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C^1-Substituted *N-tert*-butoxycarbonyl-5-*syn-tert*-butyldimethylsilyloxymethyl-2-azabicyclo[2.1.1] hexanes as conformationally constrained β-amino acid precursors

DOI 10.1515/hc-2016-0046
Received March 18, 2016; accepted October 13, 2016

Abstract: Regioselective introduction and transformation of substituents at the C^1 carbon of *N-tert*-butoxycarbonyl-5-*syn-tert*-butyldimethylsilyloxymethyl-2-azabicyclo[2.1.1] hexane (**7**) is described. These azabicycles are precursors to conformationally constrained β-amino acids with potential to form oligomers with definite secondary structures. Selected examples of these precursors are converted into their corresponding amino acid derivatives.

Keywords: β-amino acid; constrained; foldamers; pyrrolidine-3-carboxylic acids.

Introduction

Oligomers of 2,2-disubstituted pyrrolidine-4-carboxylic acids (**1**) have shown circular dichorism-based evidence of secondary structure despite the absence of hydrogen bonding [1–4] (Figure 1).

The combination of the ring structure and the presence of two substituents at C^2 of **1** has been attributed as the source of the oligomers' secondary structure. The two C^2 substituents sterically force the amide carbonyl to be in an *s-trans* conformation (Figure 2).

In this context, 2,2-disubstituted pyrrolidine-3-carboxylic acids **2** have been proposed and predicted to show a stronger rotamer bias for resulting β-peptides, but the difficulty in introducing substituents at the hindered C^2 position of **2** made the syntheses of these β-amino acids and their corresponding β-peptides unsuccessful [2]. In response to the difficulty in synthesizing **2**, we have proposed the synthesis and application of C^1-substituted 2-azabicyclo[2.1.1]hexanes **3** which can be considered as more rigid analogs of **2**. Oligomers of four to eight β-amino acids synthesized from the unsubstituted 2-azabicyclo[2.1.1]hexane (**3**, $R_1 = H$) and the C^6-substituted 2-azabicyclo[2.1.1]hexanes both show increasingly ordered secondary folding structure with increasing oligomer length [5, 6]. The C^1 substituent and the 1,3-methano bridge may mimic the expected *s-trans* conformational bias expected for the oligomers of disubstituted carboxylic acid **2** (Figure 3). In this work, we prepared precursors of **3**, which vary at the C^1 substituent (R_1) and converted selected examples into their respective β-amino acids.

Results and discussion

The synthesis of **3** started with the key compound **4** followed by reduction of ester **5** with lithium aluminum hydride (LAH). Protection of the alcohol functionality in the resultant product **6** with *tert*-butyldimethylsilyl chloride (TBDMSCl) yielded compound **7** in 63% yield (Scheme 1).

Ester **5** was prepared in four steps starting with the photochemical cross-addition of *N*-BOC-*N*-allyl-*N*-vinyl amide **4** followed by oxidation of the resulting *syn* ketone by a known procedure [7]. Utilizing Krow's already established protocol of regioselective introduction of electrophilic substituents selectively at the C^1 bridgehead of *N*-BOC-2-azabicyclo[2.1.1]hexanes [8, 9], vs. the C^3 carbon, a variety of functional groups were incorporated in **7** (Scheme 2).

Regioselective deprotonation of **7** at C^1 with *sec*-butylithium (*s*-BuLi) in the presence of TMEDA at 0°C followed by iodomethane quench of the anion resulted in the preparation of methyl-substituted compound **8a** in 70%

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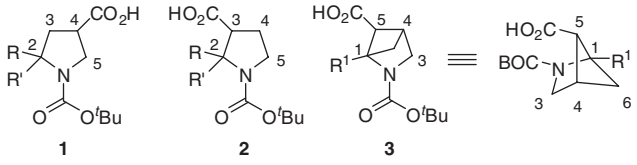


Figure 1 Disubstituted pyrrolidine carboxylic acids **1**, **2** and C[1]-substituted 2-azabicyclo[2.1.1]hexane **3**.

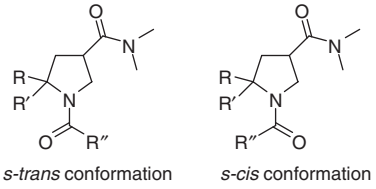


Figure 2 *s-Trans* and *s-cis* conformations of the amide carbonyl of 2,2-disubstituted pyrrolidine-4-carboxylic acids incorporated into oligomers.

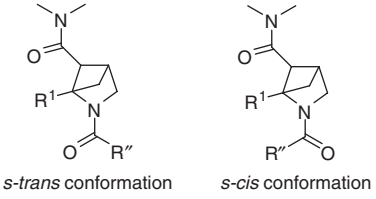


Figure 3 *s-Trans* and *s-cis* conformations of the amide carbonyl of C[1]-substituted 2-azabicyclo[2.1.1]hexanes **3** incorporated into oligomers.

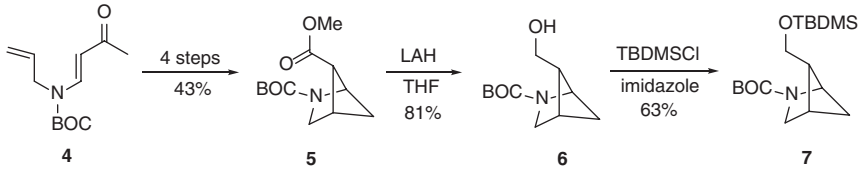
yield. The use of other electrophiles such as bromoethane and 1-bromobutane did not yield any of the expected products; only unreacted **7** was isolated. To exclude steric factors as the source of the failure of the above two alkylations, bulkier trimethylsilyl chloride was employed as an electrophile, which resulted in the formation of silylated product **8b**. Compounds **8c** ($R=CH_2OCH_3$) and **8d** ($R=CH_2$-CH=CH_2) were also prepared by quenching the C[1]-anion of **7** with methoxymethyl chloride and allyl bromide, respectively.

Surprisingly, when benzyl bromide, a more reactive electrophile, was used, 1-bromo-substituted azabicycle **8e** was isolated as the major product (63%). An ion-radical mechanism is probably operative in the incorporation of bromine in the azabicycle [10]. However, a benzyl-substituted product **8f** was isolated in low yields (14%) employing 4-methoxybenzyl bromide as the electrophile.

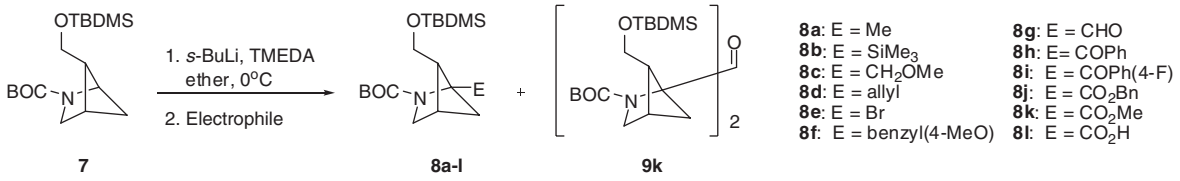
Freshly distilled *N*, *N*-dimethylformamide (DMF) was used to synthesize the desired 1-formyl-substituted azabicycle **8g**; the use of reagent grade DMF produced no product. Incorporation of benzoyl and 4-fluorobenzoyl (**8h** and **8i**) substituents was also accomplished although the latter product was isolated in a lower yield (76% and 33%, respectively).

Reactions of the lithium anion of **7** with benzyl and methyl chloroformates gave different results. The former gave only the anticipated benzyl ester **8j** (46%), while the latter resulted in the preparation of methyl ester **8k** along with the dimeric ketone by-product **9k**. The formation of **9k** may be explained by the subsequent reaction of the methyl ester **8k** with the lithium anion of **7**. To circumvent the formation of **9k**, carbon dioxide was used as electrophile resulting exclusively in the synthesis of carboxylic acid **8l**, which was then directly converted into the desired ester **8k** by treatment with $TMSCHN_2$ [11] in an overall yield of 83%.

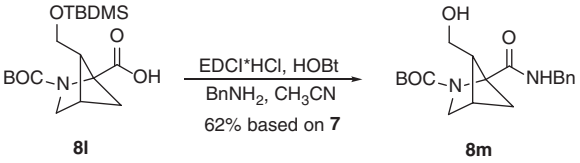
The intermediate carboxylic acid **8l** was also coupled with benzylamine in the presence of 1-[3-(dimethylamino) propyl]-3-ethylcarbodiimide hydrochloride (EDCI*HCl)



Scheme 1 Synthesis of protected alcohol **7**.



Scheme 2 Introduction of electrophilic substituents selectively at the C[1] bridgehead of **7**.



Scheme 3 Conversion of acid **8l** into amide **8m**.

and 1-hydroxybenzotriazole hydrate (HOBt) in acetonitrile to yield benzyl amide **8m** (Scheme 3) [12].

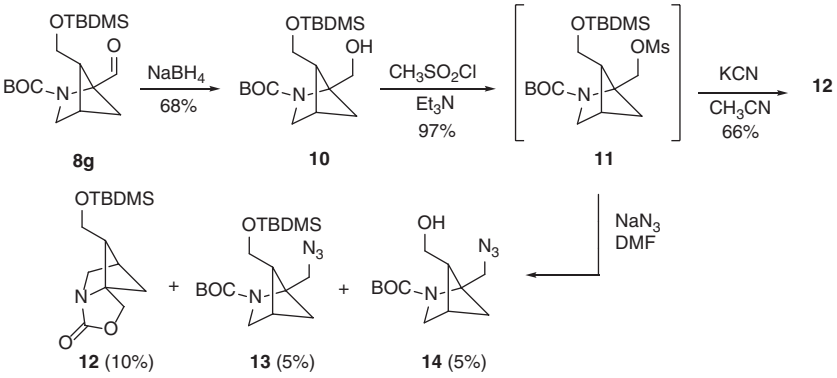
Our next goal was to modify the functional groups already introduced at C^1 in the above-generated β-amino acid precursors into biologically relevant side chains. The formyl group in compound **8g** was used as a key intermediate for these alterations. Reduction of **8g** with $NaBH_4$ gave alcohol **10** (Scheme 4). Treatment of **10** with methanesulfonyl chloride (MsCl) in the presence of triethylamine gave mesylate **11** [13]. Attempts to purify mesylate **11** by chromatography were unsuccessful; crude mesylate was therefore treated with sodium azide to give **12**–**14** although in low yields. The formation of compound **12** is a consequence of the neighboring carbamate participation in the displacement of the mesylate. The formation of a similar carbamate has been previously reported by Malpass [13]. The exclusive formation of **12** is also shown in Scheme 4 when KCN and 18-crown-6 ether [4] were used for an anticipated nucleophilic displacement of the mesylate with cyanide in **11**.

Reaction of **8g** with triphenylmethyl bromide [14] and *n*-BuLi yielded alkene **15** in 52% yield (Scheme 5). Alkene **15** was also obtained in a slightly better yield (59%) employing the Tebbe reagent [15]. Hydroboration-oxidation of the alkene side chain in **15** gave the corresponding alcohol **16** [16]. Chain extension in **8g** was carried out via a Wittig reaction with methyl(triphenylphosphoranylidene) acetate leading to the isolation of vinyl ester **17** (Scheme 6).

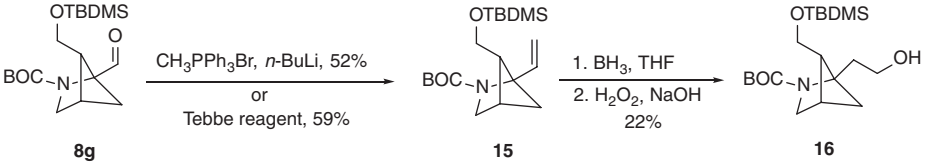
Palladium-catalyzed hydrogenation of the double bond in **17** both in protic and in aprotic solvents [17] yielded cyclobutane **20** which is a result of N-C^1 bond cleavage of the bicycle (Scheme 6). Fortunately, reduction of the same double bond with diimide (generated *in situ* from tosylhydrazine in the presence of TMEDA) [18] gave the desired product **18** with an intact [2.1.1] azabicycle core. Further, the ester group in **18** was reduced to the corresponding alcohol **19** by treatment with LAH.

The final step in the synthesis of constrained β-amino acid derivatives was oxidation of the TBDMS-protected hydroxylmethyl group at C^5 to the corresponding carboxylic acid. In two selected cases (substituent at C^5 = COPh, CO_2Me), successful oxidation with Jones reagent [19] demonstrated that there was no necessity to remove the TBDMS protecting group on the oxygen prior to oxidation (Scheme 7).

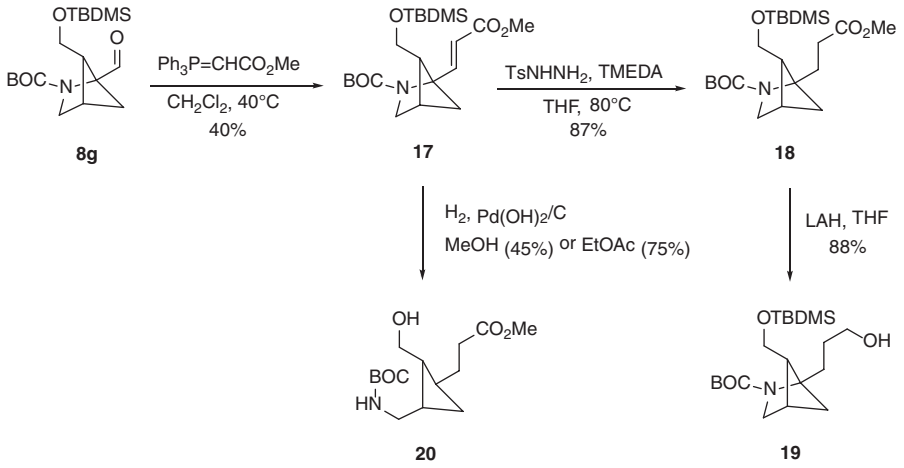
As shown in Scheme 7, both compounds **8h** and **8k** were oxidized to the corresponding acids **21h** and **21k** with CrO_3 in H_2SO_4 in reasonable yields. Acid **21h**



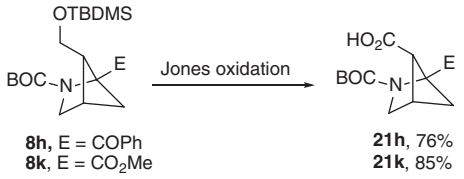
Scheme 4 Synthesis of mesylate **11** and attempted nucleophilic substitutions with KCN and NaN_3.



Scheme 5 Synthesis of alcohol **16**.



Scheme 6 Conversion of aldehyde **8g** into alcohol **19**.



Scheme 7 Direct oxidation of protected alcohols **8h** and **8k**.

was crystallized from hexane/dichloromethane and isolated as a white crystalline solid. Figure 4 shows the ORTEP of **21h** with 30% probability thermal ellipsoids. The crystal structure confirmed the endo-configuration of the carboxylic acid on C^5 (designated as C3 on the ORTEP).

The β-carboxylic acid derivative **21k** can be visualized as a constrained analog of aspartic acid (Figure 5).

Despite the successful oxidation of **8h** and **8k** to the corresponding acids, attempts to oxidize **8a** with Jones reagent to produce a constrained analog of homoalanine (**21a**) resulted in decomposition of the starting material. Likewise, oxidation under basic conditions with NaOCl and catalytic 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) [20] was also futile.

Synthesis of **21a** was eventually accomplished by deprotection of the TBDMS group of **8a** to yield **22** [21] followed by oxidation with tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO) [22]; product **21a** was obtained in a moderate yield of 33% (Scheme 8). It can be hypothesized that the presence of the methyl group at C^1 may stabilize a carbocation intermediate involved in the formation of ring cleavage products, but further investigation of the compatibility of C^1-substituted 2-azabicyclo[2.1.1]hexanes toward oxidative reaction conditions is warranted.

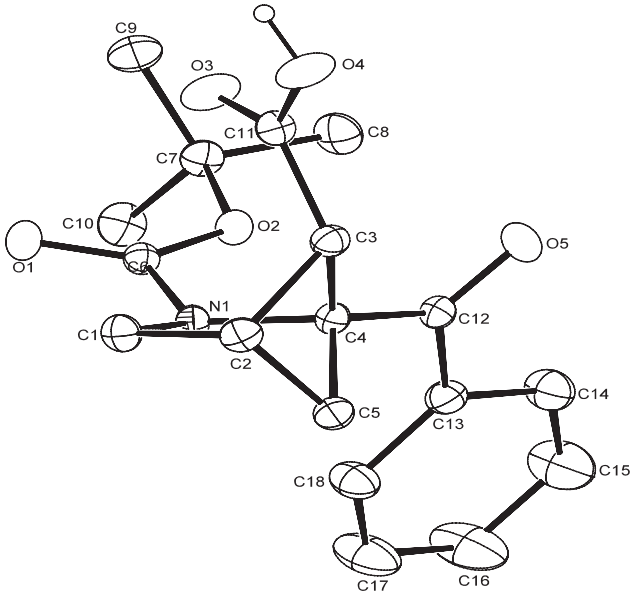


Figure 4 ORTEP of **21h** with 30% probability thermal ellipsoids.

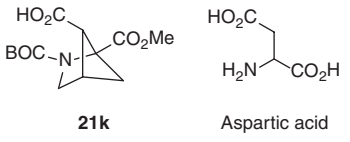
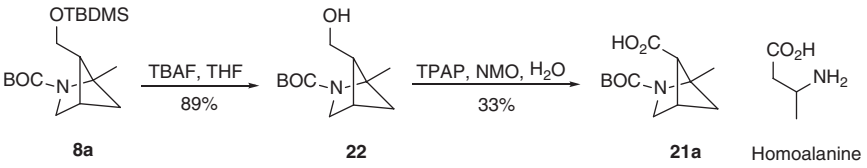


Figure 5 Structural similarity of **21k** with aspartic acid.

Conclusions

A variety of non-polar (alkyl, allyl and vinyl), polar (hydroxymethyl), potentially acidic (carboxymethyl and benzyloxycarbonyl), potentially basic (azido) and other substituents (bromo, benzoyl, formyl and MOM) were



Scheme 8 Synthesis of acid **21a**.

introduced regioselectively at C^1 of 2-azabicyclo[2.1.1] hexanes **3**. Chain homologation was also carried out with C^1-substituted CHO (**8g**). In some cases, standard functional group transformations failed or were realized in low yields due to steric congestion and neighboring group effects. Three precursors **8a, 8h** and **8k** were converted into their corresponding acids. These compounds can be visualized as β-amino acids with restricted degrees of conformational freedom; they have the potential to form oligomers with definite secondary structures.

Experimental

Thin-layer chromatography was performed on precoated plates of silica gel GF 250 μm. Column chromatography was performed on silica gel, Merck grade 60 (230–400 mesh). Reagent-grade chemicals were obtained from commercial suppliers, and reagent-grade solvents were used without further purification. Tetrahydrofuran, dichloromethane and DMF were distilled from the solvent dispensing system designed by Meyer under an argon atmosphere. DMF was additionally distilled from Linde type 4A molecular sieves. All reactions were performed under an argon atmosphere. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 300 at 298 K observing ^{1}H and ^{13}C resonances at 300 MHz and 75 MHz, respectively. The spectrometer was locked to either the deuterium or carbon resonance of $CDCl_3$ and all chemical shifts were referenced to residual $CHCl_3$. High resolution mass spectral data were acquired with a Bruker Daltonics 7 tesla Fourier transform ion cyclotron resonance (FTICR) mass spectrometer by the use of electrospray ionization. External calibration was accomplished with oligomers of polypropylene glycol, PPG 425. Melting points are uncorrected; a Thomas Hoover capillary melting point apparatus was used.

N-(*tert*-butoxycarbonyl)-5-*syn*-hydroxymethyl-2-azabicyclo[2.1.1]hexane (6)

To a solution of **5** (260 mg, 1.08 mmol) in dry THF (13 mL) at −78°C was added 1 M solution of LAH (701 μL, 0.7 mmol). The mixture was stirred at −78°C for 1 h, then brought to room temperature and stirred for an additional 2 h. The reaction was quenched by adding water (25 μL), followed by 15% NaOH (25 μL) and H_2O (100 μL). The resulting solution was dried and concentrated to give 187 mg (81%) of alcohol **6**; R_f = 0.30 (ethyl acetate/hexane, 2:1); ^{1}H NMR: δ 4.40 (d, *J* = 7.2 Hz, 1H, H_1), 3.41 (m, 4H, OCH_2 and $2H_3$), 2.82 (m, 1H, H_4), 2.25 (m, 1H, H_5), 2.00 (br, 1H, OH), 1.80 (d, *J* = 7.4 Hz, 1H, H_{6anti}), 1.45 (s, 9H), 1.40 (d, *J* = 7.4 Hz, H_{6syn}); ^{13}C NMR: δ 157.9, 79.7, 61.2, 60.8, 57.8, 49.6, 46.5, 45.3, 38.8, 37.7, 28.3. HR-MS. Calcd for $C_{11}H_{20}NO_3$ (M+H): *m/z* 214.1443. Found: *m/z* 214.1445.

N-(*tert*-butoxycarbonyl)-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (7)

To a solution of **6** (482 mg, 2.3 mmol) in dry CH_2Cl_2 (15 mL) under argon was added imidazole (770 mg, 11.3 mmol) followed by TBDMSCl (211 mg, 2.7 mmol) in small portions. The mixture was stirred at room temperature for 16 h, then transferred into a separating funnel and washed with water (10 mL), brine (10 mL) and dried with Na_2SO_4. Solvent was removed *in vacuo* to give 514 mg of the crude product. Flash chromatography on silica gel gave 475 mg (63%) of **7**; R_f = 0.60 (hexane/ether, 2:1); ^{1}H NMR: δ 4.24 (br d, *J* = 6.0 Hz, H_1), 3.30 (m, 2H, OCH_2), 3.20 (d, *J* = 9.2 Hz, H_3), 3.12 (d, *J* = 9.2 Hz, H_3), 2.70 (m, H_4), 2.13 (m, H_5), 1.67 (m, 1H, H_{6anti}), 1.44 (s, 9H, BOC), 1.26 (d, *J* = 7.2 Hz, H_{6syn}), 0.86 (s, 9H, TBDMS), 0.00 (s, 6H, TBDMS); ^{13}C NMR: δ 154.6, 77.4, 58.6, 55.4, 49.6, 39.0, 36.2, 30.7, 28.6, 26.2, 18.6,7.5. HR-MS. Calcd for $C_{17}H_{34}NO_3Si$ (M+H): *m/z* 328.2313. Found: *m/z* 328.2308. Calcd for $C_{17}H_{33}NO_3SiNa$ (M+Na): *m/z* 350.2136. Found: *m/z* 350.2127.

Synthesis of compounds 8a–l

To a solution of **7** (1 equiv) in dry ether (15 mL) at 0°C was added TMEDA (1.1 equiv) and the mixture was stirred for 15 min. To the resulting solution was added *s*-BuLi (1.4 M in cyclohexane, 1.2 equiv) dropwise. The mixture was stirred for 2 h at 0°C, treated dropwise with the electrophile (5 equiv) indicated below, slowly allowed to warm to room temperature and quenched with a saturated solution of NH_4Cl. The aqueous phase was extracted with ether three times, and the combined organic phases were washed with water, brine, dried (Na_2SO_4) and concentrated. Product **8a–m** was purified by silica gel flash chromatography eluting with ethyl acetate/heptanes (1:5).

***N*-(*tert*-butoxycarbonyl)-1-methyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8a)** This compound was obtained with methyl iodide as the electrophile; yield 70%; R_f = 0.38 (hexane/ether, 4:1); ^{1}H NMR: δ 3.43 (dd, *J* = 10.8, 6.8 Hz, 1H, OCH_2), 3.32 (dd, *J* = 10.8, 6.8 Hz, 1H, OCH_2), 3.29 (d, *J* = 9.4 Hz, 1H, H_3), 3.23 (d, *J* = 9.4 Hz, 1H, H_3), 2.58 (t, *J* = 3 Hz, H_4), 1.94 (ddd, *J* = 6.8, 6.8, 2.8 Hz, H_5), 1.64 (s, 3H, Me), 1.53 (ddd, *J* = 7.2, 3.2, 1.2 Hz, H_{6anti}), 1.46 (s, 10H, BOC), 1.43 (d, *J* = 7.2 Hz, 1H, H_{6syn}), 0.89 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR: δ 156.6 (C=O), 79.2 (O-*tert*-Bu), 71.6 (OCH_2), 59.7 and 59.5 (C_3), 54.2 (C_1), 49.5 (C_5), 43.8 (C_4), 35.6 (C_6), 28.9 (BOC), 26.7 (CH_3), 26.3 (BOC), 18.6 (TBDMS), 7.5 (TBDMS). HR-MS. Calcd for $C_{18}H_{35}NO_3SiNa$ (M+Na): *m/z* 364.2292. Found: *m/z* 364.2284.

***N*-(*tert*-butoxycarbonyl)-1-trimethylsilyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8b)** This compound was obtained with trimethylsilyl chloride as the electrophile; yield 89%; R_f = 0.78 (hexane/ether, 3:1); ^{1}H NMR: δ 3.36 (dd, *J* = 10.8, 6.4 Hz, 1H, OCH_2), 3.25 (d, *J* = 8.8 Hz, 1H, H_3), 3.19 (d, *J* = 8.8 Hz, 1H, H_3), 3.16 (dd, *J* = 10.8, 6.4 Hz, 1H, OCH_2), 2.79 (brt, *J* = 2.8 Hz, H_4), 2.17 (ddd, *J* = 6.4, 6.4, 2.8 Hz, 1H, H_5), 1.66 (ddd, *J* = 6.8, 2.8, 1.2 Hz, H_{6anti}), 1.45 (s, 9H, BOC), 1.20 (d, *J* = 6.8 Hz, 1H, H_{6syn}), 0.86 (s, 9H, TBDMS), 0.12 (s, 9H, TBDMS), 0.01 (s, 6H, TMS); ^{13}C NMR: δ 155.7, 65.8, 59.5, 51.9, 48.2, 40.0, 39.9, 28.6, 26.0,18.3, − 0.87, − 5.40, -5.50. HR-MS. Calcd for $C_{20}H_{42}NO_3Si_2$ (M+H): *m/z* 400.2698. Found: *m/z* 400.2688.

***N*-(*tert*-butoxycarbonyl)-2-azabicyclo-1-methoxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)[2.1.1]hexane (8c)** This compound was obtained with chloromethylmethyl ether as the electrophile; yield 30%; R_f = 0.53 (ethylacetate/hexane, 2:1); ^{1}H NMR: δ 3.94 (d, *J* = 11.3 Hz, 1H, OCH_2), 3.87 (m, 1H, OCH_2), 3.36 (s, 3H, OCH_3), 3.26 (m, 4H, OCH_2 and $2H_3$), 2.58 (dd, *J* = 3.0 Hz, 1H, H_4), 2.24 (ddd, *J* = 6.9, 6.3, 3.0 Hz, 1H, H_5), 1.81 (ddd, *J* = 7.0, 3.0, 1.5 Hz, 1H, H_{6anti}), 1.43 (s, 9H, BOC), 1.32 (d, *J* = 7.0 Hz, 1H, H_{6syn}), 0.86 (s, 9H, TBDMS), 0.00 (s, 6H, TBDMS); ^{13}C NMR: δ 155.8, 79.2, 70.8, 59.2, 58.8, 49.8, 49.2, 39.5, 39.0, 35.1, 28.6, 25.9. HR-MS. Calcd for $C_{19}H_{37}NO_4Si$ (M+H): *m/z* 372.3565. Found: *m/z* 372.3568. Calcd for $C_{19}H_{37}NO_4SiNa$ (M+Na): *m/z* 394.2384. Found: *m/z* 394.2388.

***N*-(*tert*-butoxycarbonyl)-1-allyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8d)** This compound was obtained with allyl bromide as the electrophile; yield 11%; R_f = 0.72 (hexane/ether, 4:1); ^{1}H NMR: δ 5.85 (m, 1H), 5.10 (d, *J* = 16.4 Hz, 1H), 5.00 (dd, *J* = 12.5 Hz, 1H), 3.41 (m, 1H, OCH_2), 3.25 (m, OCH_2, $2H_3$, 3H), 2.95 (dd, *J* = 7.9, 12.0 Hz, 1H, CH_2), 2.86 (dd, *J* = 7.9, 12.0 Hz, 1H, CH_2), 2.58 (br, H_4), 2.00 (m, 1H, H_5), 1.42 (m, 1H, H_{6anti}), 1.40 (s, 9H, BOC), 1.25 (d, *J* = 6.9 Hz, H_{6syn}), 0.95 (s, 9H, TBDMS), 0.00 (s, 6H, TBDMS); ^{13}C NMR: δ 158.0, 135.9, 117.3, 74.7, 61.0, 59.3, 57.2, 51.5, 49.8, 40.8, 36.0, 35.5, 28.9, 26.3, 18.6, 0.00. HR-MS. Calcd for $C_{20}H_{37}NO_3SiNa$ (M+Na): *m/z* 390.2434. Found: *m/z* 390.2434.

***N*-(*tert*-butoxycarbonyl)-1-bromo-5-*syn*-*tert*-butyldimethylsilyloxymethyl-2-azabicyclo[2.1.1]hexane (8e)** This compound was obtained with benzyl bromide as the electrophile; yield 63%; R_f = 0.62 (hexane/ethyl acetate, 4:1); ^{1}H NMR: δ 3.63 (dd, *J* = 11.1, 5.1 Hz, 1H, OCH_2), 3.40 (m, 3H, OCH_2 and $2H_3$), 2.89 (br, 1H, H_4), 2.41 (m, 1H, H_5), 2.05 (m, H_{6anti}), 1.89 (d, *J* = 7.2 Hz, H_{6syn}), 1.46 (s, 9H, BOC), 0.87 (s, 9H, TBDMS), 0.04 (s, 6H, TBDMS); ^{13}C NMR: δ 156.9, 80.8, 67.3, 58.5, 58.4, 47.9, 46.7, 36.2, 28.9, 26.5, 18.6, − 5.1. HR-MS. Calcd for $C_{17}H_{32}NO_3SiNa^{79}Br$ (M+Na): *m/z* 428.1232. Found: *m/z* 428.1224. Calcd for $C_{17}H_{32}NO_3SiNa^{81}Br$ (M+Na): *m/z* 430.1212. Found: *m/z* 430.1220.

***N*-(*tert*-butoxycarbonyl)-1-(*p*-methoxybenzyl)-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8f)** This compound was obtained in a mixture with **8e** using *p*-methoxybenzyl bromide as the electrophile; yield 30%; R_f = 0.47 (hexane/ethyl acetate, 4:1); ^{1}H NMR: δ 6.84 (m, 2H, Ph), 6.77 (m, 2H, Ph), 3.74 (s, 3H, OMe), 3.42 (dd, *J* = 10.0, 7.5 Hz, 1H, OCH_2), 3.33 (m, 5H, OCH_2, CH_2PMB, $2H_3$), 3.23 (m, 1H, CH_2PMB), 2.41 (br t, *J* = 3.1 Hz, H_4), 1.85 (m, H_5), 1.43 (s, 9H, BOC), 1.26 (dd, *J* = 7.7, 2.6 Hz, 1H, H_{6anti}), 1.20 (d, *J* = 7.7 Hz, 1H, H_{6syn}), 0.86 (s, 9H, TBDMS), 0.01 (s, 6H, TBDMS); ^{13}C NMR: δ 158.4, 131.9, 131.5, 114.5, 113.8, 79.5, 76.4, 59.6, 55.6, 50.3, 50.1, 47.8, 40.1, 36.5, 35.6, 29.0, 26.2, 18.7, − 5.0. HR-MS. Calcd for $C_{25}H_{42}NO_4Si$ (M+H): *m/z* 448.2878. Found: *m/z* 448.2896.

***N*-(*tert*-butoxycarbonyl)-1-formyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8g)** This compound was obtained using DMF as the electrophile; yield 52%; R_f = 0.40 (hexane/ether, 2:1); ^{1}H NMR: δ 9.80 (s, 1H, CHO), 3.58 (dd, *J* = 10.4, 6.8 Hz, 1H, OCH_2), 3.43 (brd, *J* = 9.2 Hz, H_3), 3.39 (brd, *J* = 9.2 Hz, H_3), 3.38 (dd, *J* = 10.4, 6.8 Hz, 1H, OCH_2), 2.67 (m, H_4), 2.40 (ddd, *J* = 7.2, 7.0, 3.1 Hz, H_5), 1.95 (ddd, *J* = 7.4, 3.0, 1.2 Hz, H_{6anti}), 1.45 (s and m, 10H, BOC and H_{6syn}), 0.88 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR: δ 194.4, 156.6 (C=O), 79.7, 58.6, 55.4, 49.6, 39.0, 36.2, 30.7, 28.6, 26.2,18.6, 7.5. HR-MS. Calcd for $C_{18}H_{33}NO_4SiNa$ (M+Na): *m/z* 378.2086. Found: *m/z* 378.2076.

***N*-(*tert*-butoxycarbonyl)-1-benzoyl-5-*syn*-(*tert*-butyl-dimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8h)** This compound was obtained using benzoyl chloride as the electrophile; yield 76%; R_f = 0.57 (hexane/ethyl acetate, 2:1); ^{1}H NMR: δ 8.09 (m, 2H, Ph), 7.51 (m, 1H, Ph), 7.40 (m, 2H, Ph), 3.81 (br, 1H, OCH_2), 3.62 (s, 2H, H_3), 3.23 (br, 1H, OCH_2), 2.83 (br, 1H, H_4), 2.57 (br, 1H, H_5), 2.00 (br, 1H, H_{6anti}), 1.36 (br, 1H, H_{6syn}), 1.09 (s, 9H, BOC), 0.86 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR: δ 193.0, 156.1, 141.2, 127.8, 127.6, 127.2, 81.5, 59.0, 57.9, 51.2, 49.9, 45.0, 35.6, 28.5, 28.0/ 27.5, 25.9/ 25.7, 18.3, − 5.3, − 5.5. HR-MS. Calcd for $C_{24}H_{37}NO_4SiNa$ (M+Na): *m/z* 454.2384. Found: *m/z* 454.2398.

***N*-(*tert*-butoxycarbonyl)-1-(4-fluorobenzoyl)-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8i)** This compound was obtained using *p*-fluorobenzoyl fluoride as the electrophile; yield 33%; R_f = 0.67 (hexane/ether, 4:1); ^{1}H NMR: δ 8.15 (m, 2H, Ph), 7.09 (m, 2H, Ph), 3.83 (br, 1H, OCH_2), 3.63 (s, 2H, $2H_3$), 3.22 (br, 1H, OCH_2), 2.85 (br, 1H, H_4), 2.57 (br, 1H, H_5), 2.01 (br, 1H, H_{6anti}), 1.36 (br, 1H, H_{6syn}), 1.06 (s, 9H, BOC), 0.85 (s, 9H, TBDMS), 0.05 (s, 6H, TBDMS); ^{13}C NMR: δ 191.8, 157.2, 131.3, 132.0,115.4, 115.2, 81.7, 57.9, 51.1, 50.0, 45.5, 35.6, 28.5, 27.6, 25.9, 18.3, − 5.5, − 5.3. HR-MS. Calcd for $C_{25}H_{36}O_4SiF$ (M+H): *m/z* 450.2471. Found: *m/z* 450.2466. Calcd for $C_{24}H_{36}O_4SiFNa$ (M+Na): *m/z* 472.2292. Found: *m/z* 472.2292.

***N*-(*tert*-butoxycarbonyl)-1-benzyloxycarbonyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8j)** This compound was obtained with benzyl chloroformate as the electrophile; yield 46%; R_f = 0.48 (hexane/ether, 3:1); ^{1}H NMR: δ 7.35 (m, 5H, Ph), 5.20 and 5.18 (2d, *J* = 7.5 Hz, 2H, CH_2Ph), 3.70 (dd, *J* = 10.8, 4.2 Hz, 1H, OCH_2), 3.42 (s, 2H, $2H_3$), 3.32 (m, OCH_2), 2.73 (br, 1H, H_4), 2.40 (m, H_5), 1.93 (dd, *J* = 7.2, 2.4 Hz, 1H, H_{6anti}), 1.66 (d, *J* = 7.2 Hz, H_{6syn}), 1.42 (s, 9H, BOC), 0.88 (s, 9H, TBDMS), 0.06 (s, 6H, TBDMS); ^{13}C NMR: δ 168.0, 157.3, 135.8, 128.5, 128.1, 127.9, 80.7, 66.4, 59.0, 58.1, 52.5, 48.9, 41.0, 35.8, 28.5, 28.2, 25.9, 18.3, − 5.4. HR-MS. Calcd for $C_{26}H_{40}NO_5Si$ (M+H): *m/z* 462.2620. Found: *m/z* 462.2686. Calcd for $C_{26}H_{39}NO_5SiNa$ (M+Na): *m/z* 484.2495. Found: *m/z* 484.2505.

***N*-(*tert*-butoxycarbonyl)-1-methoxycarbonyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (8k)** This compound was obtained as a mixture with **9k** using methyl chloroformate as the electrophile.

Compound 8k Yield 35%; R_f = 0.67 (hexane/ethylacetate, 2:1); ^{1}H NMR: δ 3.76 (s, 3H, OMe), 3.70 (dd, *J* = 9.5, 4.5 Hz, OCH_2), 3.37 (m, 3H, $2H_3$, OCH_2), 2.73 (dd, *J* = 3.0, 2.5 Hz, H_4) 2.38 (m, H_5), 1.92 (ddd, *J* = 8.0, 3.0, 1.0 Hz, H_{6anti}), 1.64 (d, *J* = 8.0 Hz, H_{6syn}), 1.43 (s, 9H, BOC), 0.88 (s, 9H, TBDMS), 0.04 (s, 6H, TBDMS); ^{13}C NMR: δ 169.0, 157.6, 78.7, 59.4, 58.5, 52.1, 49.3, 41.4, 39.4, 36.1, 30.7, 28.7, 18.6, − 5.0. HR-MS. Calcd for $C_{19}H_{35}NO_5SiNa$ (M+Na): *m/z* 204.2182. Found: m/z 204.2180.

Compound 9k (Scheme 2) Yield 9%; $R_f = 0.42$ (hexane/ethylacetate, 4:1); ^{1}H NMR**:** δ 3.90 (m, 2H), 3.40 (m, 2H), 2.70 (m, 2H), 2.17 (m, 8H), 1.69 (s, 18H), 1.43 (s, 18H), 0.02 (s, 12H); ^{13}C NMR: δ 198.0, 155.0/154.4, 77.5, 71.7, 56.5/56.2, 49.6, 47.5/47.2, 39.4, 33.6/33.1, 26.3, 22.9, 15.3, − 5.4. HR-MS. Calcd for $C_{35}H_{65}N_2O_7Si_2$ (M+H): m/z 681.4309. Found: 681.4330. Calcd for $C_{35}H_{64}N_2O_7Si_2Na$ (M+Na): *m/z* 703.2150. Found: *m/z* 703.2131.

***N*-(*tert*-butoxycarbonyl)-1-carboxy-5-*syn*-*tert*-butyldimethylsilyloxymethyl-2-azabicyclo[2.1.1]hexane (8l)** This compound was obtained using carbon dioxide as the electrophile (bubbling for 15 min); yield 48% of crude acid **8l**. Without further purification, the crude acid was dissolved in a mixture of isopropanol and hexane (1:1, 20 mL) and charged with $TMSCHN_2$. The solution was stirred at room temperature for 1 h. Concentration followed by silica gel chromatography gave the methyl ester **8k** in a yield of 97%.

***N*-(*tert*-butoxycarbonyl)-2-azabicyclo-1-(benzocarbamoyl)-5-*syn*-(hydroxymethyl)[2.1.1]hexane (8m)** To a solution of the acid **8l** (55 mg, 0.15 mmol) in CH_3CN (9 mL) at 0°C was added EDC*HCl (40 mg, 0.21 mmol), HOBt (28 mg, 0.21 mmol) followed by benzylamine (32 mg, 0.30 mmol). The resulting solution was slowly warmed to room temperature and stirred for 12 h. Workup was done by diluting the mixture with ether (15 mL), washing with 1N HCl (3 × 5 mL) and drying with Na_2SO_4. Removal of the solvent gave 38 mg (75%) of **8m**; $R_f = 0.33$ (ethyl acetate/hexane, 4:1); ^{1}H NMR: δ 7.33 (m, 5H, Ph), 6.45 (br, 1H, NH), 4.51 (br d, *J* = 5.1 Hz, CH_2Bn), 4.47 (br, 1H, CH_2Bn), 3.48 (dd, *J* = 11.6, 3.9 Hz, 1H, OCH_2), 3.36 (m, 3H, OCH_2, $2H_3$), 2.66 (br, $1H_4$), 2.49 (m, H_5), 1.94 (dd, *J* = 7.2, 2.8 Hz, 1H, H_{6anti}), 1.74 (d, *J* = 7.2 Hz, H_{6syn}), 1.47 (s, 9H, BOC); ^{13}C NMR: δ 168.9, 157.4, 132.0, 128.8, 127.9, 127.6, 78.6, 67.2, 58.2, 51.3, 49.4, 43.8, 36.0, 35.2, 28.2, 25.7. HR-MS. Calcd for $C_{19}H_{26}N_2O_4Na$ (M+Na): *m/z* 369.1790. Found: *m/z* 369.1786.

N-(*tert*-butoxycarbonyl)-1-hydroxymethyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo [2.1.1] hexane (10)

To a solution of the crude aldehyde **8g** (56 mg, 0.16 mmol) in dry MeOH (8 mL) at 0°C was added $NaBH_4$ (30 mg, 0.08 mmol) in small portions. The solution was stirred at 0°C for 15 min, concentrated *in vacuo* and the residue was dissolved in ether (15 mL). The ether solution was washed with water (2 × 5 mL) and dried with Na_2SO_4. Solvent was then removed *in vacuo* to give 38 mg (68%) of **10**; $R_f = 0.21$ (hexane/ether, 2:1); ^{1}H NMR**:** δ 4.62 (br, 1H, OH), 4.00 (d, *J* = 13.2, 6.6 Hz, 1H, CH_2OH), 3.97 (br dd, *J* = 12.6, 7.5 Hz, 1H, CH_2OH), 3.50 (m, 1H, H_3), 3.24 (m and s, 3H, $2CH_2$ OTBDMS and H_3), 2.60 (m, 1H, H_4), 2.15 (ddd, *J* = 7.2, 6.9, 3.0 Hz, H_5), 1.85 (d, *J* = 7.4 Hz, H_{6anti}), 1.79 (d, *J* = 7.4 Hz, H_{6syn}), 1.45 (s, 9H, BOC), 0.88 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR**:** δ 161.0, 79.7, 61.4, 58.8, 51.7, 49.2, 39.9, 35.1, 31.0, 28.5, 25.9, 18.3, 7.5. HR-MS. Calcd for $C_{18}H_{36}NO_4SiNa$ (M+H): *m/z* 358.2410. Found: *m/z* 358.2414. Calcd for $C_{18}H_{35}NO_4SiNa$ (M+Na): *m/z* 380.2235. Found: *m/z* 380.2233.

3-Oxa-5-aza-tricyclo-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)[5.1.1.$0^{1,5}$]nonan-4-one (12)

To a solution of **10** (98 mg, 0.3 mmol) in dry CH_2Cl_2 (15 mL) was added Et_3N dropwise (153 mg, 1.5 mmol) followed by MsCl (68 mg, 0.6 mmol). The resulting solution was stirred for 3 h at room temperature. Washing with water (2 × 5 mL) and drying with sodium sulfate followed by concentration gave 108 mg (97%) of mesylate **11**. To a solution of mesylate **11** (46 mg, 0.1 mmol) in acetonitrile (6 mL) was added KCN (37 mg, 0.5 mmol) and 18-crown-6 ether (6 mg). The resulting solution was heated at 70°C for 12 h. Solvent was removed *in vacuo* to give 68 mg of crude product which was purified by preparative TLC to give 21 mg (66%) of **12;** $R_f = 0.35$ (hexane/ethyl acetate, 2:1); ^{1}H NMR: δ 4.36 (d, *J* = 9.4 Hz, 1H, OCH_2), 4.29 (d, *J* = 9.4 Hz, 1H, OCH_2), 3.52 (m, 2H, OCH_2), 3.30 (d, *J* = 9 Hz, H_3), 3.18 (d, *J* = 9 Hz, H_3), 2.86 (dd, *J* = 2.1, 2.4 Hz, 1H, H_4), 2.41 (m, H_5), 1.79 (dd, *J* = 7.3, 3.3 Hz, H_{6anti}), 1.64 (d, *J* = 7.3 Hz, H_{6syn}), 0.87 (s, 9H, TBDMS), 0.05 (s, 6H, TBDMS); ^{13}C NMR: δ 156.7, 74.8, 65.8, 58.3, 52.3, 44.0, 41.3, 41.1, 25.8, 18.2, − 5.5. HR-MS. Calcd for $C_{14}H_{26}NO_3Si$ (M+H): *m/z* 284.1681. Found: *m/z* 284.1675.

N-(*tert*-butoxycarbonyl)-2-azabicyclo-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-1-azidomethyl[2.1.1]hexane (13)

A solution of mesylate **11** (117 mg, 0.3 mmol) and sodium azide (186 mg, 3.0 mmol) in DMF (5 mL) was stirred at 70°C for 12 h. Workup was done by diluting the mixture with ether (20 mL) and washing with water (4 × 5 mL). Ether was removed *in vacuo* to give 315 mg of a crude mixture which was purified on silica gel chromatography to give 6 mg (6%) of **13**, 4 mg (5%) of **14** and 7 mg (10%) of **12**.

Compound 13 $R_f = 0.27$ (hexane/ethyl acetate, 2:1); ^{1}H NMR**:** δ 4.06 (br, 1H, CH_2OH), 3.90 (d, *J* = 14.1 Hz, 1H, CH_2OH), 3.39 (m, 1H, CH_2ON_3), 3.35 (m, 1H, CH_2ON_3), 3.32 (m, 1H, H_3), 3.26 (d, *J* = 8.7 Hz, 1H, H_3), 2.63 (br, H_4), 2.22 (m, H_5), 1.70 (m, 1H, H_{6anti}), 1.47 (s and m, 9H, H_{6syn} and BOC), 0.87 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR: δ 156.7, 80.0, 72.8, 58.4, 51.7, 51.4, 49.7, 40.4, 35.8, 28.5, 18.0, − 0.05. HR-MS. Calcd for $C_{18}H_{35}N_4O_3Si$ (M+H): *m/z* 383.2473. Found: *m/z* 383.2473.

Compound 14 $R_f = 0.80$ (hexane/ethyl acetate, 2:1); ^{1}H NMR**:** δ 4.20 (br d, *J* = 13.2 Hz, 1H, CH_2OH), 3.84 (br d, *J* = 13.2 Hz, 1H, CH_2OH), 3.42 (m, 1H, CH_2ON_3), 3.35 (m, CH_2ON_3), 3.30 (d, *J* = 9.3 Hz, 1H, H_3), 3.23 (d, *J* = 9.3 Hz, 1H, H_3), 2.62 (br, H_4), 2.12 (m, H_5), 1.69 (brd, *J* = 7.5 Hz, 1H, H_{6anti}), 1.52 (br, 1H, OH), 1.40 (s and m, H_{6syn} and BOC); ^{13}C NMR**:** δ 155.7, 75.5, 73.0, 58.8, 58.5, 51.0, 49.6, 49.1, 39.9, 35.1, 28.7, 28.3. HR-MS. Calcd for $C_{12}H_{21}N_4O_3$ (M+H): *m/z* 269.1608. Found: *m/z* 269.1604.

N-(*tert*-Butoxycarbonyl)-1-vinyl-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (15)

Procedure 1 To a solution of aldehyde **8g** (57 mg, 0.16 mmol) in CH_2Cl_2 (10 mL) at 0°C was added Tebbe reagent (319 µL, 0.16 mmol). The resultant solution was slowly warmed to room temperature and stirred for 12 h. The mixture was then diluted with ether and charged with 10% NaOH (1 mL). The organic solution was dried with sodium sulfate and filtered on celite. Concentration gave 67 mg of crude product **15**; silica gel flash chromatography furnished 33 mg (59%) of pure compound **15**.

Procedure 2 To a solution of methyl(triphenylphosphonium) bromide (292 mg, 0.82 mmol) in dry THF (15 mL) at 0°C under argon

was added *n*-BuLi (457 µL, 0.73 mmol, 1.6 M in hexane). The resulting bright yellow mixture was stirred for 0.5 h at 0°C. Compound **8g** (100 mg, 0.28 mmol) in dry THF (15 mL) was cannulated to the mixture and the resulting solution was slowly brought to room temperature and stirred for 20 h under argon. Ether (10 mL) was added and the mixture was stirred for 10 min followed by addition of water (10 mL) and stirring for an additional 10 min. The organic layer was separated and the aqueous layer was extracted with ether (2×10 mL). The combined organic layers were washed with brine (5 mL), dried with Na_2SO_4 and concentrated to yield 158 mg of crude product. Silica gel flash chromatography gave 51 mg (52%) of pure compound **15**; R_f = 0.69 (hexane/ether, 4:1); ^{1}H NMR: δ 6.45 (br m, 1H), 5.16 (dd, *J* = 18, 2 Hz, 1H), 5.10 (brd, *J* = 10.5 Hz, 1H), 3.53 (dd, *J* = 11, 7 Hz, OCH_2), 3.34 (m, H_3 and OCH_2, 2H), 3.29 (d, *J* = 8.5 Hz, 1H, H_3), 2.62 (t, *J* = 3.0, 3.0 Hz, H_4), 2.20 (ddd, *J* = 7.5, 7.5, 3.5 Hz, H_5), 1.73 (d, *J* = 7.5, 3.0, 2.0, 1H, H_{6anti}), 1.55 (d, *J* = 7.0 Hz, H_{6syn}), 1.45 (s, 9H, BOC), 0.89 (s, 9H, TBDMS), 0.04 (s, 6H, TBDMS); ^{13}C NMR: δ 158.0, 135.9, 117.3, 74.7, 73.0, 57.2, 51.5, 49.8, 40.8, 35.5, 28.9, 26.3, 18.6, −5.00. HR-MS. Calcd for $C_{19}H_{35}NO_3SiNa$ (M+H): *m/z* 354.2459. Found: m/z 354.2454. Calcd for $C_{19}H_{34}NO_2SiNa$ (M+H-H_2O): *m/z* 336.2364. Found: *m/z* 336.2348.

N-(*tert*-butoxycarbonyl)-1-(2-hydroxyethyl)-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo [2.1.1]hexane (16)

To a solution of **15** (40 mg, 0.11 mmol) in THF (8 mL) at 0°C was added borane in THF (340 µL, 0.34 mmol). The mixture was stirred for 7 h at room temperature and charged with 2N NaOH (220 µL, 0.44 mmol) followed by 30% H_2O_2 (0.44 mmol) at –78°C. Potassium carbonate was added to saturate the aqueous phase. The aqueous layer was extracted with ether (10×5 mL). The ether layers were combined and dried with Na_2SO_4. Concentration and chromatography gave 9.1 mg (22%) of alcohol **16**; R_f = 0.29 (hexane/ether, 3:1); ^{1}H NMR: δ 3.75 (m, 2H, CH_2OH), 3.44 (dd, *J* = 10.4, 7.6 Hz, 1H, $CH_2OTBDMS$), 3.37 (dd, *J* = 10.8, 5.2 Hz, 1H, $CH_2OTBDMS$), 3.28 (d, *J* = 9.2 Hz, H_3), 3.19 (d, *J* = 9.2 Hz, H_3), 2.53 (brt, *J* = 3.2, 2.8 Hz, H_4), 2.37 (m, 2H, CH_2), 2.10 (m, H_5), 1.63 (m, H_{6anti}), 1.39 (s and m, 10 H, BOC and H_{6syn}), −0.83 (s, 9H, TBDMS), 0.00 (s, 6H, TBDMS); ^{13}C NMR: δ 156.2, 79.4, 73.7, 59.9, 59.5, 52.5, 49.2, 41.3, 35.1, 33.8, 28.6, 25.9, 18.3, −5.5. HR-MS. Calcd for $C_{19}H_{38}NSiO_4$ (M+H): *m/z* 372.2565. Found: *m/z* 372.2577. Calcd for $C_{19}H_{37}NSiO_4Na$ (M+Na): *m/z* 394.2384. Found: *m/z* 394.2406.

N-(*tert*-butoxycarbonyl)-1-[(2-methoxycarbonyl)-1-vinyl]-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1]hexane (17)

To a solution of **8g** (130 mg, 0.37 mmol) in dry CH_2Cl_2 (15 mL) was added methyl (triphenylphosphoranylidene)acetate (183 mg, 0.55 mmol) under argon. The resulting solution was stirred at 40°C for 2 days. Solvent was removed *in vacuo* and the crude product was purified by silica gel flash chromatography to give 29 mg (22%) of unreacted aldehyde **8g** and 61 mg (41%) of **17**; R_f = 0.42 (hexane/ethyl acetate, 4:1); ^{1}H NMR**:** δ 7.40 (br d, *J* = 15.3 Hz, 1H), 5.90 (dd, *J* = 15.9, 3 Hz, 1H), 3.69 (s, 3H, OCH_3), 3.36 (m, 4H, $2H_3$, CH_2OH), 2.64 (br, H_4), 2.21 (br, H_5), 1.74 (br, H_{6anti}), 1.57 (d, *J* = 7.2 Hz, H_{6syn}), 1.41 (s, 9H, BOC), 0.89 (s, 9H, OTBDMS), 0.00 (6H, OTBDMS); ^{13}C NMR**:** δ 167.1, 156.7, 145.0, 120.0, 80.4, 73.5, 59.0, 54.8, 51.8, 49.2, 42.8, 36.0, 28.7, 20.2, 18.5, −5.0. HR-MS. Calcd for $C_{21}H_{38}NO_5Si$ (M+H): *m/z* 412.2520. Found: *m/z* 412.2514.

N-(*tert*-butoxycarbonyl)-1-[(2-methoxycarbonyl)-1-ethyl]-5-*syn*-(*tert*-butyldimethylsilyloxy-methyl)-2-azabicyclo [2.1.1]hexane (18)

To a solution of compound **17** (45 mg, 0.11 mmol) in toluene (8 mL) was added $TsNHNH_2$ (163 mg, 0.88 mmol) and TMEDA (197 µL, 1.3 mmol). The mixture was heated under reflux for 12 h, then cooled to room temperature, washed with H_2O (5 mL), brine (5 mL) and dried with $MgSO_4$. After concentration, the residue was purified by chromatography on silica gel to give 39 mg (87%) of product **18**; R_f = 0.64 (hexane/ether, 4:1); ^{1}H NMR: δ 3.65 (s, 3H, OMe), 3.39 (dd, *J* = 10.2, 6.8 Hz, 1H, OCH_2), 3.27 (m, 3H, $2H_3$, OCH_2), 2.58 (br, 1H, H_4), 2.46 (m, 2H, CH_2), 2.28 (m, 2H, CH_2), 2.02 (ddd, *J* = 6.8, 6.8, 2.2 Hz, 1H, H_5), 1.53 (m, 1H, H_{6anti}), 1.45 (s, 9H, BOC), 1.38 (d, *J* = 7.2 Hz, 1H, H_{6syn}), 0.86 (s, 9H, TBDMS), 0.04 (s, 6H, TBDMS); ^{13}C NMR: δ 174.0, 156.0, 79.3, 74.3, 58.9, 52.3, 51.4, 49.4, 40.9, 34.9, 30.9, 28.5, 26.5, 25.8, 18.2, −5.4, −5.5. HR-MS. Calcd for $C_{21}H_{39}NO_5SiNa$ (M+Na): *m/z* 436.2495. Found: *m/z* 436.2503.

N-(*tert*-butoxycarbonyl)-1-(3-hydroxypropyl)-5-*syn*-(*tert*-butyldimethylsilyloxymethyl)-2-azabicyclo[2.1.1] hexane (19)

A solution of **18** (17 mg, 0.04 mmol) in THF (2 mL) was stirred and treated with LAH (13 µL, 0.03 mmol) at − 78°C. The mixture was slowly warmed to room temperature, stirred for an additional 1 h, diluted with ether (10 mL) and washed with water (2×5 mL). Filtration and drying with Na_2SO_4 followed by concentration gave 14 mg (88%) of **19**; R_f = 0.38 (hexane/ether, 4:1); ^{1}H NMR: δ 3.64 (m, 2H, OCH_2), 3.43 (dd, *J* = 10.8, 6.8 Hz, 1H), 3.28 (m, 3H), 2.58 (br t, *J* = 3.2, 2.8 Hz, 1H, H_4), 2.38 (br, 1H, OH), 2.04 (m, 3H, H_5 and CH_2), 1.67 (m, 2H, CH_2), 1.57 (ddd, *J* = 7.0, 3.2, 1.6 Hz, 1H, H_{6anti}), 1.39 (d, *J* = 7.0 Hz, 1H, H_{6syn}), 1.45 (s, 9H, BOC), 0.87 (s, 9H, TBDMS), 0.02 (s, 6H, TBDMS); ^{13}C NMR: δ 156.1, 79.1, 75.1, 62.7, 59.0, 52.2, 49.5, 40.8, 34.8, 29.4, 28.5 and 28.2, 26.8, 25.9 and 25.7, 18.2, −5.4, −5.5; HR-MS. Calcd for $C_{20}H_{39}NO_4SiNa$ (M+Na): *m/z* 408.2546. Found: *m/z* 408.2548.

Methyl 3-{3-[(*tert*-butoxycarbonylamino)methyl]-2-(2-hydroxymethyl)-1-cyclobutyl}propanoate (20)

To a solution of **17** (17 mg, 0.04 mmol) in ethyl acetate (8 mL) was added Pd/C (3 mg) and the mixture was stirred at room temperature for 1 h. The catalyst was filtered off and the solution was concentrated to give 9 mg (75%) of **20;** R_f = 0.24 (hexane/ethyl acetate, 2:1); ^{1}H NMR: δ 3.95 (t, *J* = 10.6 Hz, 1H, CH_2OH), 3.81 (dd, *J* = 10.4, 4.8 Hz, 1H, CH_2OH), 3.65 (s, 3H, OMe), 3.29 (dd, *J* = 14.0, 4.2 Hz, 1H, CH_2NHBOC), 3.10 (dd, *J* = 14.0, 9.6 Hz, 1H, CH_2NHBOC), 2.58 (m, 1H), 2.45 (m ,1H), 2.25 (m, 1H), 2.20 (m, 2H), 2.11 (m, 1H), 1.80 (br, 1H, OH), 1.70 (m, 2H), 1.52 (m, 1H), 1.40 (s, 9H, BOC), 1.37 (m, 1H); ^{13}C NMR**:** δ 173.9, 156.1, 79.5, 59.6, 51.9 and 51.8, 41.8, 41.2, 34.6, 33.3, 32.4, 30.0, 28.8, 26.4, 14.5. HR-MS. Calcd for $C_{15}H_{27}NO_5Na$ (M+Na): 324.1787. Found: *m/z* 324.1772.

N-(*tert*-butoxycarbonyl)-1-benzoyl-5-*syn*-carboxy-2-azabicyclo[2.1.1]hexane (21h)

A solution of **8h** (33 mg, 0.08 mmol) in acetone (5.0 mL) was treated dropwise at 0°C with Jones reagent (60 μL, 0.16 mmol, 2.7 M CrO_3 in 4N H_2SO_4). The mixture was maintained at 0°C for 1 h, followed by slow addition of isopropanol (3.0 mL) to quench excess oxidant. The resultant green biphasic mixture was stirred vigorously for 1 h at 0°C, then filtered over a pad of celite and the filter cake was washed with ethyl acetate (3×5 mL). The organic layer was washed with water (3×15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. The oil was diluted with ethyl acetate (10 mL) and stirred vigorously with 10% NaOH for 5 min. The mixture was transferred to a separatory funnel, the aqueous layer was removed and the organic layer was washed with 10% NaOH (2×5 mL). The combined basic aqueous layers were cooled to 0°C, acidified to pH 1.0 with 1.0 N HCl and extracted with ethyl acetate (5×10 mL). The extract was dried over Na_2SO_4 and concentrated *in vacuo* to yield compound **21h** as an off-white solid (19 mg, 76%); mp 133°C –134°C; ^{1}H NMR: δ 8.08 (m, 1H, Ph), 7.59 (m, 1H, Ph), 7.47 (dd, 2H, *J* = 7.8, 7.5 Hz, 2H), 3.95 (m, H_5), 3.65 (m, 1H), 3.13 (br, 2H), 2.09 (m, 2H); ^{13}C NMR**:** δ 195.8/ 195.7, 156.8, 133.6, 129.0, 128.4, 82.1, 78.5, 58.1, 51.4, 49.8, 45.7, 36.0, 28.3/ 28.1, 27.4. HR-MS. Calcd for $C_{18}H_{21}NO_5$ (M+Na): *m/z* 354.1317. Found: *m/z* 354.1307.

N-(*tert*-butoxycarbonyl)-1-methoxycarbonyl-5-*syn*-carboxy-2-azabicyclo[2.1.1]hexane (21k)

To a solution of silyl ether **8k** (80.4 mg, 0.209 mmol) in acetone (3.0 mL) at 0°C was added slowly Jones reagent (0.20 mL, 0.54 mmol, 2.7 M CrO_3 in 4N H_2SO_4). The mixture was maintained at 0°C for 1 h and then slowly treated with isopropanol (5.0 mL) to quench excess oxidant. The resultant green biphasic mixture was stirred vigorously for 1 h at 0°C, then filtered over a pad of celite and rinsed with ethyl acetate (3×15 mL). The organic layer was washed with water (3×15 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a yellow oil. The oil was diluted with ethyl acetate (10 mL) and stirred vigorously with 10% NaOH for 5 min. The mixture was transferred to a separatory funnel, then the aqueous layer was removed and the organic layer was washed with 10% NaOH (2×10 mL). The combined basic aqueous layers were cooled to 0°C, acidified to pH 1.0 with 1.0 N HCl and extracted with ethyl acetate (5×10 mL). Concentration *in vacuo* furnished compound **21k** as an off-white solid (51.0 mg, 85%); ^{1}H NMR: δ 3.88 (s, 3H), 3.70 (d, *J* = 8.9 Hz, $1H_3$), 3.43 (d, *J* = 8.9 Hz, $1H_3$), 3.04 (brs, $1H_4$), 3.00 (br, $1H_5$), 1.98 (ddd, *J* = 7.4, 3.0, 1.5 Hz, H_{6anti}), 1.75 (d, *J* = 7.4 Hz, H_{6syn}), 1.42 (s, 9H); ^{13}C NMR: δ 170.3, 169.7, 155.9, 81.2, 70.6, 53.1, 51.7, 49.3, 41.2, 37.6, 28.9. HR-MS. *m/z* 286.1306, Calcd for $C_{13}H_{20}NO_6$ (M+H) 286.1285; *m/z* 308.1131, Calcd for $C_{13}H_{19}NO_6Na$ (M+Na) 308.1104.

N-(*tert*-butoxycarbonyl)-1-methyl-5-*syn*-(hydroxymethyl)-2-azabicyclo[2.1.1]hexane (22)

To a solution of **8a** (179 mg, 0.53 mmol) in dry THF (16 mL) at 0°C was added TBAF (1.6 mL, 1.6 mmol) dropwise over a period of 5 min. The resulting solution was warmed to room temperature and stirred for 16 h. The mixture was diluted with ether (10 mL) and washed with water (5 mL), brine (5 mL) and dried with Na_2SO_4. Solvent was removed *in vacuo* to give 107 mg (89%) of crude compound **22** which was taken to the next step without further purification; R_f = 0.26 (hexane/ether, 1:1); ^{1}H NMR: δ 3.43 (dd, *J* = 10.8, 6.8 Hz, 1H, CH_2OH), 3.32 (dd, *J* = 10.8, 6.8 Hz, 1H, CH_2OH), 3.28 (d, *J* = 9.2 Hz, 1H, H_3), 3.22 (d, *J* = 9.2 Hz, 1H, H_3), 2.57 (brt, *J* = 3.0 Hz, 1H, H_4), 1.94 (ddd, *J* = 6.8, 6.8, 2.8 Hz, 1H, H_5), 1.64 (s, 3H, Me), 1.51 (ddd, *J* = 6.8, 2.8, 1.6 Hz, $1H_{6anti}$), 1.45 (s, 9H, BOC), 1.42 (d, *J* = 6.8 Hz, 1H, H_{6syn}), 0.87 (s, 9H, TBDMS), 0.03 (s, 6H, TBDMS); ^{13}C NMR**:** δ 156.9, 79.2, 71.1, 58.8, 53.2/53.0, 49.5, 43.5, 35.3/35.1, 28.5, 18.2. HR-MS. Calcd for $C_{12}H_{21}O_3NNa$ (M+Na): *m/z* 250.1419. Found: *m/z* 250.1425.

N-(*tert*-butoxycarbonyl)-1-methyl-5-*syn*-carboxy-2-azabicyclo[2.1.1]hexane (21a)

To a solution of alcohol **22** (23 mg, 0.10 mmol) and NMO (23.7 mg, 0.20 mmol) in anhydrous acetonitrile (4 mL) was added TPAP (3.6 mg, 0.01 mmol) in one portion. The resulting dark mixture was stirred at room temperature for 1 h before being treated with additional portions of TPAP (3 mg) and NMO (23.7 mg). The mixture was then immediately quenched with water (5 μL) and concentrated. The residue was treated with dichloromethane (10 mL) and the mixture was washed with 1 N NaOH (10 mL). The layers were separated and the aqueous layer was acidified to pH 3 and extracted with ethyl acetate (3×5 mL). Solvent was removed to give 8 mg (33%) of acid **21a**; ^{1}H NMR: δ 8.64 (br, 1H, CO_2H), 3.65 (d, *J* = 9.0 Hz, H_3), 3.33 (d, *J* = 9.0 Hz, H_3), 2.92 (br, H_4), 2.56 (br, H_5), 1.77 (s, 3H, Me), 1.59 (m, 1H, H_{6anti}), 1.48 (d, *J* = 8.1 Hz, 1H, H_{6syn}), 1.44 (s, 9H, BOC); ^{13}C NMR: δ 169.7, 155.9, 81.2, 70.6, 53.1, 51.7, 49.3, 41.2, 37.6, 28.2. HR-MS. Calcd for $C_{12}H_{20}NO_4$ (M+H): *m/z* 242.2915. Found: *m/z* 242.2874.

References

[1] Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. Secondary structural preferences of 2,2-disubstituted pyrrolidine-4-carboxylic acid oligomers: β-peptide foldamers that cannot form internal hydrogen bonds. *J. Am. Chem. Soc.* **2003**, *125*, 9035–9037.

[2] Huck, B. R. The development of novel β-peptide foldamers: 1. Tertiary amine β-peptide oligomers. 2. Chimeric α/β-peptide hairpins. Ph.D. thesis, University of Wisconsin-Madison, **2002**.

[3] Huck, B. R.; Langenhan, J. M.; Gellman, S. H. Non-hydrogen-bonded secondary structure in β-peptides: evidence from circular dichorism of (*S*)-pyrrolidine-3-carboxylic acid oligomers and (*S*)-nipecotic acid oligomers. *Org. Lett.* **1999**, *1*, 1717–1720.

[4] Huck, B. R.; Gellman, S. H. Synthesis of 2,2-disubstituted pyrrolidine-4-carboxylic acid derivatives and their incorporation into β-peptide oligomers. *J. Org. Chem.* **2005**, *70*, 3353–3362.

[5] Liu, N. Novel non-hydrogen-bonded 5-syn-carboxymethanopyrrolidine β-peptide oligomers. Ph.D. thesis, Temple University, **2008**.

[6] Hu, Z. Constrained β-prolines: 1. Methanopyrrolidine β-amino acids: synthesis and characterization of novel C^6-substituted analogues and peptide oligomers. 2. Synthesis of 2,2-disubstituted pyrrolidine-3-carboxylic acids. Ph.D. thesis, Temple University, **2015**.

[7] Krow, G. R.; Lin, G.; Herzon, S. B.; Thomas, A. M.; Moore, K. P.; Huang, Q.; Carroll, P. J. Convenient preparation of 2,4-methanopyrrolidine and 5-carboxy-2,4-methanopyrrolidines. *J. Org. Chem.* **2003**, *68*, 7562–7564.

[8] Krow, G. R.; Herzon, S. B.; Lin, G.; Qui, F.; Sonnet, P. E. Complex-induced proximity effects. Temperature-dependent regiochemical diversity in lithiation-electrophilic substitution reactions of *N*-BOC-2-azabicyclo[2.1.1]hexane. *Org. Lett.* **2002**, *4*, 3151–3154.

[9] Kwak, Y. S.; Winkler, J. D. Synthesis of 6-azabicyclo[3.2.1]octan-3-ones via vinylogous imide photochemistry: an approach to the synthesis of the hetisine alkaloids. *J. Am. Chem. Soc.* **2001**, *123*, 7429–7430.

[10] Bailey, W. F.; Patricia, J. J. The mechanism of the lithium - halogen interchange reaction: a review of the literature. *J. Organomet. Chem.* **1988**, *352*, 1–46.

[11] Hashimoto, N.; Aoyama, T.; Shioiri, T. New methods and reagents in organic synthesis. A simple efficient preparation of methyl esters with trimethylsilyldiazomethane ($TMSCHN_2$) and its application to gas chromatographic analysis of fatty acids. *Chem. Pharm. Bull.* **1981**, *29*, 1475–1478.

[12] Sadowsky, J. D.; Fairlie, W. D.; Hadley, E. B.; Lee, H. S.; Umezawa, N.; Nikolovska, C. Z.; Wang, S.; Huang, D. C. S.; Tomita, Y.; Gellman, S. H. ($\alpha/\beta+\alpha$)-Peptide antagonists of BH3 domain/Bcl-x_L recognition: toward general strategies for foldamer-based inhibition of protein-protein interactions. *J. Am. Chem. Soc.* **2007**, *129*, 139–154.

[13] Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. Modification of 1-substituents in the 2-azabicyclo[2.1.1]hexane ring system; approaches to potential nicotinic acetylcholine receptor ligands from 2,4-methanoproline derivatives. *J. Org. Chem.* **2003**, *68*, 9348–9355.

[14] Evans, G. B.; Furneaux, R. H.; Lenz, D. H.; Painter, G. F.; Schramm, V. L.; Singh, V.; Tyler, P. C. Second generation transition state analogue inhibitors of human 5'-methylthioadenosine phosphorylase. *J. Med. Chem.* **2005**, *48*, 4679–4689.

[15] Cuellar, M. A.; Salas, C.; Cortes, M. J.; Morello, A.; Diego, M. J.; Preite, M. D. Synthesis and in vitro trypanocide activity of several polycyclic drimane-quinone derivatives. *Bioorg. Med. Chem.* **2003**, *11*, 2489–2497.

[16] Brown, H. C.; Unni, M. K. Hydroboration. XXV. The hydroboration of 3-butenyl derivatives containing representative substituents. *J. Am. Chem. Soc.* **1968**, *90*, 2902–2905.

[17] Poon, C.; Chiu, P. A synthesis of the tetracyclic carboskeleton of isaindigotidione. *Tet. Lett.* **2004**, *45*, 2985–2988.

[18] Yin, B. L.; Fan, J. F.; Gao, Y.; Wu, Y. L. Molecular diversity from tonghaosu analogues, selective reduction of the *endo*-cyclic double bond of tonghaosu analogues and the synthesis of cyclopentenone derivatives. *Synlett* **2003**, *3*, 399–401.

[19] Lescop, C.; Mevellec, L.; Huet, F. A new synthesis of 2-azabicyclo[2.1.1]hexanes. *J. Org. Chem.* **2001**, *66*, 4187–4193.

[20] Anelli, P. F.; Biffi, C.; Montanari, F.; Quici, S. Fast and selective oxidation of primary alcohols to aldehydes or to carboxylic acids and of secondary alcohols to ketones mediated by oxoammonium salts under two-phase conditions. *J. Org. Chem.* **1987**, *52*, 2559–2562.

[21] Corey, E. J.; Venkateswarlu, A. Protection of hydroxyl groups as *tert*-butyldimethylsilyl derivative. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

[22] Hu, T.; Panek, J. S. Total synthesis of (–)-motuporin. *J. Org. Chem.* **1999**, *64*, 3000–3001.