Introduction of C(5/6) side chains onto 2-azabicyclo[2.1.1]hexanes via a 6-*anti*-bromo-5-*anti*-hydroxy derivative

Grant R. Krow, Fang Yu, Matthew Sender, Deepa Gandla, Guoliang Lin, Charles DeBrosse, and Charles W. Ross III

Abstract: Oxidation of the title bromoalcohol provided the strained ketone, 5-bromo-6-oxo-2-azabicyclo[2.1.1]hexane. Additions of nucleophiles to either this or the debrominated ketone have been used to introduce 5(6)-*syn*-alkyl and aryl groups, 5(6)-alkylidene linkages, and 5(6)-*anti*-alkyl and acyl substituents. Facial selectivity is for additions to the 6-bromo-5-ketone and 5-alkylidene azabicycles to occur from the face syn to the nitrogen atom. The bromine atom of the title alcohol has also been replaced by a 6-*anti*-(1-hydroxyethyl) substituent using a directed radical addition process. The stereoselective functionalization reactions expand the range of available methano-bridged pyrrolidines.

Key words: methanopyrrolidine, 6-oxo-2-azabicyclo[2.1.1]hexane, directed radical addition, facial selectivity and nucleophilic addition, strained ketone.

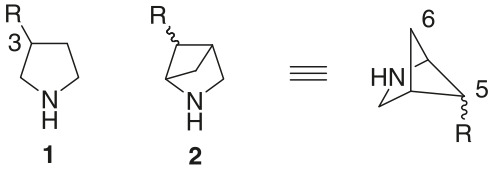
Résumé : L'oxydation du bromoalcool mentionné dans le titre conduit à une cétone tendue, le 5-bromo-6-oxo-2-azabicyclo [2.1.1]hexane. L'addition de nucléophiles aussi bien à ce produit qu'à la cétone débromée a été utilisée pour introduire des groupes 5(6)-*syn*-alkyles ou aryles, des liaisons 5(6)-alkylidènes et des substituants 5(6)-*anti*-alkyles ou acyles. La sélectivité faciale conduit à des additions sur les azabicycles avec des substituants 6-bromo et 5-cétone ou une chaîne 5-alkylidène qui se produisent par la face syn par rapport à l'atome d'azote. On a aussi remplacé l'atome de brome de l'alcool mentionné dans le titre par un substituant 6-*anti*-(1-hydroxyéthyle) en faisant appel à un processus d'addition radicalaire orienté. Les réactions de fonctionnalisations sélectives étendent la plage de pyrrolidines à pont méthano disponibles.

Mots-clés : méthanopyrrolidine, 6-oxo-2-azabicyclo[2.1.1]hexane, addition radicalaire orientée, sélectivité faciale, addition nucléophile, cétone tendue.

[Traduit par la Rédaction]

Introduction

Pyrrolidines **1** substituted with alkyl,[1,2] aryl,[3] or acyl[4] substituents at the 3-position, β to the nitrogen, are found in a number of molecules with interesting biological or structural properties. A 5-substituted 2-azabicyclo[2.1.1]hexane ring system (**2**) is a mimic of a pyrrolidine that has been constrained to exist in a single conformation in which a 2,4-methylene bridge forces the substituted C^{β} atom to be puckered out of the plane described by the other four atoms of its pyrrolidine ring. As part of a strategy to incorporate key pharmacophoric units into inflexible structures,[5] practical methods to introduce substituents in defined spatial orientations at one or both positions $C_{5(6)}$ of azabicycles such as **2** are of interest. Such molecules may prove to be valuable scaffolds for drug discovery and for incorporation into novel β-amino acids.[6]



2-Azabicyclo[2.1.1]hexanes **2** with alkyl, acyl, or aryl side chains attached at $C_{5(6)}$ are known, but effective syntheses for 5(6)-syn orientation of these groups predominate. Examples where only the C_5 bridge and the nitrogen atom have substituents are shown as follows.[7] The synthetic approaches to introduce alkyl groups include skeletal rearrangement (R = 6-*syn*-methyl, with heteroatoms in the other methylene bridge);[8] ring closure and subsequent manipulation (R = 5-*syn*-CH_2OH **3a** and R = 6-*syn*-CH_2NH_2, with a heteroatom in the 5-bridge).[9] There are photochemical cycloaddition

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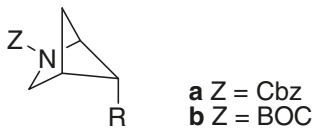
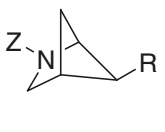
routes that introduce R/H = Me_2, along with a 1-aryl group;[10] R = $C(OR)_3$ or CH_2SiMe_3 along with acyl in the other methylene bridge;[11,12] and *R* = syn- or anti-oriented cyclohexane rings fused from C_5 to C_4 or cyclohexanone rings fused from C_5 to C_1.[13] Recently, alkylester **4b**, accompanied by some extended chain addition products, was prepared by methyl acrylate addition to radicals generated at C_5 from either a 5-*syn*-acid (**5b**) or 5-iodo-2-azabicyclo[2.1.1]hexane.[14] Phenyl substitution (R = 6-*syn*-Ph along with a 5-*anti*-heteroatom) was effected via a rearrangement route,[8] and also a 6:1 *syn*/*anti*-Ph mixture of **6b** and **7** were synthesized using a lead tetraacetate-initiated decarboxylative radical arylation of acid **5b**.[14] For 5-*syn*/*anti*-carbonyl substitution several photochemical syntheses introduced a 5-acetyl group[11,12,15] or 1,5-fused cyclohexanone ring systems.[16] Three routes to 5-carboxy azabicycles have been described. One somewhat lengthy route to the R = 5-*syn*-acid **5a** involves ring closure and subsequent modification of substituents.[9] A 6-acetyl-5-ester, of undefined stereochemistry, has been prepared from an azabicycle with an R = 5-*syn*-orthoester and a 6-*syn*-acetyl substituent using a photochemical ring closure sequence and subsequent synthetic modification of the orthoester.[11] We have described[17] a shorter approach to the preparation of R = 5-*syn*-**5b** and 5-*anti*-carboxy-2-azabicyclo[2.1.1]hexane (**8b**), useful for multigram quantities of the 5-*syn*-acid **5b**, from readily prepared and separable (9:1) 5-*syn*/*anti*-acetyl-2-azabicyclo[2.1.1]hexanes **9b/10** first described by Kwak and Winkler.[15] There remains a need for stereoselective synthetic routes that introduce 5-*anti*-alkyl and 5-*anti*-carboxy substituents onto 2-azabicyclo[2.1.1]hexanes.

A second synthetic challenge is the preparation of 2-azabicyclo[2.1.1]hexanes with functional groups and substituents on the same methylene bridge. There are two examples of such structures. These are the 6-*syn*-fluoro-6-*anti*-methyl-5-*anti*-alcohol **11** and the 6-*syn*-hydroxy-6-*anti*-methyl-5-*anti*-alcohol **12**.[8] There are no similar structures reported with the reversed stereochemistry at the tertiary carbon.

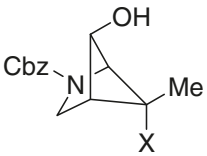


a Z = Cbz
b Z = BOC



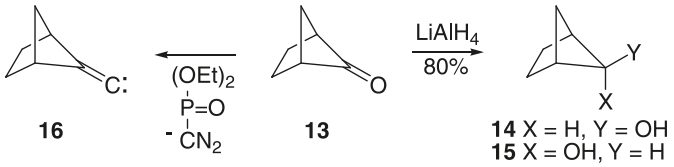
3 R = CH_2OH
4 R = $CH_2CH_2CO_2Me$
5 R = COOH
6 R = Ph
9 R = $COCH_3$

7 R = Ph
8 R = COOH
10 R = $COCH_3$



11 X = F
12 X = OH

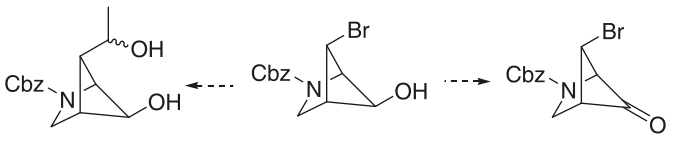
A disconnection of tertiary alcohol **12** suggested that an azabicyclic ketone might be a useful synthon for introduction of substituents at the C_5 position, although the stereochemistry of the addition to the ketone is an issue.[5a] The corresponding carbocycle (bicyclo[2.1.1]hexan-5-one **13**) has been synthesized[18] in an optimized 54% yield by alcohol oxidation,[18c] but only two nucleophilic addition reactions have been reported. Reduction of **13** gives and 82:18 exo/endo mixture of alcohols **14/15** in which the major product derives from hydride attack on the side of the ethylene bridge.[18a,18b] The only carbon nucleophile reported for reaction with ketone **13** was diethyl(diazomethyl)phosphonate; the transient alkylidene carbene **16** from this reaction does not retain evidence for the initial facial selectivity of nucleophilic attack.[19]



16 **13**

14 X = H, Y = OH
15 X = OH, Y = H

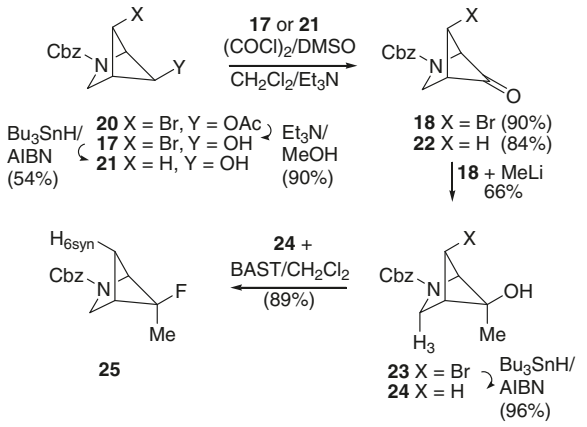
In this paper we show how a readily available pyridine-derived alcohol **17** can be oxidized to ketone **18**, and how subsequent carbonyl addition reactions provide solutions to the stereochemical problems outlined previously.[20] Stereocontrolled syntheses of tertiary alcohols with 5-*syn*-alkyl or 5-*syn*-aryl substituents, 5-*anti*-alkyl and 5-*anti*-carboxy compounds, as well as 5-*exo*-alkylidenes will be described. Additionally, we show how the bromoalcohol **17** can be used to incorporate a 6-*anti*-alkyl group onto the 2-azabicyclo [2.1.1]hexane skeleton to give diol **19** using a radical trapping process. Since 5(6)-substituents in these azabicycles are often compatible with subsequent introduction of substituents at the C_1 and C_3 positions, the functional group modifications described herein should prove useful in the preparation of more highly functionalized 5-substituted 2-azabicyclo[2.1.1]hexanes.[21]



19 **17** **18**

Results and discussion

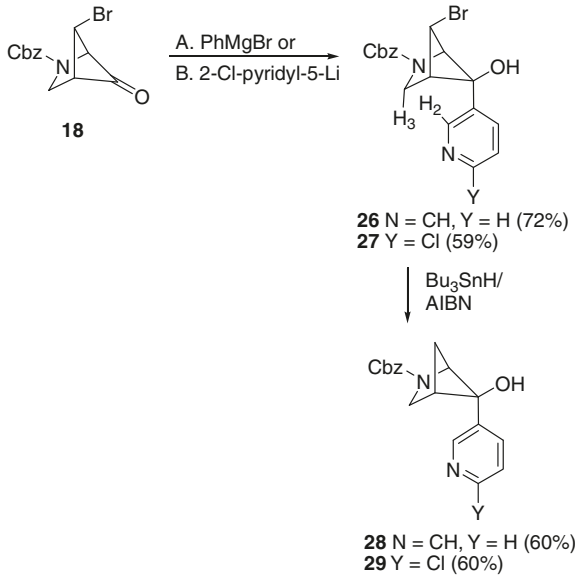
Hydrolysis of the bromoacetate **20**, prepared in three steps from pyridine,[20] afforded bromoalcohol **17** (90%), which was oxidized using Swern conditions (oxalyl chloride / DMSO / CH_2Cl_2 / Et_3N) to give the bromoketone **18** in 90% yield.[22] The ketone showed an IR carbonyl band at 1818 cm^{-1}. Debromination of bromoalcohol **17** using tributyltin hydride[23] gave alcohol **21** that was also oxidized to ketone **22** using the Swern procedure. The ketone **22** has an IR carbonyl stretch band at 1809 cm^{-1}. The parent carbocycle **13** has its carbonyl band at 1799 cm^{-1}.[18a]



[1]

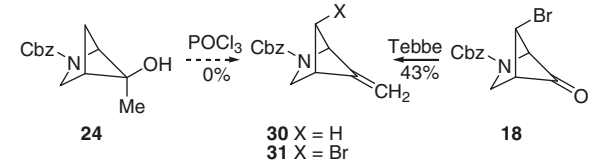
Addition of MeLi to ketone **18** afforded a single adduct **23** that was shown to have 6-*syn*-Me stereochemistry by NOE interaction of the methyl and an H_3 proton. Reductive removal of the bromine of **23** using tributyltin hydride[23] gave the alcohol **24**. Notably, the 5-*syn*-methyl and 5-*anti*-hydroxyl groups in **23** and **24** have complementary (inverted) stereochemistry relative to the tertiary alcohol **12** formed by a rearrangement pathway. The alcohol **24** was converted to the fluoride **25** by reaction with bis(2-methoxylethyl)aminosulfur trifluoride (BAST).[24] The absence of W-coupling between the 5-*anti*-fluorine atom and H_{6syn} enabled a stereochemical assignment for fluoride **25** that is consistent with precedent for retention of stereochemistry for an *anti*-alcohol displacement in this azabicyclic ring system.[25]

Addition of phenylmagnesium bromide or 2-chloro-pyridyl-5-lithium[26] to bromoketone **18** provided the arylalcohols **26** or **27**, respectively. The stereochemical assignment for both **26** and **27** were shown to be 6-*syn*-aryl by NOE interaction between H_2 of the respective aryl and pyridyl rings and H_3. The bromine atoms of **26** and **27** were reductively removed to give alcohols **28** and **29**; in the latter case with retention of the pyridyl chlorine atom. The syn relationship of the nitrogen atom in the attached chloropyridyl group at C_6 and the β-amino group embedded in the bicyclic ring is found also in epibatidine.[5a]



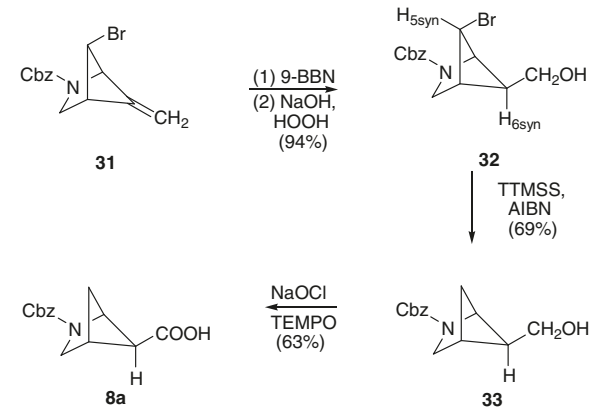
[2]

As part of an effort to prepare β-amino acids based on conformationally constrained pyrrolidines,[6] we desired a stereocontrolled synthetic route to the 5-*anti*-carboxylic acid **8b**. Toward this end, we attempted, unsuccessfully, to prepare 5-*exo*-methylene derivative **30** by dehydration of alcohol **24** using $POCl_3$/pyridine. Successful preparation of 5-*anti*-bromo-6-*exo*-methylene derivative **31** was achieved by reacting bromoketone **18** with the Tebbe reagent (48 h).[27] The Wittig reaction of bromoketone **18** with triphenylphosphonium methylide was unsuccessful as a route to 6-*exo*-methylene **31**.



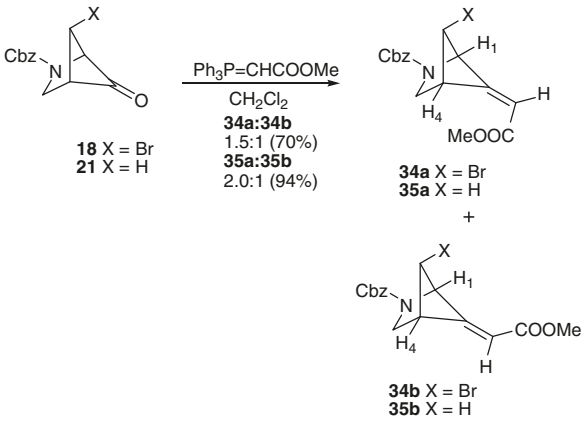
[3]

Alkene **31** was best converted to bromoalcohol **32** (94%) with 9-BBN at room temperature for 7 h, followed by basic hydrogen peroxide.[28] The 5-anti-6-anti- stereochemistry for **32** was shown by a W-plan coupling (J = 7.2 Hz) between H_{5syn} and H_{6syn}. Debromination of **32** with tris(trimethylsilyl) silane (TTMSS) gave alcohol **33** (69%)[29]; subsequent oxidation with NaOCl/TEMPO afforded the desired 5-*anti*-acid **8a**.[30]



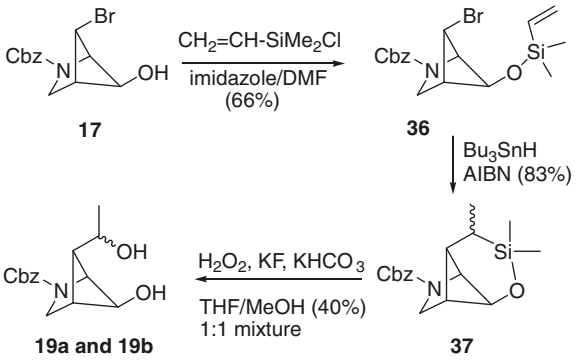
[4]

The difficulty in isolating useful product from the reaction of bromoketone **18** with $Ph_3P{=}CH_2$ was noted previously (see eq. [3]). Surprisingly, ketones **18** and **21** reacted with the conjugated ylide methyl(triphenylphosphoranylidene)acetate in CH_2Cl_2 to give mixtures of stereoisomeric esters **34a**–**34b** and **35a**–**35b**, respectively (eq. [5]).[31] This stable ylide generally reacts poorly, if at all, with ketones. The major isomers in both cases have the ester oriented toward C_4 (*E*-ester) as indicated by NOE experiments in which the vinylidene hydrogen interacts with H_1. In the minor isomer **34b**, NOE experiments indicate the vinylidene hydrogen is closer to H_4, whereas in the minor isomer **35b**, the *Z*-ester stereochemistry could not be confirmed by NOE experiments because of the overlap between H_1 and the vinylidene hydrogen.



[5]

The 5-anti-6-anti- substituents in bromoalcohol **17** are ideally situated to take advantage of an intramolecular cyclization approach to introduce a functionalized 5-*syn*-alkyl substituent by use of a silicon-containing tether.[32] Accordingly, alcohol **17** was reacted with dimethylvinylchlorosilane to afford the vinylsilyl ether **36**. The radical generated by abstraction of the bromine of **36** with tributyltin hydride (1.5 equiv) at reflux afforded tethered silyl ether **37** formed by 5-exo-cyclization (83%). Tamao oxidation of **37** gave a 1:1 mixture of alcohols **19a**–**19b** (40%), epimeric at the side-chain hydroxyl position.[33]



[6]

Conclusion

Addition reactions with bromoketone **18** and ketone **22** have been shown to extend the stereochemical diversity of alkyl-, acyl-, and aryl-substituted 2-azabicyclo[2.1.1]hexanes. It is now possible to access 2-azabicyclo[2.1.1]hexanes with 5(6)-*anti*-carboxy (or alkyl) groups and also 5(6)-*syn*-alkyl (or aryl) tertiary alcohols. Organolithium and organomagnesium carbonyl additions, as well as 9-BBN addition and catalytic hydrogenation of *exo*-alkylidines, have been shown to be stereoselective for attack from the face syn to the nitrogen-containing bridge.[34] In separate experiments the usefulness of the bromine substituent of bromoalcohol **17** for the introduction of 5-*anti*-alkyl groups by a tethering process has been demonstrated. The 5-bromine substituents in products derived from ketone **18** should prove useful in further synthetic manipulations of this azabicyclic ring system.[5a,35] The results have implications for development of bridged pyrrolidine-based pharmaceuticals and the preparation of β-amino acid oligomers with useful functionalities.

Experimental section

General procedures

Thin layer chromatography (TLC) was performed on precoated plates of silica gel GF 250–1000 μm. Column chromatography was performed on silica gel Merck grade 60 (230–400 mesh). Reagent chemicals were obtained from commercial suppliers, and reagent grade solvents were used without further purification. Both the ^{1}H and ^{13}C NMR spectra (see Supplementary data) are often complicated by the presence of carbamate conformers, and resonances are often presented as pairs. Chemical shifts are expressed in ppm relative to internal TMS (^{1}H) or solvent $CDCl_3$ (^{13}C). High-resolution mass spectra were performed at Merck Research Laboratories (West Point, Pennsylvania) using FAB ionization methods.

N-Benzyloxycarbonyl-6-*anti*-bromo-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (17)[20]

Triethylamine (20 mL) was added to the known[20] bromoacetate **20** (2.0 g, 5.6 mmol) in MeOH (10 mL) at room temperature (RT). The resulting mixture was stirred for 12 h. The solvent was removed, and purification of the resulting crude oil by column chromatography gave the known alcohol **17** (1.57 g, 90%) at R_f = 0.35 (2:1 hexanes/ether). ^{1}H NMR δ: 7.26 (s, 5H), 5.07 (s, 2H), 4.37 (d, J = 5.4 Hz, 1H), 4.19 (d, J = 7 Hz, 1H), 4.01 (d, J = 7.5 Hz, 1H), 3.53 (d, J = 8.8 Hz, 1H), 3.47 (d, J = 8.8 Hz, 1H), 3.5–3.4 (br, 1H), 2.92 (d, J = 7 Hz, 1H). ^{13}C NMR δ: 155.7, 136.5, 129.0, 128.7, 128.5, 85.4, 67.8, 66.4, 65.9, 52.4, 50.4, 49.7.

N-Benzyloxycarbonyl-5-*anti*-bromo-6-oxo-2-azabicyclo [2.1.1]hexane (18) — General procedure

Oxalyl chloride (360 mg, 2.76 mmol) dissolved in CH_2Cl_2 (10 mL) was placed in a 50 mL flask. The contents of the flask were cooled to –78 °C and DMSO (452 mg, 5.25 mmol) in CH_2Cl_2 (3 mL) was added dropwise over 5 min. Stirring was continued at –78 °C for 10 min followed by addition of the alcohol **17** (730 mg, 2.3 mmol) in CH_2Cl_2 (3 mL) over 10 min. The reaction mixture was stirred for 30 min, and triethylamine (1.16 g, 11.5 mmol) was added in over 10 min with stirring at –78 °C for 1 h. The cooling bath was removed and the reaction was stirred for an additional 3 h. Water (20 mL) was added at RT. After 10 min of stirring, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo. Column chromatography gave pure ketone **18** (642 mg, 90%) at R_f = 0.32 (1:1 hexanes / diethyl ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.16 (s, 2H), 4.76 (d, J = 6.6 Hz, 1H, H_1), 3.90 (s, 1H, H_5), 3.77 (dd, J = 9.1, 1.4 Hz, 1H, H_3), 3.61 (dd, J = 9.0, 0.9 Hz, 1H, H_3), 3.49 (dbr, J = 6.6 Hz, 1H, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 189.2 (C_6), 154.9 (C=O), 136.1, 129.1, 128.9, 128.7, 75.3 (C_1), 68.2 (CH_2Ph), 64.9 (C_4), 47.5 (C_5), 40.8 (C_3). HRMS m/z found: 310.0074; calcd for $C_{13}H_{13}{}^{79}BrNO_3$ (M + H)

310.0078; *m/z* found: 312.0053; calcd for $C_{13}H_{13}{}^{81}BrNO_3$ (M + H): 312.0058.

N-Benzyloxycarbonyl-6-*anti*-hydroxy-2-azabicyclo[2.1.1] hexane (21) — General procedure

Bromoalcohol **17** (300 mg, 0.96 mmol) dissolved in toluene (17 mL) was degassed for 30 min with argon. AIBN (16 mg, 0.96 mmol) and tristrimethylsilylsilane (0.59 mL, 1.92 mmol) were added and the reaction was heated to 100 °C for 2 h under argon.[23] The reaction was allowed to come to RT and the solvent was removed in vacuo. The resultant oil was purified by preparative silica gel TLC to yield alcohol **21** (150 mg, 67%) at $R_f = 0.38$ (1:1 ethyl acetate / hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (m, 5H), 5.19 (s, 2H), 4.26, 4.26 (2 d, J = 7.2, 7.5 Hz, 1H, H_1), 4.12 (d, J = 7.2 Hz, 1H, H_6), 3.45 (s, 2H, $2H_3$), 3.08 (br, 1H, OH), 2.97 (2 br, 1H, H_4), 2.72, 2.71 (2 d, J = 7.2, 7.2 Hz, 2H, H_{5x}), 1.68 (dd, J = 7.2, 7.2 Hz, H_{5n}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.2, 137.1, 128.9, 128.4, 128.2, 81.5 (C_6), 67.2 (CH_2Ph), 63.9 (C_1), 48.7 (C_3), 44.3 (C_4), 37.3 (C_6). HRMS *m/z* found: 256.0946: calcd for $C_{13}H_{15}NO_3Na$ (M + Na) *m/z*: 256.0950.

N-Benzyloxycarbonyl-5-oxo-2-azabicyclo[2.1.1]hexane (22)

According to the general procedure, oxalyl chloride (0.055 mL, 0.63 mmol) in dry CH_2Cl_2 (2 mL) was cooled to –78 °C. DMSO (0.09 mL, 1.26 mmol) was added by syringe, then stirred for 15 min. To this the alcohol **21** (74 mg, 0.32 mmol) dissolved in CH_2Cl_2 (1 mL) was added slowly over 15 min, followed by NEt_3 (0.18 mL, 1.26 mmol) over 10 min. After 15 min at –78 °C, the mixture was allowed to stir in a 0 °C bath for 2 h. The reaction was diluted with CH_2Cl_2 (6 mL) and washed with dilute HCl (3 × 3 mL, 0.1 N). Workup afforded ketone **22** as a pale yellow oil (64 mg, 84%) that remained at the origin when eluted with ether on a silica gel TLC plate. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.30 (m, 5H), 5.16–5.14 (m, 2H, benzyl CH_2), 4.67 (d, J = 6.3 Hz, 1H, H_1), 3.62 (m, 2H, H_3), 3.30 (dd, J = 6.5, 3.2 Hz, 1H, H_4), 1.97 (dm, 1H, J = 8.9 Hz, H_{6anti}), 1.79 (bd, 1H, J = 8.9 Hz, H_{6syn}). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 189.3, 155.2, 136.1, 128.5, 128.0, 69.6, 67.2, 55.8, 46.4, 29.6. HRMS *m/z* found: 232.0971; calcd for $C_{13}H_{14}NO_3$ (M + H) *m/z*: 232.0968.

N-Benzyloxycarbonyl-6-*anti*-bromo-5-*anti*-hydroxy-5-*syn*-methyl-2-azabicyclo[2.1.1]hexane (23)

MeLi (10.6 mg, 0.48 mmol) was added to cooled ether (5 mL, dry) at 0 °C with argon protection. After stirring for 5 min, bromoketone **18** (100 mg, 0.32 mmol) dissolved in ether (5 mL) was added dropwise over 10 min. Stirring was continued for 2 h. The cooling bath was removed and concd NH_4Cl (10 mL) was added at RT. The reaction mixture was stirred for an additional 5 min. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and chromatography of the residue gave alcohol **23** (69 mg, 66%) at $R_f = 0.31$ (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 5H), 5.16 (m, 2H), 4.36, 4.31 (2 d, J = 6.8 Hz, 1H, H_1), 4.01 (s, 1H, H_5), 3.62, 3.61 (2 s, 1H, OH), 3.53 (d, J = 9.2 Hz, 1H, H_3), 3.48 (d, J = 9.2 Hz, 1H, H_3), 2.83 (d, J = 6.8 Hz, 1H, H_4), 1.24, 1,21 (2 s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 136.4, 128.8, 128.5, 128.4, 128.2, 127.9, 86.9, 86.7 (C_6), 68.0, 67.8 (C_1), 67.4, 67.2 (CH_2Ph), 52.3 (C_3), 50.6, 50.3 (C_4), 49.2, 49.0 (C_5), 20.3 (CH_3). HRMS *m/z* found: 348.0203; calcd for $C_{14}H_{16}{}^{79}BrNNaO_3$ (M + Na): 348.0211; *m/z* found: 350.0185; calcd for $C_{14}H_{16}{}^{81}BrNNaO_3$ (M + Na): 350.0191. The stereochemistry at C_6 was confirmed by an NOE experiment that showed a Me/H_3 interaction.

N-Benzyloxycarbonyl-5-*anti*-hydroxy-5-*syn*-methyl-2-azabicyclo[2.1.1]hexane (24)

Following the general procedure, AIBN (12 mg, 0.07 mmol) was added to the bromoalcohol **23** (480 mg, 1.47 mmol) in benzene (20 mL) with argon protection. The resulting mixture was refluxed for 5 min, and Bu_3SnH (595 μL, 2.20 mmol) was added by syringe. The reaction was refluxed for an additional 10 h. The solvent was removed in vacuo and column chromatography of the residue gave alcohol **24** (350 mg, 96%) at $R_f = 0.18$ (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.16 (s, 2H), 4.18, 4.15 (2 d, J = 6.8 Hz, 1H, H_1), 3.37 (d, J = 9.2 Hz, 1H, H_3), 3.34 (d, J = 9.2 Hz, 1H, H_3), 2.85 (d, J = 7.2 Hz, 1H, H_6), 2.55 (br, 1H, H_4), 2.42 (br, 1H, OH), 1.43 (d, J = 7.2 Hz, 1H, H_6), 1.17 (s, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.5, 155.9 (C=O), 137.0, 128.6, 128.1, 128.0, 83.8, 83.5 (C_5), 67.0, 66.9 (CH_2Ph), 65.9, 65.4 (C_1), 48.5 (C_3), 46.5 (C_4), 36.2, 36.0 (C_6), 19.1. HRMS *m/z* found: 248.1285; calcd for $C_{14}H_{18}NO_3$ (M + H): 248.1281; *m/z* found: 270.1090; calcd for $C_{14}H_{17}NNaO_3$ (M + Na): 270.1100.

N-Benzyloxycarbonyl-5-*anti*-fluoro-5-*syn*-methyl-2-azabicyclo[2.1.1]hexane (25)

A 50 wt % BAST solution in THF (299 μL, 0.8 mmol) was added dropwise to a solution of tertiary alcohol **24** (100 mg, 0.4 mmol) in CH_2Cl_2 (20 mL) at RT. The solution was stirred for 16 h. The solvent was removed in vacuo and column chromatography of the residue gave the fluoride **25** (90 mg, 89%) at $R_f = 0.44$ (1:1 hexanes / diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.34 (m, 5H), 5.17 (s, 2H), 4.34. 4.30 (2 d, J = 7.2 Hz, 1H, H_1), 3.42 (d, J = 9.3 Hz, 1H, H_3), 3.34 (d, J = 9.3 Hz, 1H, H_3), 2.77 (br, 2H, H_4 and H_6), 1.56, 1.53 (2 d, J = 7.8 Hz, 1H, H_6), 1.30, 1.28 (2 d, J = 22.2 Hz, 3H, Me). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.6, 156.0 (C=O), 137.1, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 105.4, 103.4 (C_5), 67.4 (CH_2Ph), 64.8, 64.5, 64.2, 64.0 (C_1), 48.3 (C_3), 46.3, 46.2, 46.0 (C_4), 35.7, 35.6 (C_6), 15.9, 15.6 (CH_3). HRMS *m/z* found: 250.1233; calcd for $C_{14}H_{17}FNO_2$ (M + H): 250.1238.

N-Benzyloxycarbonyl-5-*anti*-bromo-6-*anti*-hydroxy-6-*syn*-phenyl-2-azabicyclo-[2.1.1]hexane (26)

Anhydrous diethyl ether (3 mL, dry) was added to bromoketone **18** (100 mg, 0.32 mmol) at 0 °C with argon protection. PhMgBr (87 mg, 0.48 mmol) was added to the mixture over 5 min. After stirring for 1 h, the cooling bath was removed and concd NH_4Cl (5 mL) was added at RT. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined ether layers were dried over $MgSO_4$ and then filtered. Solvent

removal in vacuo and column chromatography of the residue gave pure bromide **26** (90 mg, 72%) at R_f = 0.45 (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33~6.96 (m, 10H, H on Ph), 5.09, 4.94, 4.93, 4.84 (4 d, J = 12.4, 12.4, 12.8, 12.8 Hz, 2H, CH_2Ph), 4.78, 4.74 (2 d, J = 7.2 Hz, 1H, H_1), 4.07, 4.05 (2 s, 1H, H_5), 3.40, 3.38 (2 br, 1H, OH), 3.33 (d, J = 9.2 Hz, 1H, H_3), 3.22, 3.21 (2 d, J = 7.2 Hz, 1H, H_4), 2.98 (d, J = 9.2 Hz, 1H, H_3). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C) δ: 7.21 (m, 5H), 5.11~4.86 (m, 2H), 4.78, 4.74 (2 d, J = 7.0, 7.1 Hz, 1H, H_1), 4.09 (s, 1H, H_5), 3.44, 3.42 (2 br, 1H, OH), 3.38 (d, J = 9.0 Hz, 1H, H_3), 3.24, 3.22 (2 d, J = 7.2 Hz, 1H, H_4), 3.03 (d, J = 9.0 Hz, 1H, H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.5, 154.4 (C=O), 140.1, 140.0, 136.6, 136.5, 129.2, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 127.7, 125.9, 125.7 (C on Ph), 89.7, 89.5 (C_6), 67.6, 67.0 (CH_2Ph), 66.6, 65.9 (C_1), 51.7, 51.4 (C_4), 49.2, 49.0 (C_5), 48.9, 48.7 (C_3). HRMS *m/z* found: 388.0565; calcd for $C_{19}H_{19}{}^{79}BrNO_3$ (M + H): 388.0543.

N-Benzyloxycarbonyl-5-*anti*-bromo-6-*syn*-(6-chloro-3-pyridyl)-6-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (27)

At –78 °C, *n*-butyllithium in hexane (1.6 mol/L) (0.40 mL, 0.65 mmol) was added dropwise to a solution of 2-chloro-5-iodopyridine (0.155 g, 0.65 mmol) in dry THF (10 mL). The reaction was stirred for 30 min at –78 °C, whereupon the ketone **18** (0.200 g, 0.65 mmol) in dry THF (10 mL) was added slowly. The reaction was stirred at –78 °C for 0.5 h followed by 2 h at RT. The reaction was quenched with sat. aq ammonium chloride (10 mL), diluted with water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with water, dried, and solvent was evaporated in vacuo to give the crude product. Column chromatography on silica gel, eluting with 1:1 hexanes / diethyl ether, gave the alcohol **27** (160 mg, 59%) at R_f = 0.27 (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.11, 8.08 (2 br, 1H, H_2'), 7.30 (m, 5H), 7.04 (m, 2H, H_4' and H_5'), 4.95 (3 d, J = 12.0, 12.4, 12.8 Hz, 2H, CH_2Ph), 4.76 (br, 1H, H_1), 4.29 (br, 1H, OH), 4.08 (s, 1H, H_5), 3.40 (d, J = 9.2 Hz, 1H, H_{3n}), 3.25 (br, 1H, H_4), 2.88 (d, J = 9.2 Hz, 1H, H_{3x}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 154.6 (C=O), 151.4, 148.1, 137.2, 136.9, 136.3, 134.7, 129.2, 129.0, 128.7, 128.2, 125.9, 124.8, 87.6 (C_6), 68.1, 67.6 (CH_2Ph), 66.6, 65.9 (C_1), 52.0, 51.7 (C_4), 49.2 (C_3), 49.1, 48.7 (C_5). HRMS *m/z* found: 423.0105; calcd for $C_{18}H_{17}{}^{79}Br{}^{35}ClN_2O_3$ (MH): 423.0106.

N-Benzyloxycarbonyl-5-*anti*-hydroxy-5-*syn*-phenyl-2-azabicyclo[2.1.1]hexane (28)

Following the general procedure, AIBN (18 mg, 0.05 equiv) was added to the bromoalcohol **26** (0.84 g, 2.16 mmol) in benzene (25 mL) with argon protection. The resulting mixture was refluxed for 5 min and Bu_3SnH (0.87 mL, 1.5 equiv) was added. The reaction was refluxed for an additional 10 h. Workup and column chromatography gave the alcohol **28** (400 mg, 60%) at R_f = 0.32 (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: = 7.27~6.91 (m, 10H), 5.00, 4.87, 4.86, 4.74 (4 d, J = 12.8 Hz, 2H, CH_2Ph), 4.51 (multiple d, J = 7.2 Hz, 1H, H_1), 3.19 (br, 1H, OH), 3.13, 3.10 (2 d, J = 8.8 Hz, 1H, H_3), 2.89~2.80 (m, 3H, H_3, H_4, and H_6), 1.43 (d, J = 7.2 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.4, 155.3 (C=O), 140.1, 137.3, 137.2, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 128.0, 127.6, 126.5, 126.3, 87.3, 87.1 (C_6), 67.1, 66.5 (CH_2Ph), 64.4, 63.8 (C_1), 48.3, 48.1 (C_3), 46.1, 45.8 (C_4), 35.5, 35.3 (C_5). HRMS *m/z* found: 332.1251; calcd for $C_{19}H_{19}NNaO_3$ (M + Na): 332.1257.

N-Benzyloxycarbonyl-5-*syn*-(6-chloro-3-pyridyl)-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (29)

Following the general procedure, AIBN (2 mg, 0.05 equiv) was added to bromoalcohol **27** (0.130 g, 0.31 mmol) in 15 mL benzene with argon protection and Bu_3SnH (0.124 mL, 0.46 mmol) was added. After 10 h reflux, workup and column chromatography gave the alcohol **29** (60 mg, 60%) at R_f = 0.13 (1:2 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.03, 7.99 (2 s, 1H, H_2'), 7.29 (m, 5H), 7.02 (m, 2H, H_4' and H_5'), 5.02, 4.95, 4.82 (3 d, J = 12.0, 12.0, 12.8 Hz, 2H, CH_2Ph), 4.58, 4.56 (2 d, J = 7.2 Hz, 1H, H_1), 3.60~3.00 (br, 1H, OH), 3.25, 3.24 (2 d, J = 9.2 Hz, 1H, H_{3n}), 2.98 (m, 2H, H_4 and H_6), 2.76 (d, J = 9.2 Hz, 1H, H_{3x}), 1.55 (d, J = 7.2 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.3 (C=O), 151.2, 148.3, 148.1, 137.6, 137.4, 136.9, 134.8, 129.0, 128.6, 128.4, 127.9, 124.7, 84.8, 84.7 (C_5), 67.4, 66.9 (CH_2Ph), 64.4, 63.7 (C_1), 48.1, 47.9 (C_3), 46.4, 46.0 (C_4), 36.1, 35.8 (C_6). HRMS *m/z* found: 345.0989; calcd for $C_{18}H_{18}{}^{35}ClN_2O_3$ (MH): 345.1001. The stereochemistry on C_5 was confirmed by NOE. When $H_{2'}$ was irradiated, the signals of H_1, H_4, and H_{3x} were increased.

Attempted dehydration of alcohol 24 to give olefin 30

The tertiary alcohol **24** (200 mg, 0.6 mmol) in pyridine (5 mL) was placed in a 50 mL flask. To this stirred solution, phosphorus oxychloride (270 μL) was added at 0–5 °C, and the mixture was stirred for 14 h at RT. The reaction mixture was diluted with diethyl ether (10 mL) and slowly quenched with water (10 mL) to hydrolyze the excess phosphorus oxychloride. The layers were separated and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered. Solvent removal gave only 10 mg of crude oil that did not contain the desired alkene **30**.

N-Benzyloxycarbonyl-5-*anti*-bromo-6-methylene-2-azabicyclo[2.1.1]hexane (31)

To a solution of ketone **18** (1.26 mmol, 390 mg) in dry THF (15 mL) at 0 °C was added a toluene solution of the Tebbe reagent (2.52 mL of 0.5 mol/L solution, 1.26 mmol).[27] The mixture was allowed to warm to RT and stirred for 2 days, whereupon Et_2O (20 mL) was added followed slowly followed by 5 drops of aq NaOH (0.1 mol/L). After gas evolution ceased, the mixture was dried (Na_2SO_4) and filtered using a Celite pad. The solvent was removed in vacuo and purification of the residue by chromatography on silica gel (4:1 hexanes / diethyl ether) gave the bromoalkene **31** (165 mg, 43%) at R_f = 0.41 (1:1 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 5H), 5.08 (s, 2H), 4.87 (br, 1H, $=CH_2$), 4.81 (s, 1H, $=CH_2$), 4.57 (br, 1H, H_1), 3.85 (s, 1H, H_5), 3.53 (d, J = 8.5 Hz, 1H, H_3), 3.42 (d, J = 8.5 Hz, 1H, H_3), 3.19 (d, J = 6.4 Hz, 1H, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7 (C=O), 148.5 (C_6), 136.7,

128.9, 128.8, 128.7, 128.5, 128.4 (Ph), 100.9 (=CH_2), 69.4 (C_1), 67.6, 67.4 (CH_2Ph), 54.5 (C_4), 50.2 (C_6), 49.6 (C_3). HRMS *m/z* found: 330.0094 (^{79}Br), 332.0070 (^{81}Br); calcd for $C_{14}H_{14}BrNO_2Na$ (MNa): 330.0100 (^{79}Br), 332.0080 (^{81}Br).

Wittig reaction of ketone 18 — Attempted synthesis of alkene 31

To a suspension of $CH_3{}^+PPh_3Br^-$ (77 mg, 0.22 mmol) in dry THF (1.1 mL) at –78 °C was added *n*-BuLi (135 μL, 0.215 mmol, 1.6 mol/L) by syringe, resulting in the appearance of a bright yellow color. After 30 min at –78 °C, ketone **18** (63 mg, 0.20 mmol) in dry THF (1.01 mL) was added slowly and allowed to rise to RT overnight. The reaction was quenched with water, and the solvent was removed in vacuo. The mixture was taken up in CH_2Cl_2 (6 mL) and washed with water (3 × 2 mL) and once with brine (1 × 2 mL). The solvent was removed in vacuo, and the resultant oil was purified by preparative TLC (4:1 hexanes/ether). Eight UV active bands were collected as fractions (63 mg total). No fraction corresponded to either starting material or the desired alkene **31**.

***N*-Benzyloxycarbonyl-5-*anti*-bromo-6-*anti*-(hydroxymethyl)-2-azabicyclo[2.1.1]-hexane (32)**

To a stirred solution of olefin **31** (150 mg, 0.49 mmol) in THF (10 mL) at 0 °C under an argon atmosphere was added 9-BBN (2.94 mL, 1.47 mmol, 0.5 mol/L solution in hexane). After the solution was stirred at RT for 7 h, 6 mol/L NaOH (1.3 mL) and 30% H_2O_2 (1.3 mL) were added at 0 °C. After stirring at RT overnight, the reaction mixture was diluted with water and extracted with diethyl ether (3 × 15 mL). The organic phase was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. Column chromatography of the residue (2:3 hexanes / diethyl ether) gave the alcohol **32** (150 mg, 94%) at R_f = 0.27 (1:1 hexanes / ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (m, 5H), 5.16 (s, 2H), 4.54 (d, *J* = 7.2 Hz, 1H, H_1), 4,51 (d, *J* = 7.2 Hz, 2H, OCH_2), 3.96 (d, *J* = 7.2 Hz, 1H, H_{5syn}), 3.61 (d, *J* = 8.8 Hz, 1H, H_3), 3.54 (d, *J* = 8.8 Hz, 1H, H_3), 3.06 (d, *J* = 7.2 Hz, 1H, H_4), 2.44 (td, *J* = 7.2, 7.2 Hz, 1H, H_{6syn}), 2.00 (2 br, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.6 (C=O), 136.7, 128.9, 128.7, 128.5, 128.3, 67.5 (OCH_2), 65.3, 64.8 (C_1), 61.4 (CH_2Ph), 58.8 (C_3), 53.5 (C_5), 52.3 (C_4), 47.0 (C_6). HRMS *m/z* found: 326.0382; calcd for $C_{14}H_{17}{}^{79}BrNO_3$ (M + H): 326.0387.

***N*-Benzyloxycarbonyl-5-*anti*-(hydroxymethyl)-2-azabicyclo [2.1.1]hexane-2-carboxylate (33)**

To a toluene (15 mL) solution of bromide **32** (250 mg, 0.77 mmol) was added TTMSS (1.18 mL, 3.83 mmol) and a catalytic amount of AIBN. The resulting solution was refluxed under argon for 12 h until no starting material remained. The solvent was removed and purification of the residue by silica gel flash column chromatography gave alcohol **33** (130 mg, 69%) at R_f = 0.13 (1:1 hexanes / ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (m, 5H), 5.16 (s, 2H, CH_2Ph), 4.35 (d, *J* = 7.2 Hz, 1H, H_1), 3.89 (d, *J* = 7.6 Hz, 2H, OCH_2), 3.46 (d, *J* = 8.4 Hz, 1H, H_3), 3.42 (d, *J* = 8.4 Hz, 1H, H_3), 2.74, 2.73 (2 d, *J* = 7.2 Hz, 1H, H_4), 2.41 (d, *J* = 8.0 Hz, 1H, H_6), 2.15 (td, *J* = 7.6, 7.6 Hz, H_5), 1.73 (br, 1H, OH), 1.51 (dd, *J* = 8.0, 7.6 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.1, 137.1, 128.7, 128.5, 128.3, 128.1, 127.9, 66.9 (OCH_2), 61.7, 61.2 (C_1), 61.0 (CH_2Ph), 56.6 (C_3), 50.9 (C_5), 39.7 (C4), 38.0 (C_6). HRMS *m/z* found: 248.1274; calcd for $C_{14}H_{18}NO_3$ (M + H): 248.1281.

***N*-Benzyloxycarbonyl-5-*anti*-carboxy-2-azabicyclo[2.1.1] hexane (8a)**

To a stirred solution of alcohol **33** (60 mg, 0.24 mmol) in CH_2Cl_2 (3 mL) containing TEMPO (1 mg) was added $NaHCO_3$ (aq) (0.74 mL) containing KBr (3.0 mg) and Bu_4NCl (4.0 mg). The mixture was cooled to 0 °C and a solution of NaOCl (0.60 mL), $NaHCO_3$ (0.51 mL), and brine (0.55 mL) was added dropwise. After 1 h, the layers were separated. The organic layer was extracted with water (4 × 5 mL). The combined aqueous solution was acidified with 10% HCl. The resulting solution was extracted with EtOAc (4 × 10 mL). The combined organic solution was dried over Na_2SO_4. Removal of solvent and purification of the residue by column chromatography gave acid **8a** (40 mg, 63%) at R_f = 0.32 (90:10:1 CH_2Cl_2/MeOH/TFA). ^{1}H NMR (300 MHz, CD_3OD) δ: 7.41 (m, 5H), 5.20 (s, 2H), 4.58 (br, 1H, H_1), 3.48 (br, 2H, $2H_3$), 3.08, 3.06 (2 br, 1H, H_4), 2.61 (br, 2H, H_{6x} and H_5), 2.32 (t, *J* = 7.8 Hz, 1H, H_{6n}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.6 (COOH), 156.1 (C=O), 137.3, 137.0, 128.8, 128.6, 128.3, 128.1 (C on Ph), 67.1 (CH_2Ph), 63.3 (C_1), 58.7 (C_5), 50.8 (C_3), 42.3 (C_4), 39.4 (C_6). HRMS *m/z* found: 284.0898; calcd for $C_{14}H_{15}NO_4Na$ (M + Na): 284.0893. ^{1}H COSY showed couplings between H_1 and H_4 and H_{6x} and H_{6n}.

***N*-Benzyloxycarbonyl-5-[(methoxycarbonyl)methylene]-6-*anti*-bromo-2-azabicyclo[2.1.1]hexane (stereoisomers *E*-34a and *Z*-34b)**

Methyl(triphenylphosphoranylidene)acetate (582 mg, 1.74 mmol) was added to a solution of ketone **18** (360 mg, 1.16 mmol) in 20 mL CH_2Cl_2 at RT. The reaction mixture was stirred for 2 days. The solvent was removed in vacuo and purification of the residue by column chromatography on silica gel (4:1 hexanes / diethyl ether) provided stereoisomer **34a** (110 mg, 27%), stereioisomer **34b** (170 mg, 42%), and starting material (20 mg). Analytical data for product **34a** at R_f = 0.37 (1:1 hexanes / diethyl ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.24 (m, 5H), 5.72 (s, 1H, =CH), 5.08 (s, 2H), 4.68 (br, 1H, H_1), 3.96 (d, *J* = 6.8 Hz, 1H, H_4), 3.94 (s, 1H, H_5), 3.67 (s, 3H, CH_3), 3.60 (d, *J* = 8.4 Hz, 1H, H_3), 3.50 (d, *J* = 8.4 Hz, 1H, H_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 159.7 (C_6), 155.5 (CO_2Bn), 136.5, 129.0, 128.8, 128.7, 128.6, 128.5, 108.4 (=CH), 68.9 (C_1), 67.8 (CH_2Ph), 55.2 (C_4), 52.0 (CH_3), 49.2 (C_3), 48.8 (C_5). HRMS *m/z* found: 388.0152; calcd for $C_{16}H_{16}{}^{79}BrNO_4Na$ (M + Na): 388.0155; *m/z* found: 390.0132; calcd for $C_{16}H_{16}{}^{81}BrNO_4Na$ (M + Na): 390.0134. Analytical data for product **34b** at R_f = 0.29 (1:1 hexanes / diethyl ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (m, 5H), 5.64 (s, 1H, =CH), 5.28 (d, 1H, *J* = 6.8 Hz, H_1), 5.09 (m, 2H, CH_2Ph), 3.93 (s, 1H, H_5), 3.61 (s, 3H, CH_3), 3.60 (d, *J* = 8.8 Hz, 1H, H_3), 3.59 (d, *J* = 8.8 Hz, 1H, H_3), 3.33 (d, *J* = 6.4 Hz, 1H, H_4). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.8, 157.8 (C_6), 155.5 (CO_2Bn), 136.6, 128.9, 128.8, 128.7, 128.6, 128.3, 108.3 (=CH),

68.9 (C_1), 67.7, 67.6 (CH_2Ph), 54.7 (C_4), 52.0 (CH_3), 49.4 (C_3), 48.6 (C_5). HRMS *m/z* found: 388.0145; calcd for $C_{16}H_{16}{}^{79}BrNO_4Na$ (M + Na): 388.0155; *m/z* found: 390.0124; calcd for $C_{16}H_{16}{}^{81}BrNO_4Na$ (M + Na): 390.0134.

N-Benzyloxycarbonyl-5-[(methoxycarbonyl)methylene]-2-azabicyclo[2.1.1]hexane (stereoisomers *E*-35a and *Z*-35b)

According to the preceding procedure, methyl(triphenylphosphoranylidene)acetate (430 mg, 1.29 mmol) was added to a solution of ketone **21** (210 mg, 0.86 mmol) in CH_2Cl_2 (20 mL) at RT. After 36 h, workup and column chromatography on silica gel (3:1 hexanes / diethyl ether) provided alkene **35a** (155 mg, 62%) and alkene **35b** (80 mg, 32%). Analytical data for product **35a** at R_f = 0.34 (1:1 hexanes / diethyl ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25 (m, 5H), 5.38 (br, 1H, =CH), 5.07 (s, 2H), 4.66 (br, 1H, H_1), 3.89, 3.88 (2 d, J = 6.4, 6.8 Hz, 1H, H_4), 3.63 (s, 3H, CH_3), 3.45 (d, J = 8.0 Hz, 1H, H_3), 3.41 (d, J = 8.0 Hz, 1H, H_3). 1.89, 1.88 (2 d, J = 7.6 Hz, 1H, H_6), 1.68, 1.67 (2 d, J = 7.6 Hz, 1H, H_6). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2, 159.7 (C_5), 156.2, 137.0, 129.0, 128.9, 128.7, 128.6, 128.4, 128.3, 101.5 (=CH), 67.3 (CH_2Ph), 64.3 (C_1), 51.7 (CH_3), 49.2 (C_3), 47.3 (C_4), 36.9 (C_6). HRMS *m/z* found: 288.1229; calcd for $C_{16}H_{17}NO_4Na$ (M + Na): 288.1231. Analytical data for product **35b** at R_f = 0.27 (1:1 hexanes / diethyl ether): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.26 (m, 5H), 5.29 (m, 2H, =CH and H_1), 5.09 (m, 2H, CH_2Ph), 3.60 (br, 3H, CH_3), 3.44 (d, J = 8.4 Hz, 1H, H_3), 3.36 (d, J = 8.4 Hz, 1H, H_3), 3.24 (2 d, J = 6.6 Hz, 1H, H_4), 1.89, 1.88 (2 d, J = 7.2 Hz, 1H, H_5), 1.68 (d, J = 7.2 Hz, 1H, H_5). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.5, 158.9 (C_5), 156.2 (CO_2Bn), 137.1, 128.8, 128.6, 128.4, 128.3, 128.2 (C on Ph), 101.4 (=CH), 67.2 (CH_2Ph), 64.4 (C_1), 51.7 (CH_3), 49.2 (C_3), 46.8 (C_4), 36.9 (C_6). HRMS *m/z* found: 288.1230; calcd for $C_{16}H_{17}NO_4Na$ (M + Na): 288.1231.

N-Benzyloxycarbonyl-5-*anti*-bromo-6-*anti*-[dimethyl(vinyl) silyloxy]-2-azabicyclo[2.1.1]hexane (36)

Dimethylvinylchlorosilane (0.77 g, 6.4 mmol) was added to bromoalcohol **17** (2.0 g, 6.4 mmol) in DMF (1 mL) at RT followed by addition of imidazole (0.44 g, 6.4 mmol). The resulting mixture was stirred for 2 days. Diethyl ether (20 mL) and distilled water (20 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine and then dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and purification of the residue by column chromatography gave vinylsilane **36** (1.68 g, 66%) at R_f = 0.29 (4:1 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (m, 5H), 6.16 (dd, J = 20.0, 14.8 Hz, 1H, =CH), 6.05, 6.04 (2 d, J = 14.8, 14.4 Hz, 1H, $=CH_{2cis}$), 5.82, 5.81 (2 d, J = 20.0, 20.4 Hz, 1H, $=CH_{2trans}$), 5.14 (m, 2H, CH_2Ph), 4.36 (br, 1H, H_6), 4.27 (d, J = 6.4 Hz, 1H, H_1), 4.04 (d, J = 7.2 Hz, 1H, H_5), 3.53, 3.52 (2 d, J = 9.2, 8.8 Hz, 1H, H_3), 3.47 (d, J = 8.8 Hz, 1H, H_3), 2.90 (d, J = 6.4 Hz, 1H, H_4), 0.25 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 155.7, 155.2 (C=O), 137.0, 136.6 (=CH), 134.4 ($=CH_2$), 128.9, 128.5, 128.3, 83.7 (C_6), 67.5 (CH_2Ph), 66.4, 65.7 (C_1), 50.7 (C_4), 50.0 (C_5), 49.3 (C_3), –1.26, –1.55 ($2CH_3$). HRMS *m/z* found: 418.0436; calcd for $C_{17}H_{22}{}^{79}BrNaNO_3Si$ (M + Na): 418.0451; *m/z* found: 420.0423; calcd for $C_{17}H_{22}{}^{81}BrNO_3SiNa$ (M + Na): 420.0430.

N-Benzyloxycarbonyl-5-*anti*-oxy-6-*anti*-(1-ethyl)-2-azabicyclo[2.1.1]hexyl-dimethylsilane (37) (a 2,2,3-trimethyl-1,2-oxasilepane)

AIBN (3.0 mg, 0.02 mmol) was added to a solution of compound **36** (150 mg, 0.38 mmol) in benzene (20 mL) under argon. The resulting mixture was refluxed for 5 min and tributyltin hydride (165 mg, 0.57 mmol) was added immediately. The mixture was refluxed for an additional 5 h. The solvent was removed in vacuo to give a residue that after column chromatography gave tethered silane **37** (100 mg, 83%) at R_f = 0.32 (2:1 hexanes / diethyl ether). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.30 (m, 5H), 5.11 (s, 2H), 4.15, 4.13 (2 d, J = 7.6, 7.2 Hz, 1H, H_6), 4.15, 4.08 (2 br, 1H, H_1), 3.40 (m, 2H, $2H_3$), 2.55 (br, 1H, H_5), 2.32, 2.30 (2 d, J = 7.6 Hz, 1H, H_4), 1.46 (m, 1H, CHSi), 1.05, 1.03 (2 d, J = 8.4, 7.6 Hz, 3H, CH_3), 0.20, 0.17, 0.16, 0.15 (4 s, 6H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.0 (C=O), 137.2, 128.9, 128.4, 128.2, 127.9, 84.5, 84.3 (C_6), 67.1 (CH_2Ph), 66.3, 65.7, 63.2, 62.6 (C_1), 57.9 (C_3), 49.5, 49.4 (C_4), 48.7, 48.2, 44.8, 44.5 (C_5), 19.6, 18.7 (SiCH), 15.8, 15.3 (CH_3), 1.87, 1.42 (CH_3), –1.12, –1.29 (CH_3). HRMS *m/z* found: 340.1344; calcd for $C_{17}H_{23}NO_3SiNa$ (M + Na): 340.1345.

N-Benzyloxycarbonyl-5-*anti*-hydroxy-6-*anti*-(1-hydroxyethyl)-2-azabicyclo[2.1.1]hexane stereoisomers (19)

Route A: To silylether **37** (30 mg, 0.095 mmol) in 1:1 THF/MeOH (0.2 mL) was added $KHCO_3$ (10 mg, 0.10 mmol) and KF (12 mg, 0.21 mmol). To this stirred suspension was added 30% H_2O_2 (50 mL, 0.45 mmol).[33] The suspension was stirred at RT open to the air for 28 h. Because of the small reaction volume, two additional portions of 1:1 THF/MeOH were added as the reaction solvent evaporated. The reaction was quenched by addition of 50% NaS_2O_3 (0.5 mL), and the solution (0.7 mL) was applied to a preparative silica gel TLC plate that was allowed to dry. Elution with 1:1 hexanes/Et_2O gave 6 mg (20%) of unreacted **37** (R_f = 0.5, 1:1 hexanes/Et_2O). A second elution with 2:1 EtOAc/hexanes yielded 17 mg (65%) of diols **19a** + **19b** at R_f = 0.3 (2:1 EtOAc/hexanes) taken as one fraction. The ratio of isomers was 45:55 by ^{1}H NMR based on integrations of unique peaks at δ 2.81 and 2.60. Route B: To a solution of compound **37** (520 mg, 1.64 mmol) in THF/MeOH (1:1, 15 mL), $KHCO_3$ (492 mg, 4.92 mmol), KF (190 mg, 3.28 mmol), and 90% H_2O_2 (0.78 mL, 39.36 mmol) were successively added. The resulting solution was stirred at RT for 20 h and then diluted with Et_2O. The solvent was filtered over Celite and concentrated in vacuo. Column chromatography gave diol **19a** (90 mg, 20% at R_f = 0.17, 2:1 ethyl acetate / hexanes) and diol **19b** (90 mg, 20% at R_f = 0.12, 2:1 ethyl acetate / hexanes). Spectral data for **19a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (br, 5H), 5.10 (br, 2H, CH_2Ph), 4.96, 4.84 (2 br, 1H, H_6), 4.34 (d, J = 7.2 Hz, 1H, H_1), 4.12 (d, J = 7.2 Hz, 1H, OCH), 3.85, 3.10 (2 br, 1H, OH), 3.49 (d, J = 8.8 Hz, 1H, H_3), 3.44 (d, J = 8.8 Hz, 1H, H_3), 2.60 (d, J = 7.2 Hz, 1H, H_4), 2.24 (br, 1H, OH), 2.14 (m, 1H,

H_5), 1.24 (d, J = 5.6 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.0, 137.0, 128.9, 128.4, 128.2, 83.3 (C_6), 67.3 (C_1), 66.5 (OCH), 63.7 (CH_2Ph), 63.0 (C_3), 50.8 (C_4), 46.0 (C_5), 23.2 (CH_3). HRMS *m/z* found: 300.1196; calcd for $C_{15}H_{19}NaNO_4$ (M + Na): 300.1206. Spectral data for **19b**: ^1H NMR (400 MHz, $CDCl_3$) δ: 7.34 (br, 5H), 5.14 (s, 2H), 4.79 (br, 1H, OCH), 4.14 (2 d, J = 7.2 Hz, H_1 and H_6), 3.53 (d, J = 8.8 Hz, 1H, H_3), 3.45 (d, J = 8.8 Hz, 1H, H_3), 3.00 (br, 1H, OH), 2.83 (d, J = 7.2 Hz, 1H, H_4), 2.16 (m, 1H, H_5), 1.82 (br, 1H, OH), 1.26 (d, J = 6.0 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.0, 137.0, 128.8, 128.6, 128.4, 128.2, 83.4 (C_6), 67.2 (OCH), 65.9 (C_1), 64.5 (CH_2Ph), 62.5 (C_3), 50.7 (C_4), 44.9 (C_5), 23.9 (CH_3). HRMS *m/z* found: 300.1217; calcd for $C_{15}H_{19}NaNO_4$ (M + Na): 300.1206.

Supplementary data

Supplementary data (copies of reported ^1H NMR and ^{13}C NMR spectra for all new compounds) are available with this article through the journal Web site at http://nrcresearchpress.com/doi/suppl/10.1139/v11-112.

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References

(1) For a review of non-proteinogenic amino acids from *trans*-4-hydroxy-L-proline, see Remuzon, P. *Tetrahedron* **1996**, *52* (44), 13803. doi:10.1016/0040-4020(96)00822-8.

(2) (a) Del Valle, J. R.; Goodman, M. *J. Org. Chem.* **2003**, *68* (10), 3923. doi:10.1021/jo034214l; (b) For 4-phenyl or 4-cyclohexyl pralines, see Tamaki, M.; Han, G.; Hruby, V. J. *J. Org. Chem.* **2001**, *66* (10), 3593. doi:10.1021/jo005625u; (c) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rovnyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal, K. S.; Petrillo, E. W., Jr. *J. Med. Chem.* **1988**, *31* (6), 1148. doi:10.1021/jm00401a014.

(3) (a) Sonesson, C.; Wikstrom, H.; Smith, M. W.; Svennson, K.; Carlsson, A.; Waters, N. *Bioorg. Med. Chem. Lett.* **1997**, *7* (3), 241. doi:10.1016/S0960-894X(96)00618-X; (b) Ahn, K. H.; Lee, S. J.; Lee, C. H.; Hong, C. Y.; Park, T. K. *Bioorg. Med. Chem. Lett.* **1999**, *9* (10), 1379. doi:10.1016/S0960-894X(99)00201-2.

(4) (a) For leading references, see Schafmeister, C. E.; Brown, Z. Z.; Gupta, S. *Acc. Chem. Res.* **2008**, *41* (10), 1387. doi:10.1021/ar700283y; (b) Blanchet, J.; Pouliquen, M.; Lasne, M.-C.; Rouden, J. *Tetrahedron Lett.* **2007**, *48* (33), 5727, especially refs. 1–7 therein. doi:10.1016/j.tetlet.2007.06.106.

(5) (a) For leading references with bridged pyrrolidines, see Malpass, J. R.; Handa, S.; White, R. *Org. Lett.* **2005**, *7* (13), 2759. doi:10.1021/ol0510365; (b) Bunch, L.; Liljefors, T.; Greenwood, J. R.; Frydenvang, K.; Brauner-Osborne, H.; Krogsgaard-Larsen, P.; Madsen, U. *J. Org. Chem.* **2003**, *68* (4), 1489. doi:10.1021/jo026509p; (c) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64* (6), 2050. doi:10.1021/jo982327c; (d) Han, W.; Pelletier, J. C.; Mersinger, L. J.; Kettner, C. A.; Hodge, C. N. *Org. Lett.* **1999**, *1* (12), 1875. doi:10.1021/ol990294x.

(6) Krow, G. R.; Liu, N.; Sender, M.; Lin, G.; Centafont, R.; Sonnet, P. E.; DeBrosse, C.; Ross, C. W., III; Carroll, P. J.; Shoulders, M. D.; Raines, R. T. *Org. Lett.* **2010**, *12* (23), 5438. doi:10.1021/ol1022917.

(7) For a review of synthetic approaches to 2-azabicyclo[2.1.1]hexanes, see Krow, G. R.; Cannon, K. C. *Heterocycles* **2004**, *62* (1), 877. doi:10.3987/REV-03-SR(P)1.

(8) Krow, G. R.; Lin, G.; Moore, K. P.; Thomas, A. M. C.; DeBrosse, C.; Ross, C. W., III; Ramjit, H. G. *Org. Lett.* **2004**, *6* (10), 1669. doi:10.1021/ol0494818.

(9) Lescop, C.; Mevellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66* (12), 4187. doi:10.1021/jo001790y.

(10) Piotrowski, D. W. *Synlett* **1999**, *1999* (7), 1091. doi:10.1055/s-1999-2775.

(11) Winkler, J. D.; Fitzgerald, M. E. *Synlett* **2009**, *2009* (04), 562. doi:10.1055/s-0028-1087561.

(12) Ragains, J. R.; Winkler, J. D. *Org. Lett.* **2006**, *8* (20), 4437. doi:10.1021/ol061577+.

(13) (a) Ikeda, M.; Uchno, T.; Takahashi, M.; Ishibashi, H.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull. (Tokyo)* **1985**, *33*, 3279; (b) Ikeda, M.; Takahashi, M.; Ohno, K.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull. (Tokyo)* **1982**, *30*, 2269; (c) Toda, F.; Miyamoto, H.; Takeda, K.; Matsugawa, R.; Maruyama, N. *J. Org. Chem.* **1993**, *58* (23), 6208. doi:10.1021/jo00075a013.

(14) Krow, G. R.; Huang, Q.; Lin, G.; Centafont, R. A.; Thomas, A. M.; Gandla, D.; DeBrosse, C.; Carroll, P. J. *J. Org. Chem.* **2006**, *71* (5), 2090. doi:10.1021/jo052506b.

(15) Kwak, Y.-S.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123* (30), 7429. doi:10.1021/ja010542w.

(16) (a) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44* (9), 1380. doi:10.1021/jo01323a004; (b) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40* (19), 2702. doi:10.1021/jo00907a002; (c) Swindell, C. S.; Patel, B. P.; DeSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52* (12), 2346. doi:10.1021/jo00388a002; (d) Tamura, Y.; Kita, Y.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc. Chem. Commun.* **1971**, 1167; (e) Tamura, Y.; Kita, Y.; Ishibashi, H.; Ikeda, M. *Tetrahedron Lett.* **1972**, *13* (19), 1977. doi:10.1016/S0040-4039(01)84766-3.

(17) Krow, G. R.; Lin, G.; Herzon, S. B.; Thomas, A. M.; Moore, K. P.; Huang, Q.; Carroll, P. J. *J. Org. Chem.* **2003**, *68* (19), 7562. doi:10.1021/jo0348672.

(18) (a) Wiberg, K. B.; Lowry, B. R.; Colby, T. H. *J. Am. Chem. Soc.* **1961**, *83* (19), 3998. doi:10.1021/ja01480a013; (b) McDonald, R. N.; Reineke, C. E. *J. Org. Chem. Soc.* **1967**, *32* (6), 1888. doi:10.1021/jo01281a041; (c) Müller, P.; Blanc, J. *Helv. Chim. Acta* **1979**, *62* (6), 1980. doi:10.1002/hlca.19790620627; (d) Gassman, P. G.; Atkins, T. J. *J. Am. Chem. Soc.* **1970**, *92* (19), 5810. doi:10.1021/ja00722a084; (e) Wiberg, K. B.; Lowry, B. R.; Nist, B. J. *J. Am. Chem. Soc.* **1962**, *84* (9), 1594. doi:10.1021/ja00868a016.

(19) Gilbert, J. C.; Yin, J. *J. Org. Chem.* **2006**, *71* (15), 5658. doi:10.1021/jo060652r.

(20) Krow, G. R.; Lin, G.; Rapolu, D.; Fang, Y.; Lester, W. S.; Herzon, S. B.; Sonnet, P. E.. *J. Org. Chem.* **2003**, *68* (13), 5292. doi:10.1021/jo034394z.

(21) For C1 and (or) C3 α-functionalization reactions, see Krow, G.

R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 3151. doi:10.1021/ol026509b.
(22) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43* (12), 2480. doi:10.1021/jo00406a041.
(23) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63* (23), 8558. doi:10.1021/jo9808472.
(24) (a) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M. *J. Chem. Soc. Chem. Commun.* **1999**, 215; (b) Lal, G. S.; Pez, G. P.; Pesaresi, R. J.; Prozonic, F. M.; Cheng, H. *J. Org. Chem.* **1999**, *64* (19), 7048. doi:10.1021/jo990566+; (c) For a review see Krow, G.; Cannon, K. *e-EROS;* J. Wiley & Sons: New York; October, 2010.
(25) Jenkins, C. L.; Lin, G.; Duo, J.; Rapolu, D.; Guzei, I. A.; Raines, R. T.; Krow, G. R. *J. Org. Chem.* **2004**, *69* (25), 8565. doi:10.1021/jo049242y.
(26) (a) Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59* (7), 1771. doi:10.1021/jo00086a030; (b) Hodgson, D. M.; Maxwell, C. R.; Wisedale, R.; Matthews, I. R.; Carpenter, K. J.; Dickenson, A. H.; Wonnacott, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, *2001* (23), 3150. doi:10.1039/b107414h.
(27) (a) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, *1991* (02), 165. doi:10.1055/s-1991-26406; (b) Barrett, A. G. M.; Damiani, F. *J. Org. Chem.* **1999**, *64* (4), 1410. doi:10.1021/jo9820972.
(28) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90* (19), 5281. doi:10.1021/ja01021a047.
(29) Ballestri, M.; Chatgilialoglu, C.; Clark, K. B.; Griller, D.; Giese, B.; Kopping, B. *J. Org. Chem.* **1991**, *56* (2), 678. doi:10.1021/jo00002a035.
(30) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52* (12), 2559. doi:10.1021/jo00388a038.
(31) Isaacs, N. S.; El-Din, G. N. *Tetrahedron Lett.* **1987**, *28* (19), 2191. doi:10.1016/S0040-4039(00)96078-7.
(32) Shuto, S.; Kanazaki, M.; Ichikawa, S.; Matsuda, A. *J. Org. Chem.* **1997**, *62* (17), 5676. doi:10.1021/jo970867o.
(33) (a) Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96; (b) Blaszykowski, C.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2003**, *5* (8), 1341. doi:10.1021/ol034288j.
(34) Kaselj, M.; Chung, W.-S.; le Noble, W. J. *Chem. Rev.* **1999**, *99* (5), 1387. doi:10.1021/cr980364y.
(35) Krow, G. R.; Edupuganti, R.; Gandla, D.; Choudhary, A.; Lin, G.; Sonnet, P. E.; DeBrosse, C.; Ross, C. W., III; Cannon, K. C.; Raines, R. T. *J. Org. Chem.* **2009**, *74* (21), 8232. doi:10.1021/jo901725k.