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N-Acyldihydropyridones as Synthetic Intermediates. A Stereoselective Synthesis of Acyclic Amino Alcohols Containing Multiple Chiral Centers

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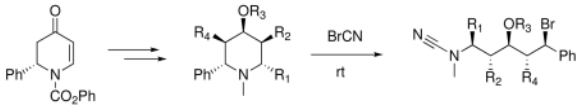
Abstract



Various multisubstituted piperidines containing a phenyl group at C-2 can be opened regio- and stereoselectively with cyanogen bromide. The ring-opened products contain useful cyanamide and benzylic bromide functional groups. The benzyl bromide can be cleanly reduced, or substituted with various nucleophiles via an S_N2 process to add additional heteroatoms stereoselectively. This methodology is useful for the stereoselective synthesis of uniquely substituted alkylamine derivatives containing multiple chiral centers and various functionality. Diastereomerically pure amino alcohols containing three to five contiguous stereocenters were prepared using this strategy.

Keywords

Dihydropyridones; piperidines; von Braun reaction; cyanogen bromide; piperidinols; amino alcohols; cyanamides

Introduction

Compared to acyclic intermediates, the stereocontrolled introduction of stereocenters into cyclic systems is generally easier to accomplish. This concept has been used often by organic chemists in designing routes to stereoselectively synthesize acyclic synthetic intermediates containing multiple chiral centers. Substituents are introduced into a cyclic building block with stereocontrol and then the ring is opened to yield the open chain intermediate with translation of stereochemistry. Historically, this approach to stereodefined acyclic intermediates has been designed and utilized for the synthesis of a specific target molecule, and few general methodologies have been developed to prepare chiral acyclic intermediates in this manner. This is particularly evident in piperidine chemistry and in the construction of chiral alkylamines. The stereoselective preparation of chiral amino alcohols is of particular importance to medicinal chemistry as they are found as fragments in numerous antiviral drugs, natural products, and various biologically active compounds.[1] The opening of chiral piperidinols appeared to have considerable potential for the facile formation of these valuable functionalized intermediates.

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Over the years, several methodologies have been developed in our labs in support of ongoing efforts to synthesize complex alkaloid natural products utilizing the dihydropyridone ring system as a building block.[2] These versatile heterocycles are readily synthesized from 1-acylpyridinium salts of 4-methoxypyridines and a nucleophile. If a chiral chloroformate is used in the formation of the 1-acylpyridinium salt, the dihydropyridones can be obtained in a highly diastereoselective fashion providing ready access to either antipode for synthetic purposes.[3] The functionality and conformational bias present in these heterocycles allow regio and stereoselective substitutions to be carried out at every carbon on the ring. This chemistry is powerful for the stereocontrolled synthesis of piperidines with multiple chiral centers.[2]

We felt that the development of a general piperidine ring-opening reaction would broaden the scope of our dihydropyridone chemistry by allowing chiral acyclic amino alcohol derivatives with 2–5 contiguous or discontinuous stereocenters to be prepared from stereodefined piperidines with control of relative and absolute stereochemistry.

As previously described in our preliminary publication,[4] we discovered that the von Braun tertiary amine cleavage reaction[5] gave both stereo and regiocontrolled ring opening in high yield at the 2-position of substituted 2-phenyl-*N*-methylpiperidines **1** (Scheme 1). Herein we describe the synthesis of various piperidinols containing multiple chiral centers, and their conversion to the corresponding acyclic intermediates. This methodlogy gives rapid entry into chiral acyclic amino alcohol derivatives of the type **2** with functionality that may be manipulated in a myriad of interesting directions depending on the subsequent chemistry that is desired. The work reported herein illustrates that the methodology is general and may be applied to the preparation of various chiral amino alcohols with excellent stereocontrol.

Results and Discussion

The first system we chose to investigate was a piperidine containing 3 stereocenters. Treatment of commercially available 4-methoxypyridine, phenyl chloroformate, and phenylmagnesium bromide followed by acidic workup gave the desired dihydropyridone **3** in 83% recrystalized yield[6] (Scheme 2). Compound 3 was then subjected to copper-mediated conjugate addition of methyl Grignard to afford preferentially the *cis* substituted piperidone **4**.[7] The diasteroselectivity was 5:1 favoring the *cis* isomer which was separated by column chromatography. LAH reduction provided the 4-piperidinol **5** as a single diastereomer. The complete facial selectivity observed during the reduction step can be explained by examining the low-energy conformation of piperidone **4** (Figure 1). Due to $A^{(1,3)}$ strain, both the C-2 and C-6 substituents are held in the axial orientation. Facile reduction of the ketone carbonyl with LAH on the less hindered face occurs prior to carbamate reduction. This result is an illustrative example of how the conformational bias of these heterocycles can be effectively used for stereocontrol. The piperidinol was protected to give **6** as either an acetate or a TBS derivative.

The ring-opening reactions of piperidines **6** were carried out under standard von Braun conditions using cyanogen bromide in refluxing CH_2Cl_2. The only products observed were the targeted acyclic cyanamides **7** as single diastereomers, due to both regio- and stereospecific ring opening of the intermediate cyanoammonium salt. The regioselectivity is a result of activation of the C-2, C-N bond by the phenyl substituent at the C-2 position. Structure elucidation of the precursor **6b** through 2-D NOESY studies gave a tentative assignment of relative stereochemistry. We anticipated that the reaction would proceed through an S_N2 mechanism and assumed as such based on literature precedent;[8] the resulting relative stereochemical assignment for products **7** would be as shown in Scheme 2. Isolation of the von Braun product **7b** as an X-ray quality crystal confirmed the assignment[4] and proved unequivocally that the reaction did in fact proceed through an S_N2 mechanism with inversion of configuration.

The functionalities resulting from the ring-opening von Braun reaction are a benzylic bromide as well as a cyanamide. The benzylic bromide is synthetically useful due to its ability to be readily substituted by various nucleophiles with inversion of stereochemistry resulting in a preserved stereocenter. The cyanamide can act as an amine protecting group, or it can be modified under a variety of conditions.[9] This functional group versatility broadens the scope of the methodology for use in the synthesis of diverse, chiral 1,3-amino alcohols.[10] Scheme 3 shows some of the chemistry that we carried out on the ring-opened products **7** and illustrates the utility and general reactivity of these intermediates.

Substitution of the bromide **7b** with sodium azide by S_N2 gave the intermediate azide **8** in high yield. Selective reduction using Pearlman's catalyst ($Pd(OH)_2$) and H_2 in EtOAc in the presence of Boc_2O afforded the Boc protected amine **9**.[11] The bromide **7b** was carried through a double inversion sequence involving reaction with sodium picolinate and mild copper-mediated methanolysis to provide **10**, and a subsequent Mitsunobu reaction to give alcohol **11**.[12] Direct substitution of **7b** with sodium benzoate in DMPU at room temperature gave the ester **12**.

Catalytic hydrogenation of **7a** and **7b**, again with Pearlman's catalyst in EtOAc, provided **13a** and **13b** via hydrogenolysis of the benzylic bromide while the rest of the molecule remained intact. If the reaction solvent for reduction of **7b** was changed to methanol instead of EtOAc, not only did hydrogenolysis of the benzylic bromide occur, but concomitant reduction of the cyanamide to the formamidine **14** was observed. This functionality proved to be very stable, and under several conditions attempted, no further reduction of the formamidine occurred. Following the method of Meyers[13], the formamidine was converted to the Cbz protected counterpart **15**, which on treatment with hydrazine under mild conditions afforded amine **16**.

Since the number and type of substituents on the piperidine could affect the ring-opening step, examples with four and five stereocenters were studied. The synthesis of the four-center precursor began with 2-phenyl-2,3-dihydropyridone **3** which was alkylated at the 3-position to give, as a single diastereomer, compound **17** (Scheme 4). Michael addition of methyl cuprate under our standard conditions afforded 4-piperidone **18**. It is worthy of note at this point that the conjugate addition, with an axial substituent at the 3-position of **17**, gives a single diastereomer via axial attack. A similar result was observed during a study of the Mukaiyama-Michael reaction of certain *N*-acyl-2,3-dihydro-4-pyridones.[14] LAH reduction proceeded smoothly to give a 7:1 mixture of piperidinols which on subsequent protection and purification provided the TBS ether **19** in 55% yield for the two steps. The relative stereochemistry assignment for **19** was confirmed through 2-D NOESY experiments. As in the reaction of **4** with LAH, the reduction of ketone **18** gave the axial alcohol intermediate as the major isomer. The von Braun reaction was carried out on substrate **19**. Once again, total regioselectivity imparted by the 2-phenyl substituent occurred, as well as inversion of configuration indicative of an S_N2 reaction to afford bromide **20** in 88% yield. It was found at this time that the von Braun ring-opening reaction of our 2-phenylpiperidines proceeds smoothly at room temperature. As before, S_N2 substitution of the bromide with sodium azide provided the corresponding azide **21**.

The possibility of opening a fully substituted piperidine ring was investigated next. Dihydropyridone **18** was methylated at C-5 with LiHMDS and methyl iodide to afford the all axial tetrasubstituted piperidone **22** (Scheme 5). Stereospecific reduction of the ketone carbonyl with L-Selectride provided the equatorial alcohol **23** as a single diastereomer. This time the facial selectivity observed is a result of the presence of axial C-3 and C-5 methyl groups in the low energy conformation (Figure 2). Reduction with LAH gave the *N*-methylpiperidinol **24** in 98% yield. Since the sterically hindered hydroxyl of **24** proved difficult to protect, the von Brawn ring-opening was carried out directly. It was hoped that alcohol

protection would not be needed, since an example of the von Braun reaction proceeding in the presence of hydroxyl groups has been reported.[15]

The fully substituted piperidine **24** was treated with cyanogen bromide at room temperature to afford **25** in good yield. X-ray analysis of minor byproduct **26** confirmed the stereochemical assignments for **23** and **24**.[4]

To broaden the scope of this methodology, the preparation of polyhydroxy piperidines via a tetrahydropyridine intermediate was examined.[16] The 2-alkyldihydropyridone **27** was reduced under Luche conditions to the corresponding *trans*-alcohol which was methylated to provide ether **28**.[17] Lewis acid mediated phenylzinc addition, via an intermediate iminium ion, gave tetrahydropyridine **29**.[18] With the C-2 and C-6 substituents of **29** pseudo axial, dihydroxylation with OsO_4 would certainly lead to the β-diol. Since flexible stereocontrol in the incorporation of functionality is important to the scope of this methodology, we were interested to see if the all cis diol **31** could be prepared. To this end, **29** was subjected to the Woodward dihydroxylation reaction.[19] To our delight, the all *cis* piperidine **30** was obtained in 60% yield. Deprotection and reductive methylation of **30** using a one-pot procedure gave the *N*-methyl derivative **31**.[20] The hydroxyl groups were protected as benzyl ethers to provide **32**. Cyanogen bromide ring-opening was again highly efficient affording a 96% yield of cyanamide **33**. The bromine of **33** was reductively removed in the presence of the benzyl ethers and cyanamide group using mild catalytic hydrogenation conditions to give **34** in near quantitative yield.

Conclusion

This methodology is of broad scope as it has the potential for use in the preparation of uniquely substituted amine derivatives containing multiple chiral centers and various functionality. The relative stereochemistry can be introduced with a high degree of control and with considerable variability. Contiguous or skip stereocenters can be introduced via appropriate conversions of the *N*-acyldihydropyridone precursor. Since introduction of substituents onto the dihydropyridone or tetrahydropyridine intermediates can be accomplished stereoselectively through direct addition[2] or epimerization,[2h,21] most desired diastereomers can be prepared efficiently in a few number of steps. The potential is there for incorporating quaternary centers,[2h,21] and for using other aryl or non-aryl ring-opening activating groups at the C-2 position. Although this study used racemic materials, enantiopure diastereomeric products of either antipode can be prepared by starting with readily available nonracemic dihydropyridones.[3] This methodology should be amenable to the asymmetric synthesis of natural products and other biologically active compounds.

Experimental Section

The synthesis and characterization of compounds **3–5**, **6b**, **7b**, **8–9**, **12**, **17–18**, and **22–26** have been previously reported.[4]

(2*S**,4*R**,6*S**)-1,2-Dimethyl-6-phenylpiperidin-4-yl acetate (6a)

To a solution of **5** (115 mg, 0.56 mmol) in 4 mL of THF was added acetic anhydride (62.8 mg, 0.62 mmol), TEA (75.3 mg, 0.616 mmol), and DMAP (2.8 mg, 0.03 mmol). The mixture was allowed to stir at rt for 18 h. After the reaction was deemed complete by TLC, the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by radial PLC (30% EtOAc/hexanes) to give 109 mg (79%) of **6a** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, 1H, *J* = 8 Hz), 1.54 (q, 1H, *J* = 15.6 Hz), 1.68 (q, 1H, *J* = 15.6 Hz), 1.96 (s, 3H), 1.98 (s, 3H), 1.91–2.04 (m, 2H), 2.17–2.27 (m, 1H), 3.03 (dd, 1H, *J* = 12.4, 3.6 Hz), 4.76–4.87 (m, 1H), 7.20–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 39.9, 40.2, 41.4, 58.0, 68.9, 71.0, 127.4, 127.6, 128.7, 144.4, 170.7; IR (neat)

1434, 1453, 1494, 1602, 1740, 2779, 2845, 2970, 3027, 3062 cm^{-1}; HRMS: $(M+H)^+$ calcd for $C_{15}H_{21}NO_2$ 248.1651; found 248.1647.

(1*R**,3*R**,5*S**)-1-Bromo-5-(isocyano(methyl)amino)-1-phenylhexan-3-yl acetate (7a)

Protected piperidinol **6a** (270 mg, 1.09 mmol) was dissolved in CH_2Cl_2 (40 mL). A solution of BrCN (1.8 mL, 5.4 mmol, 3.0 M in CH_2Cl_2) was added and the reaction mixture was brought to reflux. The reaction was monitored by TLC analysis. After 3 h, the reaction mixture was cooled and concentrated under reduced pressure. The crude residue was purified by radial PLC (20–30% EtOAc/hexanes) to give compound **7a** (364 mg, 95%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.1 (s, 6H), 0.9 (s, 9H), 1.21 (d, 3H, *J* = 8.8 Hz), 1.53 (m, 1H), 1.89 (m, 1H), 2.17 (m, 1H), 2.56 (m, 1H), 5.03 (dd, 1H, *J* = 6.8 Hz), 7.26–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.2, −3.7, 18.2, 36.9, 41.9, 47.7, 51.1, 54.5, 68.2, 117.3, 127.4, 128.8, 129.1, 142.1; IR (neat) 1508, 1560, 1655, 1685, 2209, 2362, 2857, 2896, 2930, 2954, 3032 cm^{-1}; HRMS: $(M+H)^+$ calcd for $C_{20}H_{33}BrN_2OSi$: 425.1624; found, 425.1629.

N-((2*S**,4*R**,6*S**)-4-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-6-phenylhexan-2-yl)-*N*-methylcyanamide (10)

To bromide **7b** (80 mg, 0.19 mmol) in 2.7 mL of HMPA was added freshly prepared sodium picolinate (32 mg, 0.23 mmol). The reaction was allowed to stir at rt for 18 h at which time 3 mL of brine was added along with 3 mL of Et_2O. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 3 mL). The organic extracts were combined, washed with H_2O (2 × 2 mL) and brine (1 × 2 mL), and dried over $MgSO_4$. Filtration and concentration gave an oil that was dissolved in 5 mL of $CHCl_3$. MeOH (49 μL, 1.197 mmol) and $Cu(OAc)_2$ (27 mg, 0.15 mmol) were added and the mixture was stirred at rt for 18 h. Concentration afforded a crude oil that was dissolved in CH_2Cl_2. The solution was washed with 50:50 saturated NH_4Cl/20% NH_4OH solution and the layers separated. The organic layer was dried over $MgSO_4$ and concentrated. Purification by radial PLC (EtOAc/hexanes) gave 45 mg of benzyl alcohol **10** (63% yield overall) as an oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.13 (d, 6H, *J* = 24.4 Hz), 0.93 (s, 9H), 1.27 (d, 3H, *J* = 6.4 Hz), 1.75–2.02 (m, 4), 2.84 (s, 3H), 3.09 (m, 1H), 4.12 (sextet, 1H, *J* = 4.4 Hz), 4.98 (dd, 1H, *J* = 2.8, 10.4 Hz), 7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.6, −4.0, 18.2, 26.1, 37.4, 41.8, 45.8, 54.8, 68.4, 71.5, 117.2, 125.9, 127.7, 128.7, 144.8; IR (neat) 1063, 1256, 1458, 2211, 2858, 2932, 2954, 3445 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{34}N_2O_2Si$ 363.2468, found 363.2462.

N-((2*S**,4*R**,6*R**)-4-(*tert*-Butyldimethylsilyloxy)-6-hydroxy-6-phenylhexan-2-yl)-*N*-methylcyanamide (11)

To benzyl alcohol **10** (45 mg, 0.12 mmol) in 2 mL of THF at −20 °C was added triphenylphosphine (65 mg, 0.25 mmol) and picolinic acid (31 mg, 0.25 mmol). After stirring for 20 min, DEAD (39 μl, 0.25 mmol) was added dropwise over 5 min and then the mixture was allowed to warm to rt over a 4 h period. The reaction mixture was concentrated under reduced pressure. The residue was triturated with hot hexanes and filtered. The filtrate was concentrated to give an oil that was taken directly on to the next step. To the crude ester was added 6 mL of $CHCl_3$, MeOH (39 μL, 2.7 mmol), and $Cu(OAc)_2$ (23 mg, 0.12 mmol), and the mixture was stirred at rt for 20 h. The reaction was quenched with 50:50 saturated NH_4Cl/25% NH_4OH solution, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by radial PLC (EtOAc/hexanes) gave **11** (23 mg, 53% over 2 steps) as a white solid, mp 82–83 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.11 (d, 6H, *J* = 5.2 Hz), 0.9 (s, 9H), 1.23 (d, 3H, *J* = 6.0 Hz), 1.65 (m, 1H), 1.77 (m, 1H), 1.99 (m, 2H), 2.73 (bs, 1H), 2.84 (s, 3H), 3.12 (m, 1H), 4.14 (m, 1H), 4.83 (d, 1H, *J* = 10 Hz), 7.26–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.3, −3.8, 18.4, 26.1, 37.3, 42.4, 47.0, 54.4, 67.8, 71.7, 117.6, 125.8, 127.7, 128.7,

145.1; IR (neat) 775, 836, 1061, 2209, 2855, 2929, 2952 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{34}N_2O_2Si$ 363.2468, found 363.2457.

(3*S**,5*S**)-5-(*N*-Methylcyanamido)-1-phenylhexan-3-yl acetate (13a)

To bromide **7a** (51 mg, 0.145 mmol) in EtOAc (3 mL) was added $Pd(OH)_2$ (40 mg, 0.06 mmol) and NaOAc (30 mg, 0.36 mmol), and the mixture was placed under a balloon pressurized atmosphere of H_2 with good stirring. After 15 h, the reaction mixture was filtered through Celite and concentrated to give 33 mg (83%) of **13a** which was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (d, 3H, *J* = 8.8 Hz), 1.65–1.74 (m, 1H), 1.83–1.99 (m, 2H), 2.04 (s, 3H), 2.64 (t, 2H, *J* = 10.8 Hz), 2.81 (s, 3H), 2.87–2.94 (m, 1H), 5.05–5.13 (m, 1H), 7.15–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.4, 21.4, 31.8, 36.6, 37.9, 39.7, 54.9, 71.0, 116.9, 126.3, 128.5, 128.7, 141.4, 170.9; IR (neat) 701, 749, 939, 1023, 1041, 1135, 1167, 1239, 1374, 1434, 1455, 1496, 1557, 1603, 1652, 1735, 2207, 2360, 2933, 2969, 3027, 3646, 3673, 3748, 3851 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{16}H_{22}N_2O_2$ 275.1760, found 275.1750.

N-((2*S**,4*S**)-4-(*tert*-Butyldimethylsilyloxy)-6-phenylhexan-2-yl)-*N*-methylcyanamide (13b)

To benzyl bromide **7b** (28 mg, 0.06 mmol) in 3 mL of dry EtOAc was added $Pd(OH)_2$ (19 mg, 0.03 mmol) and NaOAc (11 mg, 0.13 mmol). The mixture was stirred under an atmosphere of H_2 at balloon pressure for 12 h. The mixture was filtered through a Celite pad with an EtOAc wash. The solvent was removed under reduced pressure to yield **13b** (23 mg, 100%) as an oil which did not need further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (d, 6H, *J* = 6.9 Hz), 0.90 (s, 9H), 1.23 (d, 3H, *J* = 6.6 Hz), 1.55–1.64 (m, 1H), 1.76–1.89 (m, 2H), 2.56–2.71 (m, 2H), 2.83 (s, 3H), 3.07–3.16 (m, 1H), 3.87–3.94 (m, 1H), 7.17–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.4, −3.7, 18.3, 26.1, 19.9, 31.0, 37.4, 39.9, 42.0, 54.7, 68.5, 117.4, 126.0, 128.6, 128.7, 142.4; IR (neat) 776, 1063, 1254, 1458, 2208, 2857, 2932, 2952 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{34}N_2OSi$ 347.2519, found 347.2528.

N-((2*S**,4*S**)-4-(*tert*-Butyldimethylsilyloxy)-6-phenylhexan-2-yl)-*N*-methylformimidamide (14)

To bromocyanamide **7b** (30 mg, 0.07 mmol) in 2.5 mL of EtOH was added Pearlman's Catalyst ($Pd(OH)_2$, 4 mg, 0.03 mmol) and NaOAc (6 mg, 0.07 mmol). The mixture was placed under a balloon pressurized atmosphere of H_2 and stirred at rt for 15 h at which time the reaction was deemed complete by TLC. The mixture was filtered through a pad of Celite and then concentrated. The crude solid was triturated with CH_2Cl_2. The hot mixture was filtered and the remaining solids washed with hot CH_2Cl_2. The filtrate was concentrated under reduced pressure and the crude solid residue was recrystallized from EtOAc to give **14** (24.2 mg, 99%) as a white solid, mp 184–185 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.07 (d, 6H, *J* = 7.2 Hz), 0.90 (s, 9H), 1.32 (d, 3H, *J* = 6.6), 1.65–1.82 (m, 4H), 2.61 (m, 1H), 3.14 (s, 3H), 3.64 (bs, 1H), 3.81 (m, 1H), 7.14–7.33 (m, 5H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −3.9, −3.4, 20.3, 26.2, 31.1, 32.0, 39.0, 40.9, 59.2, 68.9, 126.4, 128.5, 128.5, 153.7; IR (neat) 836.1, 1063, 1255, 1699, 2358, 2857, 2954 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{19}NO_3$ 349.2675, found 349.2680.

(*E*)-Benzyl(((2*S**,4*S**)-4-(*tert*-butyldimethylsilyloxy)-6-phenylhexan-2-yl)(methyl)amino) methylenecarbamate (15)

To formamidine **14** (30 mg, 0.087) in 3 mL of Et_2O was added 3 mL of saturated aqueous $NaHCO_3$. The biphasic reaction mixture was cooled to 0 °C and benzyl chloroformate (16.2 mg, 0.1 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 10 min and then warmed to rt. After stirring for 1 h, the layers were separated and the aqueous layer was extracted with Et_2O. The combined extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by radial PLC

(EtOAc/hexanes) to give **15** (40 mg, 97%) as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.29 (d, 6H, *J* = 15.6 Hz), 0.91 (s, 9H), 1.28 (d, 3H, *J* = 6 Hz), 1.58–1.84 (m, 14H), 2.60 (m, 2H), 2.93 (s, 3H), 3.62 (m, 1H), 3.80 (m, 1H), 4.71 (s and 5.19 s, due to rotamers, 2H), 7.14–7.43 (m, 10H), 8.44 (s and 8.55 s, due to rotamers, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.4, −3.4, 18.3, 20.3, 26.2, 29.0, 31.1, 39.5, 41.0, 56.5, 67.6, 68.7, 126.2, 127.2, 12.4, 128.6, 128.8, 137.0, 141.9, 163.1, 164.4; IR (neat) 1062, 1211, 1378, 1657, 2285, 2928, 2949, 3027 cm^{-1}. HRMS $(M+H)^+$ calcd for $C_{28}H_{42}N_2O_3Si$ 483.3043, found 483.3033.

(2*S**,4*S**)-4-(*tert*-Butyldimethylsilyloxy)-*N*-methyl-6-phenylhexan-2-amine (16)

To the protected formamidine **15** (19 mg, 0.039 mmol) in 2 mL of a 6/4 EtOH/H_2O solution was added one drop of glacial acetic acid along with N_2H_4•H_2O (5 μl, 0.11 mmol). The reaction was stirred at rt for 15 h and then 1 mL of water and 3 mL of Et_2O were added. The layers were separated and the water layer was extracted with Et_2O. The combined extracts were washed with brine, dried over K_2CO_3, and concentrated under reduced pressure. The residue was purified by radial PLC (EtOAc/hexanes) to give 11 mg (88%) of **16** as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6H), 0.90 (s, 9H), 1.04 (d, 3H, *J* = 6.0 Hz), 1.25 (s, 1H), 1.48–1.81 (m, 4H), 2.38 (s, 3H), 2.63 (m, 3H), 3.86 (m, 1H), 7.17–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.2, 18.3, 20.6, 26.1, 31.9, 33.9, 39.3, 44.0, 51.8, 70.1, 126.0, 128.6, 142.7; IR (neat) 1057, 1256, 1373, 1472, 1604, 2793, 2856, 2929, 2955 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{19}H_{35}NOSi$ 322.2566, found 322.2574.

(2*S**,3*R**,4*R**,6*S**)-4-(*tert*-Butyldimethylsilyloxy)-1,3,6-trimethyl-2-phenylpiperidine (19)

To piperidone **18** (347 mg, 1.07 mmol) in 20 mL of THF was added portionwise LAH (241 mg, 6.44 mmol), and the mixture was heated at reflux for 4 h. The reaction was cooled to 0 °C and quenched by careful addition of 10% NaOH (0.72 mL) and H_2O (0.5 mL). Celite (3.5 g) was added and the mixture was allowed to warm to rt with stirring for 1.5 h. The mixture was filtered through a pad of Celite and concentrated under reduced pressure. A portion of the crude alcohol (115 mg, 0.52 mmol) was stirred in 10 mL of dry CH_2Cl_2 with TBSOTf (277 mg, 1.05 mmol), Et_3N (83 mg, 0.68 mmol), and a catalytic amount of imidazole (3 mg, 0.03 mmol) at rt for 1.5 h. The reaction mixture was quenched with 8 mL of saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The organics were combined and washed with H_2O and brine, and dried over $MgSO_4$. Filtration and concentration under reduced pressure gave a crude oil which was purified by radial PLC (EtOAc/hexanes) to afford 96 mg (55%) of **19** as a clear oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.08 (d, 6H, *J* = 6.3 Hz), 0.6 (d, 3H, *J* = 6.3 Hz), 0.90 (s, 9H), 1.17 (d, 3H, *J* = 6 Hz), 1.63 (m, 2H), 1.89 (s, 3H), 2.14 (m, 1H), 2.54 (d, 1H, *J* = 9.9 Hz), 3.3 (dt, 1H, *J* = 4.5, 5.4 Hz), 7.73 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.4, −3.7, 15.8, 18.3, 21.9, 26.1, 40.7, 44.5, 46.1, 58.2, 74.9, 127.2, 128.0, 128.5, 128.7, 143.7, 149.9; IR (neat) 702, 835, 873, 1086, 1249, 1375, 2777, 2850, 2933, 2964 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{20}H_{35}NOSi$ 334.2566, found 334.2560.

N-((2*S**,4*R**,5*R**,6*R**)-6-Bromo-4-(*tert*-butyldimethylsilyloxy)-5-methyl-6-phenylhexan-2-yl)-*N*-methylcyanamide (20)

To a solution of piperidine **19** (96 mg, 0.288 mmol) in 7 mL of $CHCl_3$ was added BrCN (0.47 mL, 1.4 mmol, 3.0 M in CH_2Cl_2). The mixture was allowed to stir at rt for 5 h and then concentrated under reduced pressure to give a yellow oil. The crude product was freed of residual BrCN under high vacuum. The crude yield was quantitative, but purification by radial PLC (EtOAc/hexanes) gave 110 mg (88%) of **20** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ −0.09 (d, 6H, *J* = 12.6 Hz), 0.89 (s, 9H), 1.09 (d, 3H, *J* = 6.3 Hz), 1.28 (d, 3H, *J* = 6.9 Hz), 1.63 (m, 1H), 1.88 (m, 1H), 2.23 (m, 1H), 2.74 (s, 3H), 2.85 (m, 1H), 3.58 (m, 1H), 5.04 (d, 1H, *J* = 8.7 Hz) 7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.1, −3.7, 13.1, 17.9, 18.4, 26.1, 37.3, 40.5, 45.8, 55.3, 59.5, 69.8, 117.0, 128.0, 128.5, 128.9, 142.0; IR (neat) 775, 836, 1078,

1254,1384, 1454, 2208, 2856, 2931, 2953, 3464 cm^{-1}; HRMS $(M+H)^+$ calcd for $C_{21}H_{35}BrN_2OSi$ 439.1780, found 439.1765.

N-((2*S**,4*R**,5*S**,6*S**)-6-Azido-4-(*tert*-butyldimethylsilyloxy)-5-methyl-6-phenylhexan-2-yl)-*N*-methylcyanamide (21)

To a solution of bromocyanamide **20** (43 mg, 0.10 mmol) in 2 mL of freshly distilled DMSO was added NaN_3 (19 mg, 0.29 mmol). The mixture was stirred at rt for 18 h and then diluted with saturated aqueous $NaHCO_3$ (2 mL). The aqueous phase was extracted with Et_2O, and the combined extracts were washed with H_2O and brine. The mixture was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude product was purified by radial PLC (EtOAc/hexanes) to give 31 mg (77%) of **21** as a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.09 (m, 1H), 0.16 (d, 6H, *J* = 15.3 Hz), 0.60 (d, 3H, *J* = 6.9 Hz), 0.9 (m, 3H), 0.94 (s, 9H), 1.27 (d, 3H, *J* = 6.3 Hz), 1.58–1.86 (m, 4H), 2.86 (s, 3H), 2.96 (m, 1H), 4.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ −4.5, −3.7, 18.2, 26.1, 37.2, 41.6, 42.6, 54.6, 68.2, 117.4, 134.1, 134.2, 136.5, 181.4; HRMS $(M+H)^+$ calcd for $C_{21}H_{35}N_5OSi$ 402.2689, found 402.2689.

2-Nonyl-4-oxo-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (27)

Prepared as an oil (76%) according to the literature procedure.[6] ^1H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1H, *J* = 4.8 Hz), 7.37 (s, 5H), 5.32-5.21 (m, 3H), 4.58 (m, 1H), 2.79 (dd, 1H, *J* = 6.4, 16.4), 2.45 (d, 1H, *J* = 16.4), 1.61 (m, 2H), 1.25 (m, 13H), 0.8 (t, 3H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 193.3, 141.7, 141.6, 135.1, 128.9, 128.8, 128.6, 107.3, 69.1, 53.6, 39.8, 31.9, 30.6, 29.6, 29.4, 25.8, 22.8, 14.3; HRMS $(M+H)^+$ calcd for $C_{22}H_{31}NO_3$ 358.2382, found 358.2380.

(2*R*,*4*R**)-4-Methoxy-2-nonyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (28)

To compound **27** (733 mg, 2.05 mmol) in 80 mL of MeOH was added solid $CeCl_3 \cdot 7H_2O$ (1.53 g, 4.10 mmol) at rt and the mixture was allowed to stir for 15 min. After cooling to −40 °C, $NaBH_4$ (232 mg, 6.15 mmol) was added and the reaction progress was monitored by TLC. After disappearance of starting material showed completion of the reaction, acetone was added to quench excess $NaBH_4$. Solvent was removed *in vacuo*, and water was added to the crude residue. The aqueous mixture was extracted with EtOAc. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure to give an oil. The oil was taken on to the next step without further purification. The oil from above was dissolved in THF (5 mL) and cooled to −40 °C and then *t*-BuOK (1.0 M, THF, 2.46 mmol) was added. After stirring for 20 min, MeI (0.76 mL, 12.3 mmol) was added and the mixture was allowed to slowly warm to rt. After 1 h, saturated aqueous $NaHCO_3$ was added. The aqueous layer was extracted with 3 × 10 mL of EtOAc. The combined extracts were washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated to give an oil (**28**, 675 mg, 87% yield) that was used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36 (s, 5H), 6.82 (brs, 1H), 5.20 (d, 3H, *J* = 12.6 Hz), 4.96 (brs, 1H), 4.29 (brs, 1H), 3.97 (m, 1H), 3.36 (s, 3H), 2.20 (brs, 1H), 1.72 (m, 16H), 0.88 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.2, 128.7, 128.4, 128.3, 125.1, 106.5, 77.4, 70.1, 67.8, 55.9, 51.8, 32.0, 31.4, 26.1, 25.8, 22.8, 14.3; HRMS $(M+H)^+$ calcd for $C_{23}H_{34}NO_3$ 374.2695, found 374.2709.

(2*R**,6*R**)-4-Methoxy-2-nonyl-3,4-dihydro-2H-pyridine-1-carboxylic acid benzyl ester (29)

To anhydrous $ZnBr_2$ (1.85 g, 8.2 mmol) in 10 mL of toluene at rt was added PhMgBr (8.2 mL, 8.2 mmol, 1.0 M in THF), and the mixture was stirred for 1 h at rt. Methyl ether **28** (675 mg, 1.81 mmol) in 10 mL of toluene at 0 °C was added followed immediately by addition of $BF_3 \cdot OEt_2$ (2.7 mmol). The mixture was stirred at 0 °C for 1 h and then allowed to slowly warm to rt and quenched with 10% HCl. The crude reaction mixture was extracted with Et_2O. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, and

concentrated under reduced pressure. Purification by radial PLC (5–10% EtOAc/hexanes) gave upon reiterative purification 535 mg (73%) of the *cis* diastereoemer **29** as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (brs, 1H), 7.31-7.21 (m, 10H), 5.95 (s, 2H), 5.71 (brs, 1H), 5.19 (s, 2H), 4.50 (m, 1H), 2.44 (ddd, 1H, *J* = 3.0, 5.2, 13.1 Hz), 2.01 (d, 1H, *J* = 13.1), 1.44 (m, 1H), 1.28-0.80 (m, 14H), 0.87 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 142.4, 136.9, 128.6, 128.4, 128.2, 128.0, 127.2, 125.9, 124.4, 67.4, 53.6, 49.4, 34.2, 32.0, 29.8, 29.6, 29.4, 28.9, 28.8, 26.7, 22.8, 14.3; HRMS $(M+H)^+$ calcd for $C_{28}H_{34}NO_2$ 419.2824, found 419.2792.

(2*S**,3*R**,4*S**,6*R**)-3,4-Dihydroxy-6-nonyl-2-phenyl-piperidine-1-carboxylic acid benzyl ester (30)

To olefin **29** (336 mg, 0.83 mmol) in 4 mL of AcOH was added AgOAc (288 mg, 1.64 mmol) and I_2 (208 mg, 0.83 mmol). The mixture was allowed to stir at rt for 12 h and then AcOH:H_2O (24:1) was added and stirring was continued for 2 h. Saturated brine was added and the reaction mixture was filtered through Celite. The Celite pad was washed with EtOAc and MeOH. The filtrate was concentrated to remove solvent and then a solution of 2.0 M KOH/MeOH was added. The mixture was stirred at rt for 4 h. Brine was added and the aqueous layer was extracted with CH_2Cl_2, and the combined extracts were dried over $MgSO_4$. Concentration and purification by radial PLC (20–50% EtOAc/hexanes) gave 218 mg (60%) of diol **30** as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.19 (m, 8H), 6.95 (m, 2H), 5.10 (d, 1H, *J* = 5.2 Hz), 4.99 (d, 1H, *J* = 12.4 Hz), 4.92 (d, 1H, *J* = 12.4 Hz), 4.32 (m, 1H), 4.16 (m, 1H), 3.93 (m, 1H), 2.31 (ddd, 1H, *J* = 6.4, 10.8, 12.4 Hz), 1.93 (m, 1H), 1.84 (m, 1H), 1.75 (ddd, 1H, *J* = 5.2, 10.8, 12.8 Hz), 1.33-1.25 (m, 14H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 140.0, 136.5, 128.9, 128.4, 127.9, 127.8, 127.4, 126.8, 71.2, 68.0, 67.5, 63.1, 51.0, 38.4, 32.1, 31.1, 29.9, 29.7, 29.5, 26.9, 22.9, 14.3.

(2*S**,3*R**,4*S**,6*R**)-1-Methyl-6-nonyl-2-phenyl-piperidine-3,4-diol (31)

A mixture of piperindiol **30** (40 mg, 0.09 mmol), formaldehyde (0.4 mL, 37% in H_2O), and $Pd(OH)_2$ in 9 mL of MeOH was placed under a hydrogen atmosphere (50 psi, Parr shaker overnight) at rt. The reaction mixture was filtered through Celite and the filter pad was washed with copious amounts of methanol. The filtrate was concentrated *in vacuo*, and residue was purified by column chromatography (0–20% EtOAc/hexanes) to give 20 mg (70%) of the desired *N*-methylpiperidinol **31** as an oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.27 (m, 5H), 3.66 (brs, 2H), 3.14 (s, 1H), 2.21-2.19 (m, 2H), 2.11 (m, 1H), 2.03 (s, 3H), 1.87 (m, 1H), 1.69 (dd, 1H, *J* = 9.0, 18.6, 12.4 Hz), 1.60-1.40 (m, 4H), 1.29-1.25 (m, 22H), 0.87 (t, 3H, *J* = 5.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 140.9, 128.7, 128.5, 128.3, 127.7, 73.3, 72.8, 70.6, 62.4, 40.1, 34.3, 33.8, 32.1, 30.3, 29.9, 29.8, 29.6, 24.6, 22.9, 14.3.

(2*S**,3*R**,4*S**,6*R**)-3,4-Bis-benzyloxy-1-methyl-6-nonyl-2-phenylpiperidine (32)

Diol **31** (50 mg, 0.15 mmol) was dissolved in 1.5 mL of THF and cooled to −40 °C. A solution of *t*-BuOK (1.0 M in THF, 0.45 mL) was added dropwise and the mixture was allowed to stir at −40 °C for 30 min. Benzyl bromide (0.053 mL, 0.45 mmol) was added and the reaction was allowed to warm slowly to rt over 2 h. Saturated NH_4Cl was added and the aqueous layer was extracted with Et_2O. The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by radial PLC (0–20% EtOAc/hexanes) gave 64 mg (84%) of compound **32** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (m, 2H), 7.33-7.24 (m, 9H) 7.16 (m, 2H), 7.03 (m, 2H), 4.55 (s, 2H), 4.48 (d, 1H, *J* = 11.2 Hz), 4.06 (d, 3H, *J* = 11.2 Hz), 3.71 (s, 1H), 3.54 (ddd, 1H, *J* = 2.0, 4.0, 6.4 Hz), 3.06 (s, 1H), 2.13 (m, 1H), 2.01 (s, 3H), 1.90 (m, 1H), 1.67 (m, 2H), 1.52 (m, 2H), 1.40-1.20 (m, 13H), 1.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 129.3, 128.6, 128.3, 128.1, 128.0, 127.6, 127.4, 127.2, 127.1, 79.9, 78.1, 74.6, 73.0, 70.3, 63.5, 40.8, 34.1, 32.1, 31.5, 30.3, 29.8, 29.6, 25.7, 22.9, 14.4. EIMS $(M+1)^+$ 514.

N-((1*S**,2*S**,3*S**,5*S**)-2,3-Bis(benzyloxy-1-bromo-1-phenyltetradecan-5-yl)-*N*-methylcyanamide (33)

The protected alcohol **32** (20 mg, 0.039 mmol) was dissolved in 2 mL of $CHCl_3$. To this was added a 3.0 M solution of BrCN (0.15 mL) and the mixture was heated to reflux. After 2 h, the reaction mixture was cooled and filtered through a Celite plug with a $CHCl_3$ wash. The filtrate was concentrated *in vacuo* to give **33** as an oil (23 mg) in 96% yield. ^{1}H NMR analysis showed complete conversion and no further purification was necessary. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.25 (m, 10H), 7.19 (m, 3H), 6.82 (m, 2H), 4.76 (d, 1H, *J* = 7.0 Hz), 4.74 (d, 1H, *J* = 8.4 Hz), 4.62 (d, 1H, *J* = 8.4 Hz), 4.54 (d, 1H, *J* = 7.8 Hz), 4.30 (t, 2H, *J* = 9.6 Hz), 4.13 (d, 1H, *J* = 7.8 Hz), 3.11 (m, 1H), 2.62 (s, 3H), 1.86 (ddd, 1H, *J* = 2.1, 7.5, 9.9 Hz), 1.70 (ddd, 1H, *J* = 1.5, 8.1, 9.9 Hz), 1.50-1.20 (m, 15H), 0.88 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.9, 138.2, 137.8, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 127.9, 118.3, 82.5, 77.3, 75.4, 72.0, 59.2, 52.5, 35.8, 33.4, 32.5, 32.1, 29.8, 29.7, 29.6, 29.5, 26.4, 22.9, 14.3; LCMS $(M+1)^+$ 621.

N-((2*R**,3*S**,5*S**)-2,3-Bis(benzyloxy)-1-phenyltetradecan-5-yl)-*N*-methylcyanamide (34)

Crude bromide **33** (23 mg, 0.037 mmol) was dissolved in 2 mL of EtOAc. $Pd(OH)_2$ (10 mol %) and NaOAc (15 mg, 0.186 mmol) were added and the reaction was placed under a H_2 atmosphere (balloon pressure) and allowed to stir at rt for 12 h. The reaction mixture was then filtered through Celite with EtOAc. The filtrate was concentrated under reduced pressure to give 19 mg (99%) of pure **34** as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.20 (m, 15H), 4.66 (d, 1H, *J* = 11.6 Hz), 4.64 (d, 1H, *J* = 11.6 Hz), 4.50 (d, 1H, *J* = 12.0 Hz), 4.29 (d, 1H, *J* = 11.6 Hz), 3.90 (td, 1H, *J* = 1.2, 7.2 Hz), 3.57 (d, 1H, *J* = 10.0 Hz), 2.96 (dd, 1H, *J* = 7.2, 14.0 Hz), 2.90 (m, 1H), 2.75 (dd, 1H, *J* = 6.4, 14.0 Hz), 2.50 (s, 3H), 1.77 (m, 2H), 1.58 (m, 1H), 1.43 (m, 1H), 1.40-1.20 (m, 14H), 0.89 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 138.7, 138.3, 129.7, 128.8, 128.7, 128.6, 128.5, 128.0, 127.7, 126.5, 117.8, 81.1, 76.8, 72.9, 71.7, 59.3, 37.5, 33.7, 32.1, 29.8, 29.7, 29.6, 29.5, 26.3, 22.9, 14.3.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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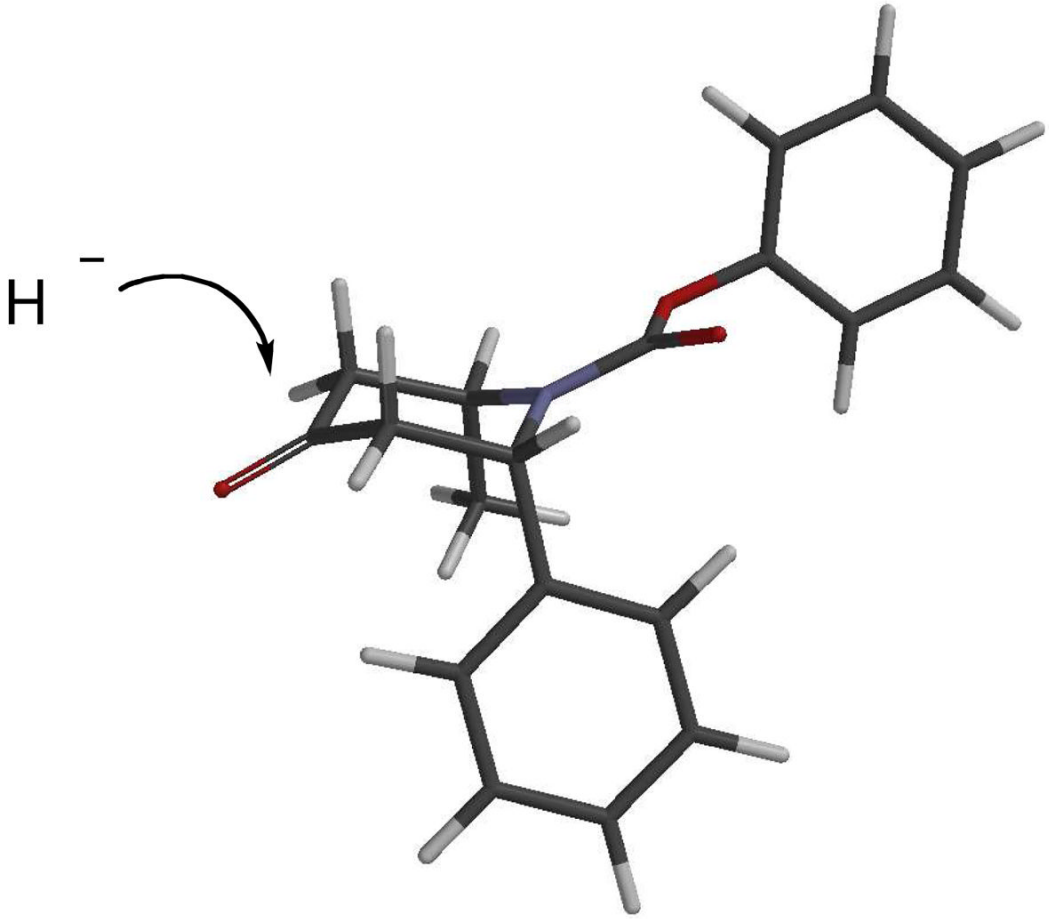


Figure 1.
Calculated lowest energy conformation of **4** (MMFF)

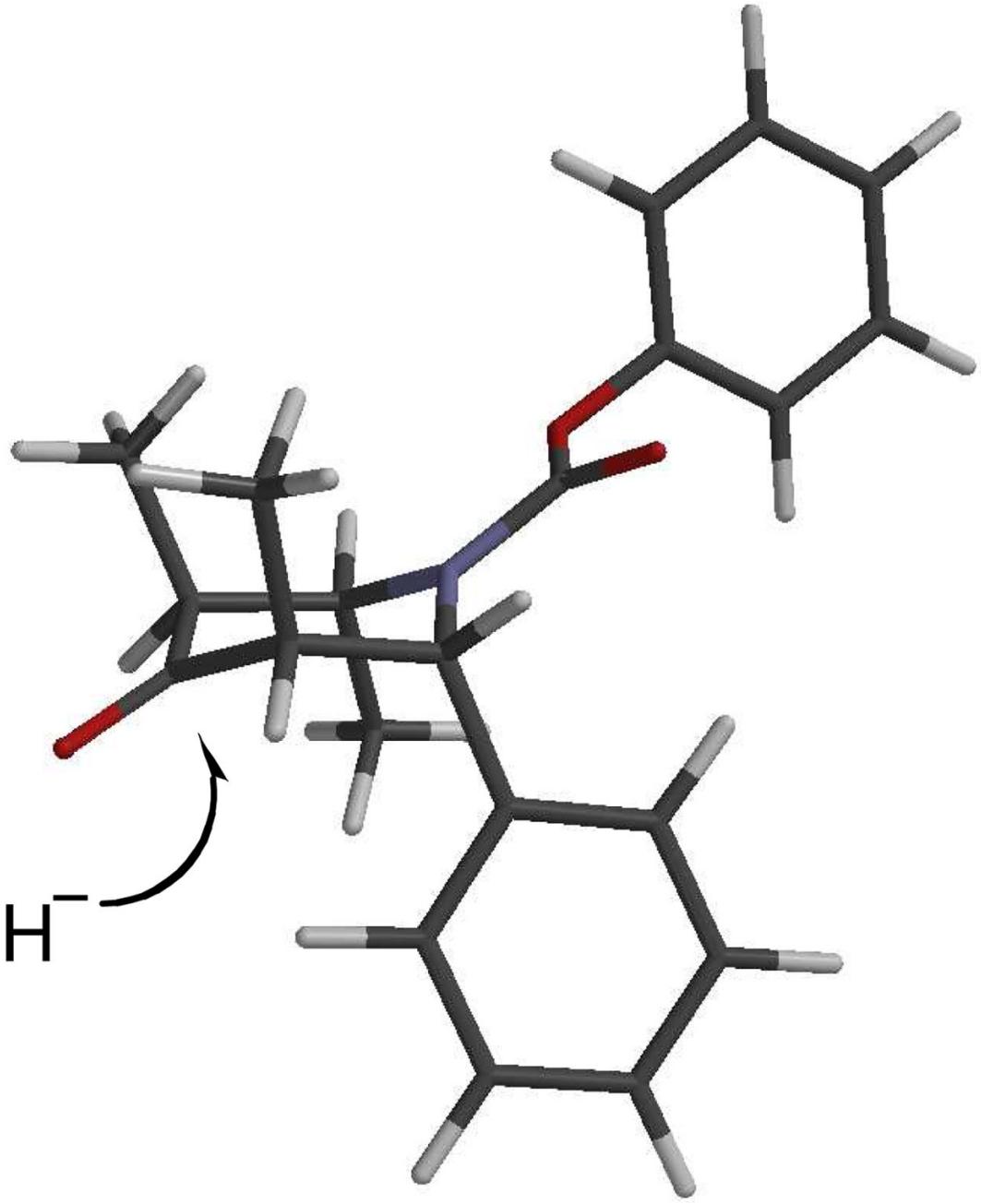
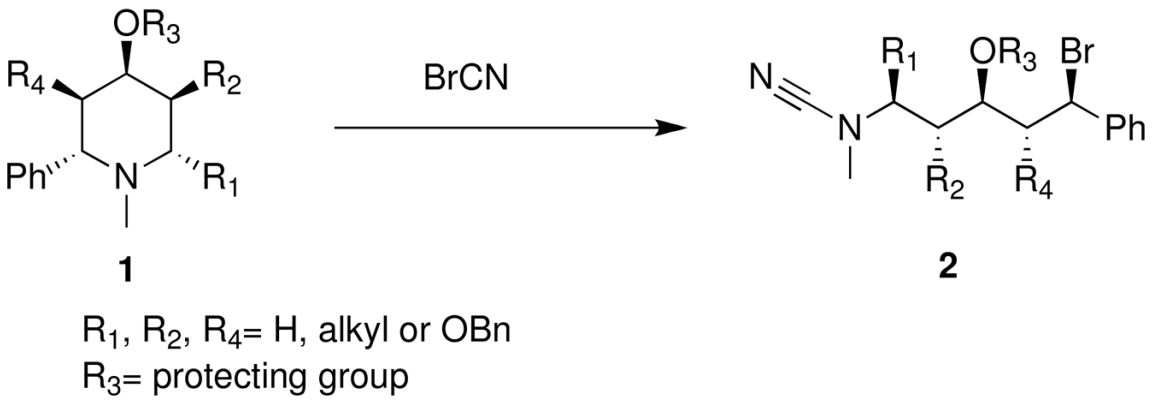
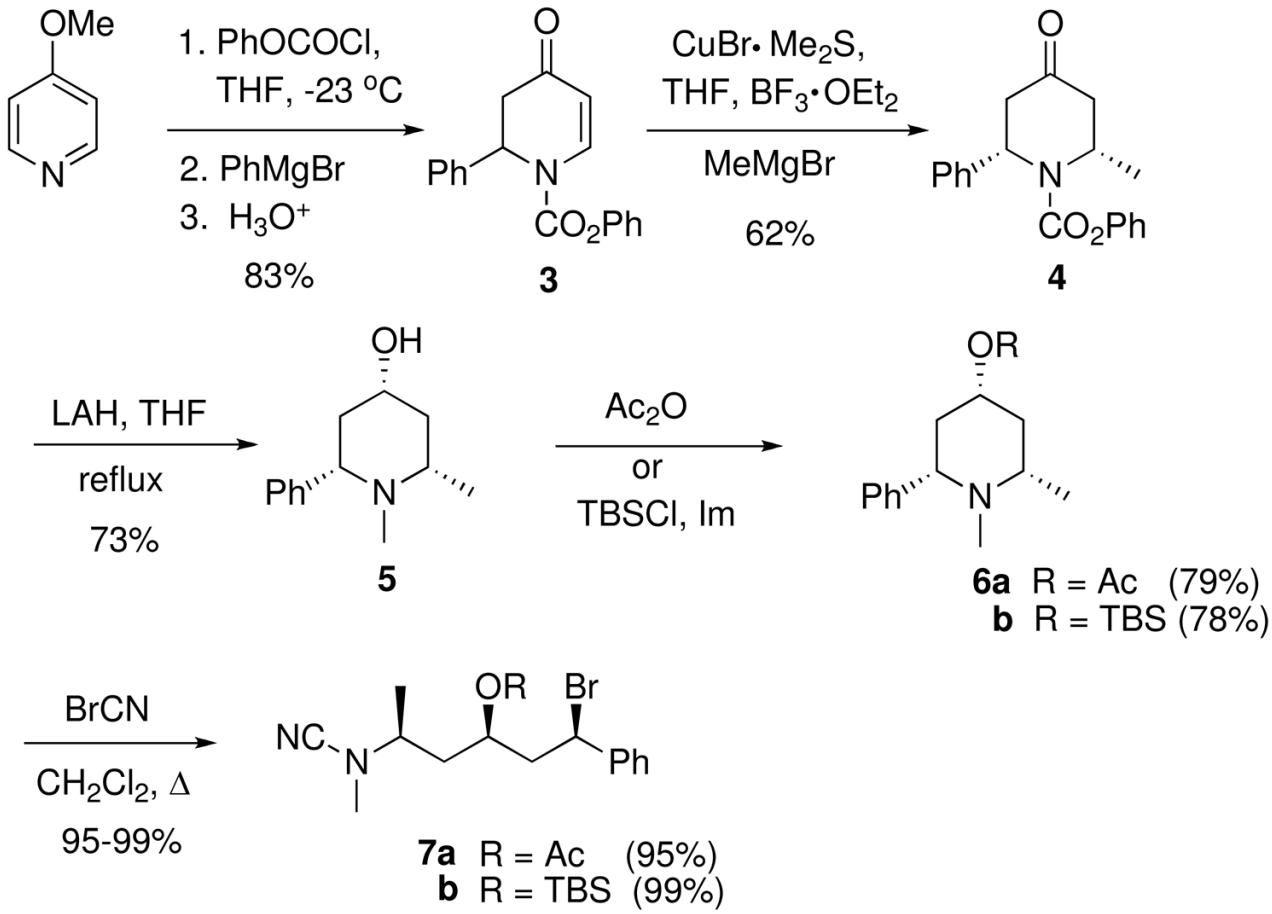


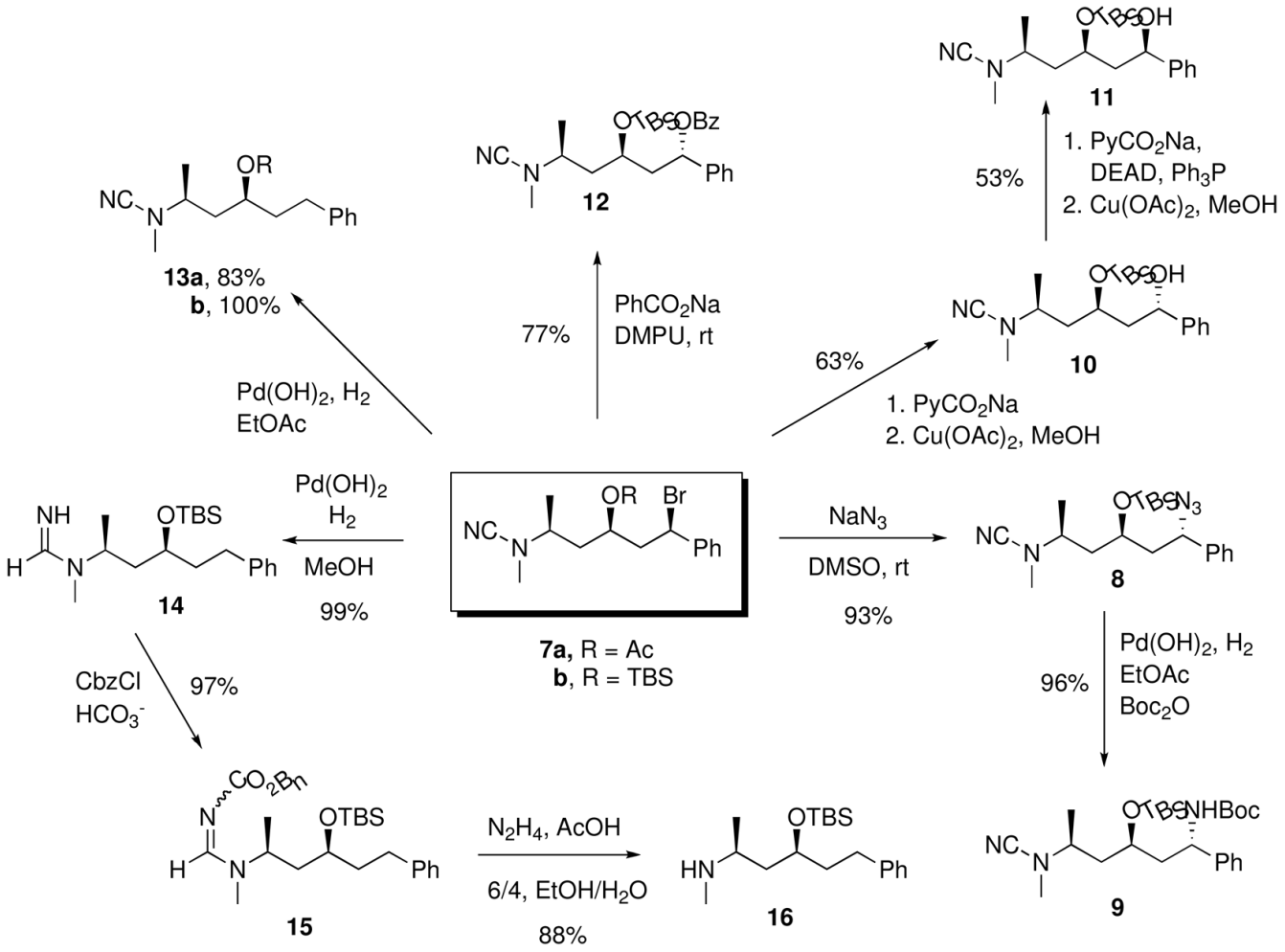
Figure 2.
Calculated lowest energy conformation of **22** (MMFF).



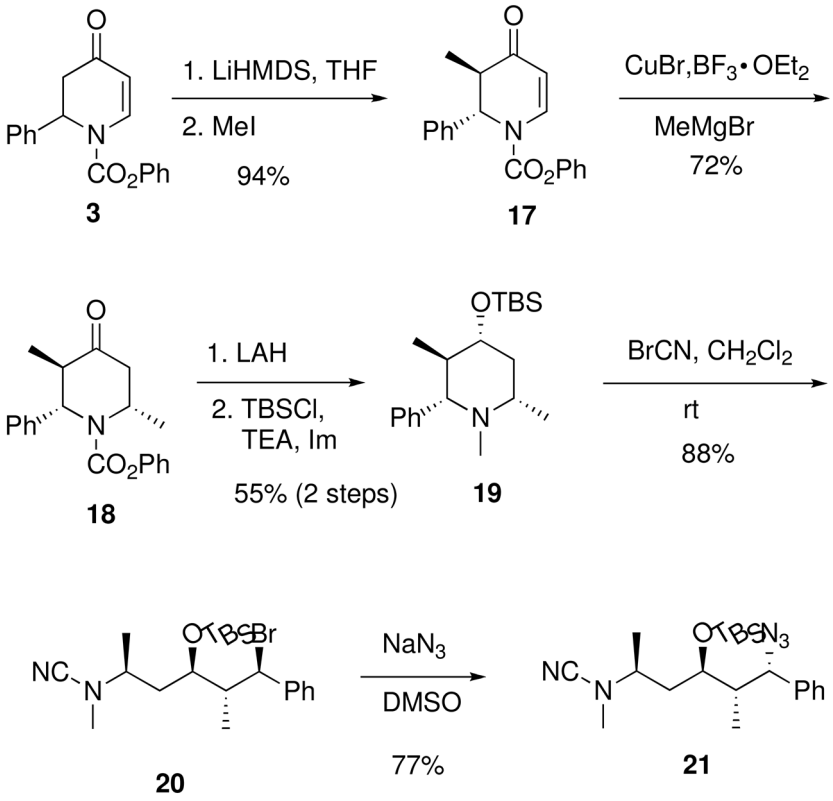
SCHEME 1.
The von Braun ring-opening reaction



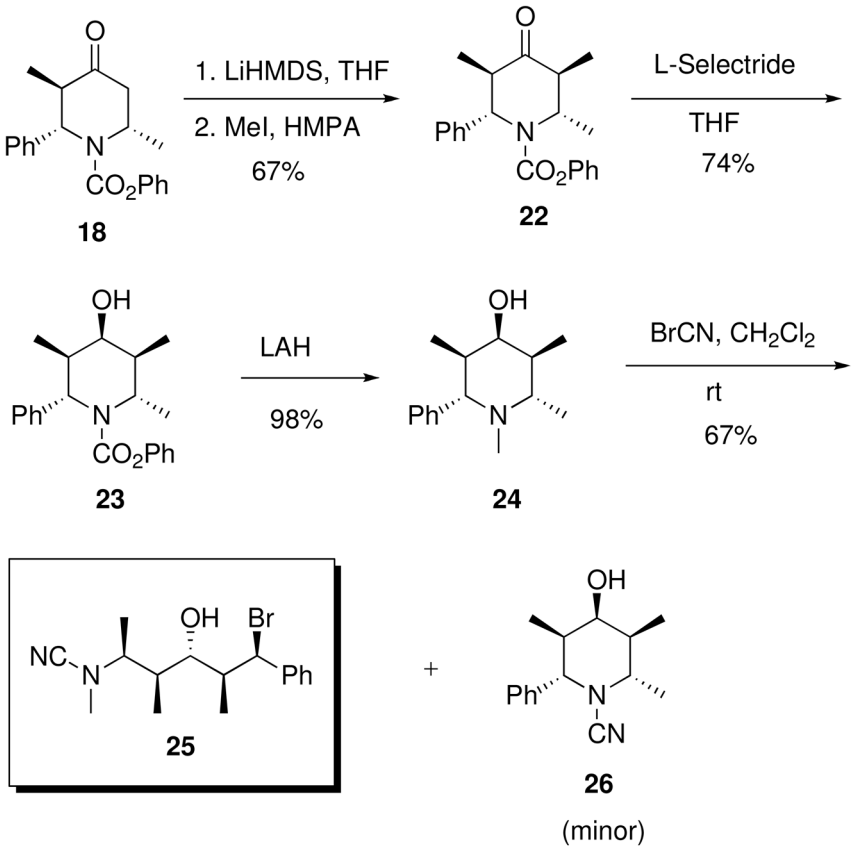
SCHEME 2.
Synthesis of cyanamides 7



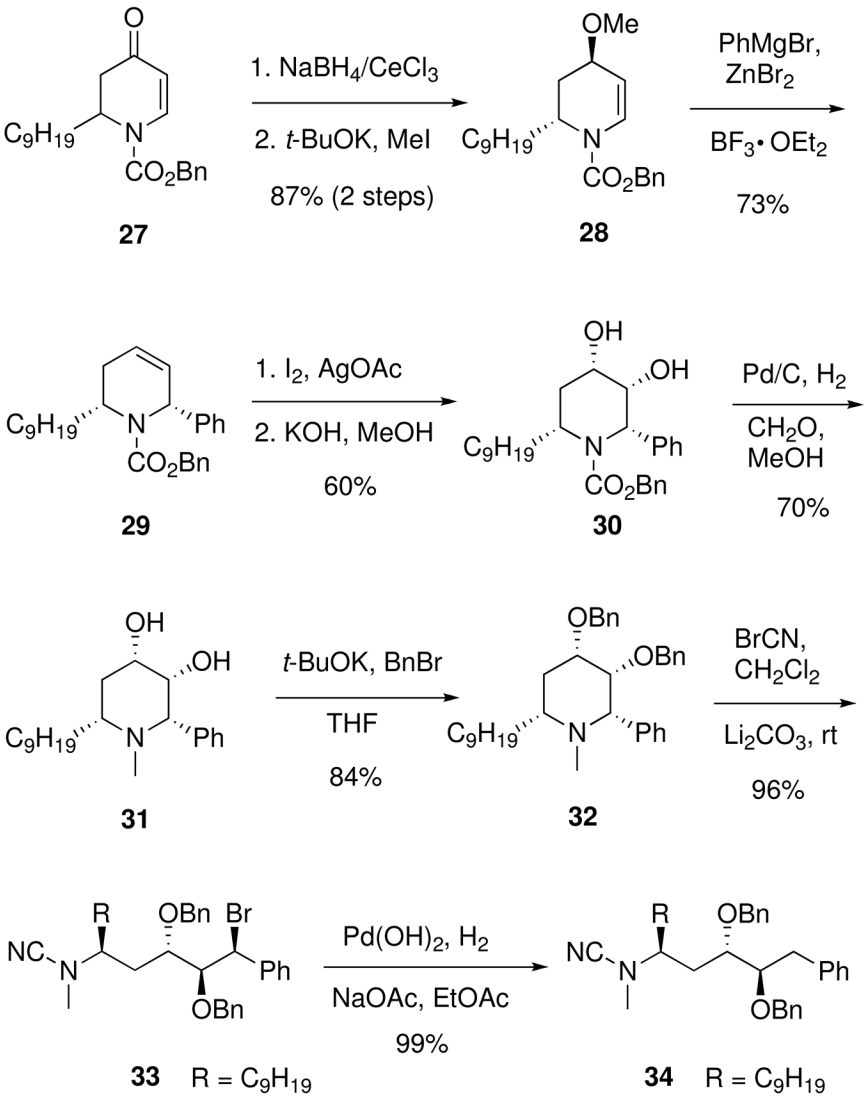
SCHEME 3.
Reactions of Bromide 7



SCHEME 4.
Synthesis of Cyanamide 21



SCHEME 5.
Synthesis of Cyanamide 25



SCHEME 6.
Synthesis of Cyanamide 34