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A TANDEM 1,3-DIPOLAR CYCLOADDITION/ELECTROPHILIC CYCLIZATION SEQUENCE: γ,δ-UNSATURATED ISOXAZOLINES AS PRECURSORS TO RING-FUSED ETHERS

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Abstract: *A tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence affords cis-fused octahydrobenzo- and hexahydro-2H-cyclopenta[b]furans via the intermediacy of γ,δ-unsaturated isoxazolines.*

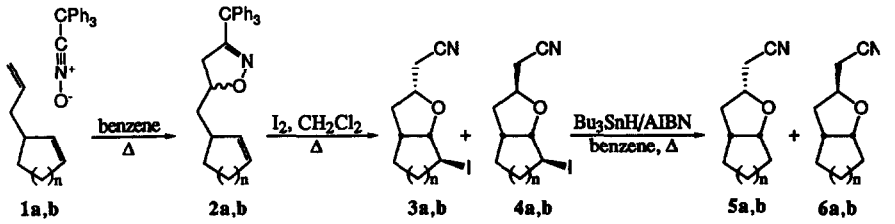
We recently described a new strategy for the construction of tetrahydrofurans by bis-addition of an oxygen nucleophile across a 1,5-diene moiety.[2] That study, in which functionalized 2,5-disubstituted tetrahydrofurans were obtained from 1,5-hexadiene by a tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence, has opened up a variety of promising avenues for the synthesis of other cyclic ethers. Herein, we report the application of this isoxazoline-based strategy to the synthesis of cis-fused octahydrobenzo- and hexahydro-2*H*-cyclopenta[b]furans; substructures of considerable importance in natural products chemistry.[3]

In contrast to a simple starting substrate like 1,5-hexadiene which delivers 2-(cyanomethyl)-5-(iodomethyl)-tetrahydrofuran, employing an unsymmetrical 1,5-diene as the starting material for this two-step sequence affords the potential to construct more elaborate cyclic ethers. However, this extension introduces two new issues: namely, the questions of regio- and chemoselectivity in the 1,3-dipolar cycloaddition step. It is generally found that the rate of nitrile oxide•alkene 1,3-dipolar cycloaddition increases as olefin substitution (i.e., steric hinderance) decreases. Indeed nitrile oxides generally react selectively with a terminal double bond in the presence of an internal double bond and cyclic alkenes, such as cyclohexene and cyclopentene, show higher dipolarophilicity than the corresponding 1,2-disubstituted acyclic olefins.[4] Thus exploiting this 1,3-dipolar cycloaddition/electrophilic cylization sequence in the construction of more elaborate cyclic ethers necessitates employing starting 1,5-dienes in which the two olefins differ markedly in dipolarophilicity.

As illustrated in **Scheme I**, 1,5-dienes **1a** and **1b** both require olefin selectivity in the 1,3-dipolar cycloaddition step. Fortunately, triphenylacetonitrile oxide[5] is a highly selective 1,3-dipolar reagent[6] and, as hoped, undergoes cycloaddition exclusively on the terminal olefin with complete regioselectivity. An added consequence of this olefin selectivity is that, unlike symmetrical dienes where a large excess of 1,3-dipolarophile must be employed to avoid the formation of bis-cycloadducts, these unsymmetrical dienes can be used in

stoichiometric amount, giving isoxazoline **2** in excellent yield (**1a**→**2a** in 80% and **1b**→**2b** in 85%). Subsequent intramolecular cyclization with iodine in CH_2Cl_2 under gentle reflux gave the desired oxabicyclic tetrahydrofuran derivatives (**3** + **4**) as a mixture of diastereomers.

Scheme I



a, n = 2; b, n = 1

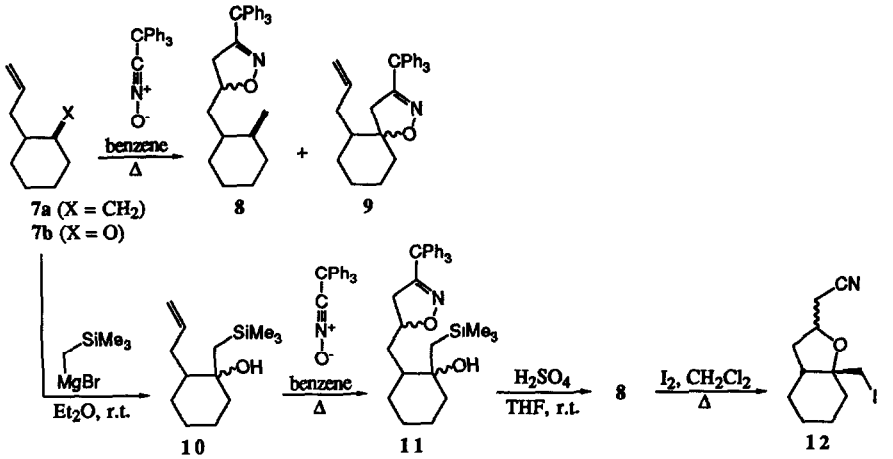
Iodocyclization of **2** proceeds regiospecifically producing either the [4.3.0] (**2a**→**3a** + **4a** in 82% yield) or the [3.3.0] (**2b**→**3b** + **4b** in 59% yield) oxabicycle with exclusive *cis* ring-fusion (complete internal asymmetric induction). These ring-fusion stereochemical assignments were made on the basis of literature ^{1}H-NMR data for the octahydrobenzofuran ring system and by analogy in the hexahydro-2*H*-cyclopenta[b]furan ring system.[7] Thus, H-7a and H-2 in **6a** and H-6a and H-2 in **6b** are deshielded relative to those protons in **5a** and **5b**, respectively (see **Table I**). In addition, 2-(2-cyclopenten-1-yl)ethanol is reported to undergo electrophilic cyclization with complete *cis* ring-fusion selectivity.[8] Endo/exo stereochemical assignments in **3** and **4** follow from the corresponding assignments in **5** and **6**, in turn prepared by Bu_3SnH/AIBN deiodination. These C-2 stereochemical assignments were further verified by 2-D NOESY correlation techniques. For example, while **5a** and **6a** both show an H-2⇔$CH_2C{\equiv}N$ NOE cross peak, only **6a** shows an H-7a⇔$CH_2C{\equiv}N$ NOE cross peak. The implications of this observations, spatial proximity between H-7a and the $CH_2C{\equiv}N$ moiety in **6a** but not **5a**, are in accord with these chemical shift based stereochemical assignments.

Table I. Partial 300 MHz ^{1}H-NMR Data for **5** and **6**.

proton	5a	6a	5b	6b
H-2	4.18 δ	4.42 δ	4.45 δ	4.67 δ
H-7a	3.90 δ	4.13 δ	--	--
H-6a	--	--	3.92 δ	4.31 δ

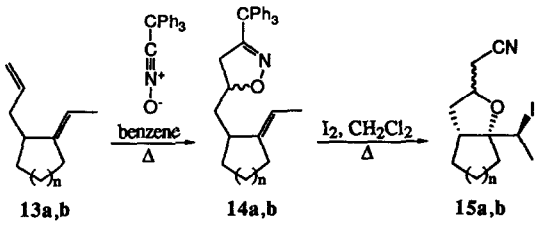
In **7a**, the next substrate investigated, triphenylacetonitrile oxide was not capable of clearly differentiating the mono- and disubstituted olefins and the anticipated isoxazoline product (**8**) was contaminated with ≈30% of spiro isoxazoline **9**. To circumvent this selectivity problem, the offending disubstituted olefin was not introduced until after the 1,3-dipolar cycloaddition step. This was accomplished via a modified Peterson olefination[9] 'protection sequence' starting from 2-allylcyclohexanone (**7b**) as outlined in **Scheme II**. The 1,3-dipolar cycloaddition reaction of **10** delivers isoxazoline **11** which, upon exposure to concentrated sulfuric acid/THF at room temperature, leads to **8** in 57% overall yield from **7b**. As anticipated, subsequent treatment with iodine in CH_2Cl_2 under gentle reflux provided the desired *cis*-fused tetrahydrofuran **12** in moderate yield (45%).

Scheme II



As a final demonstration of the synthetic versatility of this tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence, iodoethyl tetrahydrofurans **15a,b** were easily prepared starting from dienes **13a,b**.[10] In this case, cycloaddition proceeds exclusively and in quantitative yield on the terminal olefin, not on the more hindered trisubstituted exocyclic double bond, giving isoxazoline **14** as a mixture of diastereomers (**13a→14a** in 84% yield; **13b→14b** in 71% yield). Subsequent iodocyclization with iodine in CH_2Cl_2 under gentle reflux gives **15**. None of the alternate tetrahydropyran products were detected in the crude reaction mixture.

Scheme III



a, n = 2; **b**, n = 1

In conclusion, the synthetic potential of this tandem 1,3-dipolar cycloaddition/electrophilic cyclization sequence in the construction of highly functionalized cyclic ethers is evident. The methodology reported here complements existing methods for the preparation of oxabicyclic ring systems[11] and extends the utility of isoxazoline-based chemistry.

Experimental Section

General Experimental. Infrared spectra were determined on a IBM FTIR-32 with IBM 9000 data system. NMR Spectra were determined on a Varian EM390 spectrometer (^1H at 90 MHz), or a General Electric QE-300 spectrometer (^1H at 300 MHz and ^{13}C at 75 MHz). Mass spectra were determined on a Dupont 21-492B mass spectrometer. Melting points were determined on a Thomas Hoover Uni-Melt melting point apparatus and are uncorrected. MPLC refers to column chromatography done at 10-50 psi through EM Lobar™ columns packed with LiChroprep Si60 (40-63 μm) or prepared columns packed with Florisil™ (60-100 mesh) with hexane/EtOAc eluent and monitored by refractive index detection. Chromatron refers to preparative, centrifugally accelerated, radial, thin-layer chromatography with silica gel 60 as stationary phase. Analytical thin layer chromatrography (TLC) was performed with

Kodak 100 micron thick silica gel plates. Capillary gas chromatography (GC) was performed on a Hewlett-Packard 5890A gas chromatograph using a DB-1701 column (30 m X .259 mm; film thickness = 0.25 mm): initial temperature = 90°C; initial time = 1 min; rate = 2°C/min; gas pressures (psi: He = 60; N_2 = 32; air = 34; H_2 = 20).

3-Triphenylmethyl-5-[(2-cyclohexen-1-yl)methyl]-2-isoxazoline (2a): General Procedure A. An anhydrous benzene (25 mL) solution of triphenylmethylacetonitrile oxide (970 mg, 3.39 mmol) and 3-allylcyclohexene (440 mg, 3.60 mmol) in a sealed tube was heated at 85°C for 48 h. After cooling to room temperature, the crude reaction mixture was concentrated under reduced pressure and purified by MPLC (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) giving **2a** (1.1 g, 80%) as a white solid [mp 125-127°C (benzene); R_f = 0.83 (20:80 EtOAc:hexane); diastereomeric mixture: FT-IR (KBr) 3202, 2927, 2295, 1597 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21-2.37 (m, 9 H), 2.44 (dd, J = 9, 14 Hz, 1 H, N=C-CHH), 2.92 (dd, J = 9, 14 Hz, 1 H, N=C-CHH), 4.70 (m, 1H, HCO), 5.51 (m, 1H, CH=CH), 5.81 (m, 1 H, CH=CH), 7.51 (m, 15H, Ar-H). Anal. Calcd for $C_{29}H_{29}NO$: C, 85.46; H, 7.18; N, 3.44. Found: C, 85.18; H, 7.11; N, 3.29].

3-Triphenylmethyl-5-[(2-cyclopenten-1-yl)methyl]-2-isoxazoline (2b). As in **Procedure A**, triphenylmethylacetonitrile oxide (894 mg, 3.13 mmol), 3-allylcyclopentene (388 mg, 3.59 mmol), and MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **2b** (1.05 g, 85%) as a white solid [mp 108-110°C (benzene); R_f = 0.80 (20:80 EtOAc:hexane); diastereomeric mixture: FT-IR (KBr) 3059, 2942, 2853, 1597 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.48 (m, 2 H), 1.85 (m, 1 H), 2.18 (m, 1 H), 2.42 (m, 2 H), 2.60 (dd, J = 9, 15 Hz, 1 H, N=C-CHH), 2.71 (m, 1 H), 2.95 (dd, J = 9, 15 Hz, 1 H, N=C-CHH), 4.68 (m, 1 H, HCO), 5.78 (m, 2 H), 7.51 (m, 15H, Ar-H); HRMS calcd for $C_{28}H_{27}NO$ 393.2093, found 393.2092].

(1S*,5R*,6R*,8R*)- and (1S*,5R*,6R*,8S*)-5-Iodo-8-cyanomethyl-7-oxabicyclo[4.3.0]-nonane (3a) and (4a): General Procedure B. Solid iodine (1.24 g, 4.89 mmol) was added in one portion to a methylene chloride (40 mL) solution of isoxazoline **2a** (997 mg, 2.46 mmol) and the resulting mixture heated at reflux under nitrogen for 36 h at which time the starting isoxazoline was no longer detectable by thin layer chromatography. Ether (30mL) and a saturated aqueous $Na_2S_2O_5$ solution (10 mL) were added to the cooled reaction mixture, the layers were separated, and the aqueous phase was extracted with ether (3 x 25 mL). The combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting oil by MPLC (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave, in order of elution, **3a** (185 mg, 26%) [R_f = 0.67 (25:75 EtOAc:hexanes); FT-IR (neat) 2878, 2251 (CN), 1061, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.41-2.31 (m, 9 H), 2.57 (m, 1 H), 2.71 (m, 2 H, CH_2CN), 4.29 (m, 2 H, 2 HCO); ^{13}C ($CDCl_3$) δ 22.6, 25.9, 27.2, 32.6, 33.3, 36.9 (HCI), 37.1, 74.2 (HCO), 84.8 (HCO), 119 (CN); HRMS calcd for $C_{10}H_{14}INO$ 291.0122, found 291.0119] and **4a** (369 mg, 56%) [R_f = 0.50 25:75 EtOAc:hexane); FT-IR (neat) 2878, 2251 (CN), 1061, 1097 cm-1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25-2.30 (m, 9 H), 2.60 (m, 3 H, CH_2CN/HCHCO), 4.41 (m, 2 H, 2 HCO); ^{13}C ($CDCl_3$) δ 23.8, 25.7, 27.3, 34.3, 35.5, 36.3, 39.3 (HCI), 74.9 (HCO), 85.8 (HCO), 119 (CN); HRMS calcd for $C_{10}H_{14}INO$ 291.0122, found 291.0120. Anal. Calcd for $C_{10}H_{14}INO$: C, 41.26; H, 4.85; N, 4.81. Found: C, 41.75; H, 5.12; N, 4.95].

(1R*,3R*,5S*,8R*)- and (1R*,3S*,5S*,8R*)-8-Iodo-3-cyanomethyl-2-oxabicyclo[3.3.0]-octane (3b) and (4b). As in **Procedure A**, iodine (1.07 g, 4.22 mmol) and **2b** (830 mg, 2.11 mmol) followed by MPLC purification (25:75 EtOAc:hexanes, 2.5 mL/min, RI detector) gave an inseparable 1:1.7 mixture of **3b** and **4b** (340 mg, 59%) as a yellow oil [diastereomeric mixture: FT-IR (neat) 2871, 2251 (CN), 1072 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.87-2.82 (m, 8H), 2.86-3.19 (m, 1H), 3.80-4.29 (m, 1H), 4.29-4.99 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 24.9, 32.1, 33.8, 37.7, 40.3, 42.4 (HCI), 75.3/76.7 (HCO), 94.6/95 (HCO), 118.1/118.3 (CN); HRMS calcd for $C_9H_{12}INO$ 276.9965, found 276.9956].

(1S*,6R*,8R*)-8-Cyanomethyl-7-oxabicyclo[4.3.0]nonane (5a): General Procedure C. A benzene (2 mL) solution of **3a** (40 mg, 0.14 mmol), Bu_3SnH (60 mg, 0.21 mmol), and AIBN (2.2 mg, 0.014 mmol) was refluxed for 12 h under nitrogen. After cooling and concentration of the mixture under reduced pressure, ether (10mL) and saturated aqueous KF (2mL) were added and the mixture allowed to stir for 1 h at room temperature. The layers were separated, the aqueous phase was extracted with ether (3 x 25 mL), and the combined organics were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting oil by MPLC (20:80 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **5a** (19 mg, 85%) as a yellow oil [Rf = 0.45 (25:75 EtOAc:hexanes); FT-IR (neat) 2932, 2858, 2249 (CN), 1111 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.2-2.0 (m, 9 H), 2.21 (m, 2H), 2.63 (dd, J = 5, 13 Hz, 1 H, CHHCN), 2.69 (dd, J = 5, 13 Hz, 1 H, CHHCN), 3.90 (m, 1 H, HCO), 4.18 (m, 1 H, HCO); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1156].

(1S*,6R*,8S*)-8-Cyanomethyl-7-oxabicyclo[4.3.0]nonane (6a). As in **Procedure C**, **4a** (61 mg, 0.21 mmol), Bu_3SnH (91 mg, 0.32 mmol), and AIBN (3.3 mg, 0.021 mmol) followed by MPLC purification (20:80 EtOAc:hexanes, 2.5 mL/min,

RI detector) gave **6a** (28 mg, 80%) as a yellow oil [FT-IR (neat) 2932, 2858, 2249 (CN), 1111 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.21-2.25 (m, 11 H), 2.48 (dd, J = 4.5, 15 Hz, 1 H, CHHCN), 2.60 (dd, J = 4, 15 Hz, 1 H, CHHCN), 4.13 (m, 1 H, HCO), 4.42 (m, 1 H, HCO); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1153].

(1R*,3R*,5S*)- and (1R*,3S*,5S*)-3-Cyanomethyl-2-oxabicyclo[3.3.0]octane (5b) and (6b). As in **Procedure C**, a **3b/4b** mixture (21.8 mg, 0.079 mmol), Bu_3SnH (34.0 mg, 0.118 mmol), and AIBN (1.3 mg, 0.008 mmol) followed by MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave, in order of elution, **5b** (4.1 mg, 37%) [R_f = 0.45 (20:80 EtOAc:hexanes); FT-IR (neat) 2961, 2870, 2251 (CN), 1049 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.2-2.0 (m, 7 H), 2.35 (m, 1 H), 2.62 (m, 2 H, CH_2CN), 2.68 (m, 1 H), 3.92 (d, J = 4.4 Hz, 1 H HCO), 4.45 (t, J = 6.5 Hz, 1 H, HCO); HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.0997] and **6b** (3.1 mg, 44%) [R_f = 0.3 (20:80 EtOAc:hexanes); FT-IR (neat) 2961, 2871, 2251 (CN), 1049 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.2-2.0 (m, 8 H), 2.58 (m, 2 H, CH_2CN), 2.81 (m, 1 H), 4.31 (q, J = 6.4 Hz, 1 H, HCO), 4.67 (bt, J = 4.5, 1 H, HCO); HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.0994] as yellow oils.

Trimethyl[(1-hydroxy-2-allylcyclohexyl)methyl]silane (10)[10]. 2-Allylcyclohexanone (4.0 g, 28.9 mmol) in ether (20 mL) was added dropwise via a syringe pump to a 0°C solution of trimethylsilylmethylmagnesium bromide (72.3 mmol) in anhydrous ether (30 mL). When the addition was complete, the mixture was heated at 40°C for 48 h, then cooled to 0°C and quenched with 5% sodium hydroxide. After stirring the mixture at room temperature for 1 h, the layers were separated, the aqueous phase was extracted with ether (3 x 30 ml), and the combined organic extracts were washed with brine (1 x 20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the resulting oil by Kugelröhr distillation (230°C) gave **10** (6.5 g, 99%) as a pale yellow oil [FT-IR (neat) 3200-3600 (OH), 2934, 1248, 862 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.18 (s, 9 H, 3 CH_3), 1.0-1.7 (m, 12 H), 1.9 (m, 1 H), 2.4 (m, 1 H, OH), 5.0 (m, 2 H, CH=CH_2), 5.8 (m, 1 H, CH=CH_2)].

3-Triphenylmethyl-5-[((2-hydroxyl-2-trimethylsilyoxymethyl)-cyclohex-1-yl)methyl]-2-isoxazoline (11). As in **Procedure A**, triphenylmethylacetonitrile oxide (1.34 g, 4.69 mmol) and **10** (1.06 g, 4.69 mmol) followed by MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **11** (1.9 g, 80%) as a colorless oil [Rf = 0.75 (25:75 EtOAc:hexanes); diastereomeric mixture: FT-IR (neat) 3850, 3518, 3059, 2855, 1034 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 0.35 (s, 9H), 0.85-2.01 (m, 14H), 2.45 (m, 1H, N=C-CHH), 2.93 (s, 1H, N=C-CHH), 4.68 (m, 1H, HCO), 7.54 (m, 15H); HRMS calcd for $C_{33}H_{41}NO_2Si$ 511.2906, found 511.2905].

3-Triphenylmethyl-5-[((2-methylene)-cyclohex-1-yl)methyl]-2-isoxazoline (8). Concentrated sulfuric acid (0.92 g) was added to a tetrahydrofuran (20 mL) solution of isoxazoline **11** (1.62 g, 3.3 mmol) and the solution was allowed to stir at room temperature for 48 h. Ether (30mL) and water (20mL) were then added, the layers were separated, and the aqueous phase was extracted with ether (3 x 30 mL). The combined organic extracts were washed with 10% aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried (K_2CO_3), filtered, and concentrated under reduced pressure. Purification of the resulting oil by MPLC (4:96 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **8** (1.0 g, 72%) as a colorless oil [R_f = 0.64 (10:90 EtOAc:hexanes); FT-IR (neat) 3061, 2928, 1643, 1493, 1084 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08-2.30 (m, 11H), 2.41 (dd, J = 4.5, 13 Hz, 1 H, N=C-CHH), 2.90 (m, 1 H, N=C-CHH), 4.55 (bd, J = 4.5 Hz, 1 H, C=CHH), 4.60 (bd, J = 4.5 Hz, 1 H, C=CHH), 7.42 (m, 15H); HRMS calcd for $C_{30}H_{31}NO$ 421.2406, found 421.2413].

(1S*,6R*,8R*)- and (1S*,6R*,8S*)-8-Cyanomethyl-6-iodomethyl-7-oxabicyclo[4.3.0]-nonane (12). As in **Procedure A**, iodine (1.15 g, 4.3 mmol) and **8** (926 mg, 2.19 mmol) followed by MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **12** (1:3 mixture as a yellow oil, 288 mg, 45%) as an inseparable mixture of diastereomers [R_f = 0.67 (25:75 EtOAc:hexane); diastereomeric mixture: FT-IR (neat) 2965, 2249 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08-2.31 (complex, 13 H), 2.63 (d, J = 6.8, 2 H, CH_2CN), 4.2-4.4 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 20.3/20.7, 22.2/22.4, 24.1, 24.6, 24.8, 24.9, 25.1/25.6, 33.3/34.3, 35.2/35.4, 41.4/42.9, 70.3/71.3 (HCO), 80.2/81.1, 119 (CN); HRMS calcd for $C_{11}H_{16}NO$ (-I) Fab+ 178.1232, found 178.1230].

3-Triphenylmethyl-5-[((2-ethylidene)-cyclohex-1-yl)methyl]-2-isoxazoline (14a). As in **Procedure A**, triphenylmethylacetonitrile oxide (1.0 g, 3.5 mmol) and **13a** (540 mg, 3.6 mmol) followed by MPLC purification (5:95 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **14a** (colorless oil, 1.3 g, 84%) as an inseparable mixture of diastereomers [R_f = 0.64 (10:90 EtOAc:hexane); FT-IR (neat) 3059, 2855, 1493, 1034 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.05-3.12 (m, 14 H), 2.12 (m, 1 H, N=C-CHH), 2.77 (dd, J = 7, 13 Hz, 1 H, N=C-CHH), 4.45 (m, 1 H, HCO), 5.01-5.23 (m, 1 H, CH_3-CH=), 7.43 (m, 15 H, Ar-H); HRMS calcd for $C_{31}H_{33}NO$ 435.2562, found 435.2560].

3-Triphenylmethyl-5-[((2-ethylene)-cyclopent-1-yl)methyl]-2-isoxazoline (14b). As in **Procedure A**, triphenylmethylacetonitrile oxide (134 mg, 0.47 mmol) and **13b** (71 mg, 0.58 mmol) followed by MPLC purification (2:98 EtOAc:hexanes, 2.5 mL/min, RI detector) gave **14b** (colorless oil, 120 mg, 71%) as an inseparable mixture of diastereomers [R_f = 0.54 (10:90 EtOAc:hexane); FT-IR (neat) 3032, 2862, 1597, 1493 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.46-2.2 (m, 12 H), 2.35 (m, 1 H), 2.93 (m, 1 H), 4.65 (m, 1 H, HCO), 5.20-5.41 (m, 1 H, CH_3-CH=), 7.50 (m, 15 H, Ar-H); HRMS calcd for $C_{30}H_{31}NO$ 421.2406, found 421.2406].

(1S*,6R*,8R*)- and (1S*,6R*,8S*)-8-Cyanomethyl-6-(2-iodoethyl)-7-oxabicyclo[4.3.0]-nonane (15a). As in **Procedure A**, iodine (0.99 g, 3.9 mmol) and **14a** (0.85 g, 1.82 mmol) followed by MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave, in order of elution, endo-**15a** (71 mg, 12%) [R_f = 0.66 (25:75 EtOAc:hexane); FT-IR (neat) 2930, 2860, 2251 (CN) 1415, 1091 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7 Hz, 3 H, CH_3), 1.20-2.23 (m, 10 H), 2.18 (m, 2 H), 2.63 (d, J = 4 Hz, 2 H, CH_2CN), 4.18 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 8.8 (CH_3), 22.0, 23.8, 26.5, 26.8, 31.1, 32.5, 36.0, 40.6, 72.1 (HCO), 88.1, 119 (CN); HRMS calcd for $C_{12}H_{18}INO$ (-I) 192.1388, found 192.1389] and exo-**15a** (129 mg, 22%) [R_f = 0.50 (25:75 EtOAc:hexane); FT-IR (neat) 2930, 2862, 2251 (CN), 1414, 1092 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.95 (t, J = 7 Hz, 3 H, CH_3), 1.2-2.0 (m, 10 H), 2.21 (m, 2 H), 2.56 (d, J = 5 Hz, 2 H, CH_2CN), 4.3 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 6.9 (CH_3), 20.6, 21.9, 24.0, 25.5, 28.9, 32.9, 35.2, 40.1, 71 (HCO), 83, 118 (CN); HRMS calcd for $C_{12}H_{18}INO$ (-I) 192.1388, found 192.1382].

(1R*,3R*,5S*)- and (1R*,3S*,5S*)-3-Cyanomethyl-1-(2-iodoethyl)-2-oxabicyclo[3.3.0]-octane (15b). As in **Procedure A**, iodine (120 mg, 0.47 mmol) and **14b** (100 mg, 0.24 mmol) followed by MPLC purification (10:90 EtOAc:hexanes, 2.5 mL/min, RI detector) gave, in order of elution, endo-**15b** (21 mg, 28%) [R_f = 0.66 (25:75 EtOAc:hexane); FT-IR (neat) 2868, 2253 (CN), 1464, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.0 (t, J = 7 Hz, 3 H, CH_3), 1.22-1.80 (m, 9 H), 2.39 (m, 1 H), 2.61 (m, 2 H, CH_2CN), 4.0 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 10.0 (CH_3), 26.6, 31.8, 33.5, 34.3, 39.8, 40.3, 47.5 (HCl), 73.1 (HCO), 96.5, 117.3 (CN); HRMS calcd for $C_{11}H_{16}INO$ (+H) FAB+ 306.0357, found 306.0358] and exo-**15b** (23 mg, 31%) [R_f = 0.50 (25:75 EtOAc:hexane); FT-IR (neat) 2868, 2253 (CN), 1464, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7 Hz, 3 H, CH_3), 1.3-2.0 (m, 9 H), 2.39 (m, 1 H), 2.60 (m, 2 H, CH_2CN), 4.2 (m, 1 H, HCO); ^{13}C ($CDCl_3$) δ 9.1 (CH_3), 23.9, 25.6, 32.5, 33.3, 38.8, 39.3, 46.5 (HCl), 73.7 (HCO), 96.6, 117.3 (CN); HRMS calcd for $C_{11}H_{16}INO$ (+H) FAB+ 306.0357, found 306.0358].

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