dd, $J$ = 9.4, 5.0, 1H); $^{13}$C NMR $\delta$ 171.6, 156.4, 136.1, 128.5, 128.2, 128.0, 119.3, 66.9, 52.6, 38.2, 30.7, 23.2, 23.0, 16.6. Anal. Calcd for $C_{16}H_{18}NO_6$: C, 63.6; H, 6.0; N, 9.3. Found: C, 63.7; H, 6.0; N, 9.2.

**(1*S*,2*S*)-1-[*N*-((Benzyloxy)carbonyl)amino]-1-(methoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)cyclopropane (24).** Hydrogen chloride gas was bubbled into an ice-cooled solution of **23** (3.8 g, 12.7 mmol) in $Et_2O$/MeOH (4/1, 100 mL) for 2 h. The reaction mixture was warmed to rt and stirred for 1.5 h and then evaporated. The residue was suspended in EtOAc (150 mL), HCl (30 mL of 6 M) and brine (20 mL) were added, and the mixture was stirred vigorously for 2.5 h. After extraction with EtOAc (3 × 100 mL), the combined organic extracts were washed with brine. Evaporation and chromatography (33% EtOAc/hexane) gave 4.0 g (94%) of **24** as a white solid: mp 55–57 °C; $[\alpha]^{20}_D$ +6.5° (*c* 0.5, $CHCl_3$; $^1$H NMR (acetone-$d_6$) $\delta$ 7.36–7.28 (m, 5H), 7.02 (bs, 1H), 5.06 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 2.43–2.32 (m, 2H), 1.94 (m, 1H), 1.62 (m, 1H), 1.40 (dd, $J$ = 7.8, 4.9, 1H), 1.25 (dd, $J$ = 9.4, 4.9, 1H); $^{13}$C NMR $\delta$ 173.4, 171.7, 156.3, 136.3, 128.4, 128.0, 127.9, 66.7, 52.3, 51.4, 38.6, 33.2, 31.0, 23.2, 22.3. Anal. Calcd for $C_{17}H_{21}NO_6$: C, 60.9; H, 6.3; N, 4.2. Found: C, 61.0; H, 6.4; N, 4.4.

**(1*S*,2*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-1-(methoxycarbonyl)-2-(2-(methoxycarbonyl)ethyl)cyclopropane (25).** A mixture of **24** (3.0 g, 8.9 mmol), $(BOC)_2O$ (2.9 g, 13.5 mmol), and 10% Pd/C was stirred under an atmosphere of $H_2$ (balloon) for 18 h. The reaction mixture was filtered and evaporated. Chromatography (33% EtOAc/hexane) of the residue gave 2.3 g (88%) of **25** as an oil: $[\alpha]^{20}_D$ +11.0° (*c* 0.5, $CHCl_3$); $^1$H NMR (acetone-$d_6$) $\delta$ 6.60 (bs, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 2.42–2.29 (m, 2H), 1.90 (m, 1H), 1.76 (m, 1H), 1.57 (m, 1H), 1.36 (s overlapping m, 10H), 1.18 (dd, $J$ = 9.4, 4.8, 1H); $^{13}$C NMR $\delta$ 173.4, 172.0, 155.8, 77.8, 52.2, 51.4, 38.6, 33.2, 30.7, 28.2, 23.1. Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.8; H, 7.7; N, 4.6. Found: C, 55.7; H, 7.8; N, 4.6.

**(1*S*,2*R*/*S*,3*R*/*S*,5*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-2-hydroxy-3-(methoxycarbonyl)bicyclo[3.1.0]hexane (27).** KHMDS (8.9 mL of a 1 M solution in THF, 8.9 mmol) was added to a −78 °C solution of **25** (0.87 g, 3.0 mmol) in THF (20 mL). The reaction was stirred for 1 h and then poured into an ice-cold mixture of EtOAc (50 mL) and 1 M citric acid (50 mL). The mixture was extracted with EtOAc (2 × 50 mL), and the combined organic extracts were washed with a saturated $NaHCO_3$ solution and brine. Evaporation gave **26** as an unstable oil which was used immediately: $^1$H NMR (acetone-$d_6$) $\delta$ 6.56 (bs, 0.75H), 6.21 (bs, 0.25H), 3.70 (s, 2.25H), 3.64 (s, 0.75H), 3.40 (t, 0.75H), 1.56 (m, 0.75H), 3.30 (dd, $J$ = 0.25H), 2.63 (m, 0.75H), 2.52 (m, 0.25H), 2.19 (m, 1.5H), 2.05 (m, 0.5H), 1.56 (m, 0.75H), 1.50 (m, 0.25H), 1.38 (s, overlapping m, 10H). To an ice-cooled solution of the previously prepared **26** in THF/MeOH (1/1.2 mL) was added $NaBH_4$ (113 mg, 3.0 mmol). After the solution was stirred for 30 min, 1 M $KH_2PO_4$ (2.5 mL) was added and the reaction mixture was extracted with EtOAc (2 × 50 mL). Evaporation and chromatography (44% EtOAc/hexane) gave 0.75 g (92%) of **27** as a 18/3/2/1 mixture of diastereomers as shown by $^1$H NMR: $^1$H NMR (key resonances) $\delta$ 3.67, 3.66, 3.63 (s, MeO). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.5; H, 7.8; N, 5.2. Found: C, 57.5; H, 7.8; N, 4.9.

**(1*S*,5*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(methoxycarbonyl)bicyclo[3.1.0]-2-hexene (29).** *N*,*N*′-(Thiocarbonyl)diimidazole (660 mg, 3.7 mmol) was added to a solution of **27** (500 mg, 1.8 mmol) in $CH_2Cl_2$ which was then heated to reflux for 18 h. The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and washed with water, cold 1 M HCl, saturated $NaHCO_3$, and brine (50 mL portions). Evaporation gave 695 mg (99%) of crude **28**. This material was dissolved in THF (15 mL) and cooled in an ice bath, NaH (987 mg of 60% in oil, 2.2 mmol) was added, and the reaction mixture warmed to rt and stirred for 30 min. It was then poured into 1 M citric acid (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic phase was washed with saturated $NaHCO_3$ and brine. Evaporation and chromatography gave 403 mg (86%) of **29** as a white solid: mp 100–102 °C; $[\alpha]^{20}_D$ −50° (*c* 0.3, $CHCl_3$); $^1$H NMR (acetone-$d_6$) $\delta$ 6.81 (s, 1H), 6.62 (bs, 1H), 3.64 (s, 3H), 2.82 (ddd, $J$ = 17.8, 7.1, 2.0, 1H), 2.40 (d, $J$ = 17.8, 1H), 1.81 (m, 1H), 1.39 (s, 9H), 1.32 (dd, $J$ = 8.6, 4.6 1H), 0.25 (t, $J$ = 4.7, 1H); $^{13}$C NMR $\delta$ 165.3, 155.8, 147.0, 130.8, 79.8, 51.2, 45.7, 34.4, 28.2, 24.3, 24.0. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.6; H, 7.6; N, 5.5. Found: C, 61.8; H, 7.7; N, 5.5.

**(1*R*,3*R*,5*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(methoxycarbonyl)bicyclo[3.1.0]hexane (30).** A mixture of **29** (264 mg, 1.1 mmol) and 10% Pd/C (26 mg) was stirred in MeOH (6 mL) under $H_2$ (balloon) for 18 h. The reaction was filtered through Celite and washed with MeOH. Concentration and chromatography (14% EtOAc/hexane) gave first 28 mg (11%) of **32** followed by 178 mg (67%) of **31** and then 20 mg (7.5%) of **30**. A solution of **30** and **31** (1/9, 146 mg, 0.57 mmol) in THF (15 mL) was cooled to −78 °C, treated with KHMDS (0.17 mL of a 1 M solution in THF, 0.17 mmol), then warmed to 0 °C for 1.5 h. The reaction was poured into saturated $NH_4Cl$ and extracted with EtOAc. Concentration and chromatography (14% EtOAc/hexane) gave first 21 mg (14%) of **31** followed by 82 mg (56%) of **30**. **30**: mp 54–55 °C; $[\alpha]^{20}_D$ −5.9° (*c* 0.3 $CHCl_3$); $^1$H NMR (acetone-$d_6$) $\delta$ 6.34 (bs, 1H), 3.60 (s, 3H), 2.45 (m, 1H), 2.21–2.05 (m, 3H), 1.87 (dd 12.3, 7.7, 1H), 1.40, 1.38 (overlapping s, 10H), 0.69 (d, $J$ = 6.3, 2H); $^{13}$C NMR $\delta$ 175.0, 155.5, 79.3, 51.7, 39.9, 34.9, 30.6, 28.3, 24.9, 23.6, 15.2. Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.1; H, 8.3; N, 5.5 Found: C, 61.3; H, 8.2; N, 5.4. **31**: $[\alpha]^{20}_D$ +12.6° (*c* 1.3, $CHCl_3$); $^1$H NMR (acetone-$d_6$) $\delta$ 6.32 (bs, 1H), 3.60 (s, 3H), 3.0 (m, 1H), 2.35 (dd $J$ = 12.8, 2.2, 1H), 2.28–2.25 (m, 2H), 2.0 (m, 1H), 1.38, 1.34 (s overlapping m, 10H), 0.75 (m, 1H), 0.44 (t, $J$ = 5.2, 1H); $^{13}$C NMR $\delta$ 176.6, 155.5, 79.3, 51.7, 41.5, 40.9, 34.5, 30.4, 28.2, 25.1, 17.5. **32**: mp 103–104 °C; $^1$H NMR $\delta$ 7.96 (s, 1H), 7.71 (d, $J$ = 7.8, 1H), 7.67 (d, $J$ = 7.2, 1H), 7.36 (t, $J$ = 7.9, 1H), 6.6 (bs, 1H, N-H), 3.91 (s, 3H), 1.53 (s, 9H); $^{13}$C NMR $\delta$ 166.8, 152.6, 138.6, 130.9, 129.1, 124.1, 122.8, 119.4, 80.9, 52.1, 28.3. Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.8; N, 5.6. Found: C, 61.8; H, 6.6; N, 5.6.

**(1*R*,3*R*,5*S*)-1-[*N*-(*tert*-Butoxycarbonyl)amino]-3-(hydroxymethyl)bicyclo[3.1.0]hexane (33).** To an ice-cooled solution of 30 (82 mg, 0.32 mmol) in THF (3 mL) was added $LiAlH_4$ (24 mg, 0.64 mmol), the mixture was warmed to rt and stirred for 1 h, and then it was poured into a solution of $KHSO_4$ (100 mg) in water (1 mL) and stirred for 20 min. After extraction

with EtOAc (2 × 10mL), the combined organic extract was washed with brine and evaporated. Chromatography (33% EtOAc/hexane) gave 60 mg (82%) of **33** as an oil: $[\alpha]^{20}_D$ +2.3° (*c* 0.7, $CHCl_3$); $^1H$ NMR (MeOH-$d_4$) δ 3.45 (d, *J* = 5.8, 2H), 2.05 (m, 1H), 1.75–1.62 (m, 4H), 1.42 (s, 9H), 0.72 (m, 1H), 0.65 (m, 1H); $^{13}C$ NMR δ 155.6, 79.2, 66.5, 40.2, 38.2, 35.1, 30.4, 28.4, 15.9. Anal. Calcd for $C_{12}H_{21}NO_3$: C, 63.4; H, 9.3; N, 6.2. Found: C, 63.8; H, 9.7; N, 6.4.

**(1*R*,3*R*,5*S*)-1-Amino-3-(hydroxymethyl)bicyclo[3.1.0]-hexane Hydrochloride (4).** To an ice-cooled solution of **33** (20 mg, 0.09 mmol) in $CH_2Cl_2$ (2 mL) was added a 1 M solution of HCl in $CH_2Cl_2$ (2 mL). The reaction mixture was warmed to rt, stirred for 8 h, and filtered to give 10 mg (70%) of **4** as a white solid: mp 170–172 °C; $[\alpha]^{20}_D$ +23.8° (*c* 0.3, $D_2O$); $^1H$ NMR ($D_2O$) δ 3.41 (dd, *J* = 2.1, 6.2 2H), 2.08 (dd, *J* = 11.8, 7.1 1H), 1.82–1.74 (m, 1H), 1.67 (dd, *J* = 12.5, 7.3, 1H), 1.59–1.49 (m, 3H), 0.84–0.79 (m, 2H); $^{13}C$ NMR ($D_2O$) δ 66.9, 42.7, 39.3, 35.5, 31.9, 28.9, 14.1; HRMS calcd for $C_{12}H_{21}NO$ ($MH^+$) 127.0997, found 127.0994.

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