CHIRAL SYNTHESIS OF A PYRROLIZIDINE ALKALOID, (-)-HELIOTRIDANE

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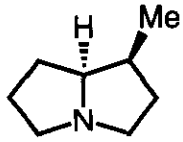
Abstract--Chiral synthesis of the necic base, heliotridane has been achieved by employing a samarium diiodide-promoted regioselective carbon-carbon bond cleavage reaction of the γ-halo ester (**17**), as a key step.

Recently we developed samarium(II) diiodide-promoted carbon-carbon bond cleavage reaction of γ-halo carbonyl compounds[1] and this novel fragmentation reaction was expected to have broad utility in the synthesis of natural products. In the continuation of a research program to exploit this synthetic strategy in the natural products synthesis,[2,3] we planned the synthesis of pyrrolizidine alkaloids, and here report a chiral synthesis of the necic base, heliotridane (**1**), in natural enantiomeric form, together with a stereoselective synthesis of pseudoheliotridane (**2**).



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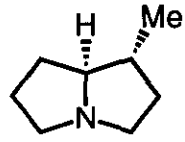

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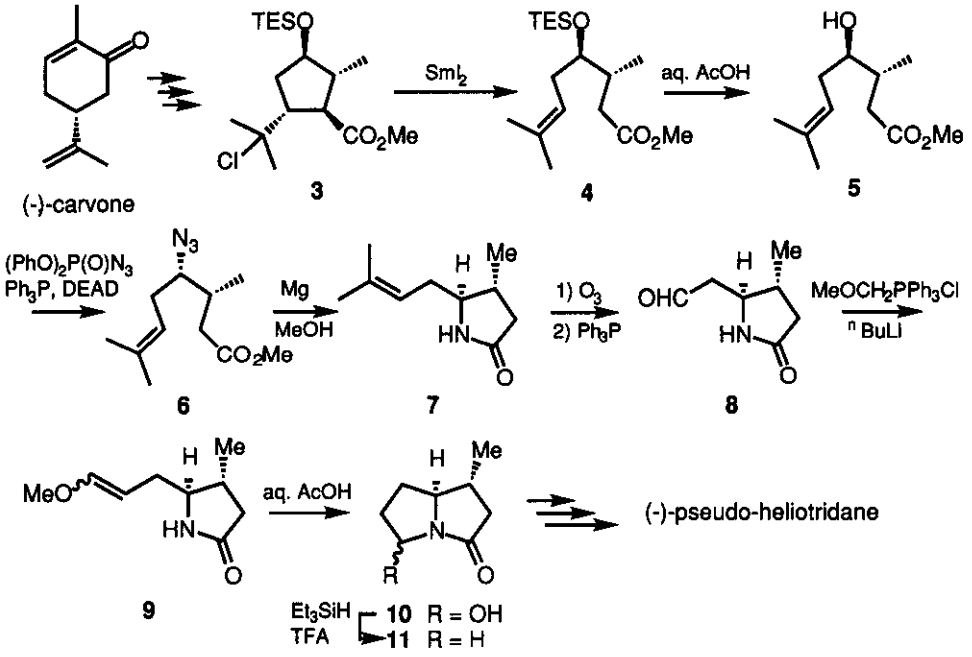
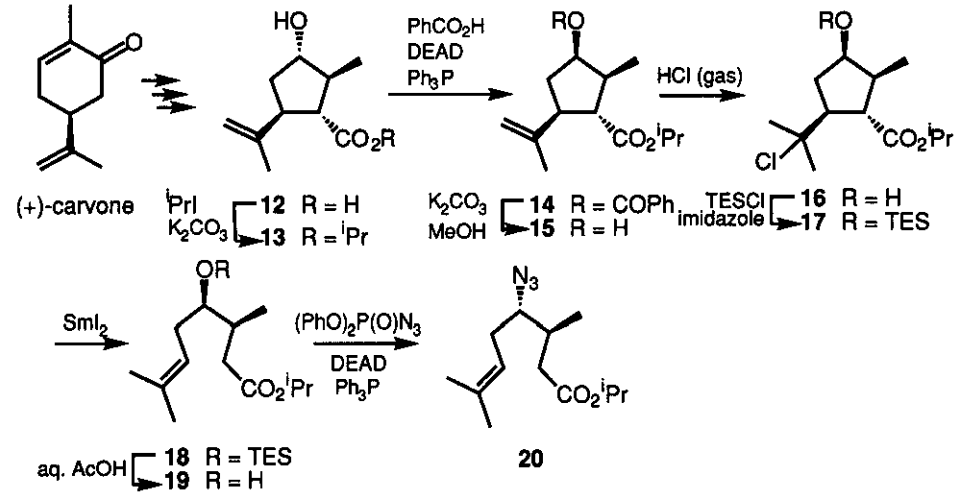
First we investigated the synthesis of (-)-pseudo-heliotridane (**2**) starting from the ester (**4**),[2] readily obtained from (-)-carvone, *via* the γ-halo ester (**3**) utilizing a regioselective fragmentation reaction as a key step, as follows.

Removal of triethylsilyl group of **4** in acetic acid-water-THF (3:1:1) afforded the alcohol (**5**) in quantitative yield, which on treatment with diphenylphosphoryl azide according to the Lal's procedure[4] provided the azide (**6**) with the desired stereochemistry in 77.2% yield. Reduction of **6** with magnesium powder in methanol[5] for 3 h at 0°C proceeded smoothly to give the lactam (**7**) in 94.3% yield. In order to synthesize a bicyclic ring system, the olefinic lactam (**7**) was subjected to ozonolysis to afford the aldehyde (**8**) in quantitative yield. Wittig reaction of the aldehyde (**8**) using methoxymethyltriphenylphosphonium chloride and *n*-butyllithium provided the enol ether (**9**) as a mixture of *E*/*Z* (*ca.* 1:1 ratio) stereoisomers, which on treatment with aqueous acetic acid gave the cyclized product (**10**) as a single stereoisomer, in 24.3% yield from **8**. Although the

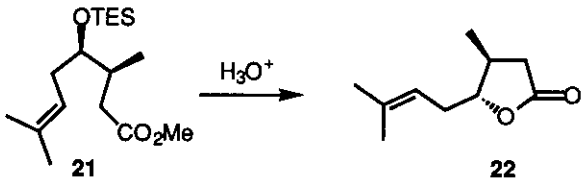
stereochemistry of the hydroxyl group of **10** could not be determined at this stage, we used this compound for further conversion into **11**, since this stereogenic center would be removed in the next step of this synthesis.



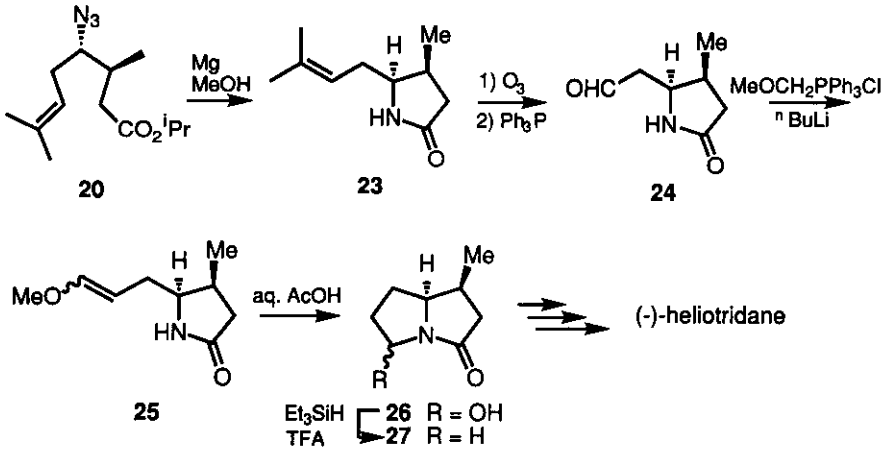
Reduction of **10** with triethylsilane in trifluoroacetic acid furnished the bicyclic lactam (**11**), {[α]D -63.5° ($CHCl_3$), lit.,[6] [α]D -43.8° ($CHCl_3$)}, in 56.9% yield, whose spectroscopic data including specific optical



rotation were similar to those reported.[6] Since this lactam was already converted into pseudo-heliotridane,[7,8] this synthesis constitutes its chiral synthesis. Establishing the synthetic procedure for pyrrolizidine ring system from carvone as above, we next attempted the synthesis of the simplest pyrrolizidine alkaloid, (-)-heliotridane. The acid (**12**),[2] easily prepared from (+)-carvone, was converted into the isopropyl ester (**13**), which was converted to the alcohol (**15**) with the inversion of the configuration under the Mitsunobu reaction conditions[9] employing benzoic acid, triphenylphosphine and diethyl azodicarboxylate, followed by alkaline hydrolysis of the resulting benzoate (**14**), in 83.5% overall yield from **13**. Addition of hydrogen chloride to the ester (**15**) and subsequent protection of the hydroxyl group of **16** with triethylsilyl chloride afforded the chloride (**17**) in 92.4% yield in two steps. Samarium(II) diiodide-promoted fragmentation of **17** provided the olefinic ester (**18**)



in 91.7% yield. Removal of triethylsilyl group of **18** in acetic acid-water-THF (3:1:1) gave the alcohol (**19**), which on treatment with diphenylphosphoryl azide using the Lal's reaction conditions furnished the azide (**20**) in 57.7% yield from **18**. When the methyl ester (**21**) was employed in the above reaction, the lactone formation occurred very fast to give the γ-lactone (**22**).[2] Transformation of the azide (**20**) into (-)-heliotridane was achieved using the similar reaction conditions as described for the synthesis of (-)-pseudo-heliotridane as



above. Thus, the azide (**20**) was reduced with magnesium powder in methanol[6] to give the lactam (**23**), whose ozonolysis, and subsequent Wittig reaction of the aldehyde (**24**) afforded the enol ether (**25**)(*E*/*Z*=1:1). Acid treatment of **25**, followed by reduction of the resulting aminal (**26**), a single stereoisomer, with triethylsilane in trifluoroacetic acid yielded the lactam (**27**), {$[\alpha]_D$ -57.63° ($CHCl_3$), lit.,[6] $[\alpha]_D$ -52.4° ($CHCl_3$)}, whose spectroscopic data including specific optical rotation supported its structure. Since this lactam (**27**) was already converted into (-)-heliotridane (**1**),[7,8] this synthesis also constitutes its formal chiral synthesis.

Thus, we could achieve the chiral synthesis of (-)-heliotridane and (-)-pseudo-heliotridane starting from carvone by utilizing a samarium(II)-promoted carbon-carbon bond cleavage reaction as a key step, and the synthetic strategy developed here would be applicable to the synthesis of other types of pyrrolizidine alkaloids.

EXPERIMENTAL SECTION

Ir spectra were recorded on a Hitachi 260-10 spectophotometer. ^{1}H-Nmr spectra were obtained for solution in $CDCl_3$ on a JEOL GSX-270 instrument, and chemical shifts are reported on the δ-scale from internal TMS. Mass spectra were measured with a JEOL JMS D-300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter.

Methyl (3*R*,4*R*)-3,7-Dimethyl-4-hydroxy-octanoate (**5**)

A solution of the ester (**4**)(1.0 g, 3.2 mmol) in AcOH-H_2O-THF (3:1:1 $^v/_v$)(30 ml) was stirred at ambient temperature for 1 h. After evaporation of the solvent, a residue was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (5:1 v/v) afforded the alcohol (**5**)(640 mg, 100%) as a colorless oil; ir ($CHCl_3$) 3500 and 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.96 (3H, d, J=6.7 Hz, Me), 1.64 and 1.74 (each 3H, each s, 2×C=CMe), 1.79 (1H, br s, OH), 2.08-2.56 (5H, m, 2-H_2, 3-H, and 5-H_2), 3.56 (1H, ddd, J=3.7, 4.9, and 8.5 Hz, 4-H), 3.68 (3H, s, OMe), 5.12-5.18 (1H, m, C=CH); $[\alpha]_D$ +7.53° (c=0.7, $CHCl_3$).

Methyl (3*R*,4*S*)-4-Azido-3,7-dimethyl-6-octanoate (**6**)

To a stirred solution of the alcohol (**5**)(1.0 g, 5 mmol), triphenylphosphine (1.4 g, 5.5 mmol) and diphenylphosphoryl azide (1.2 ml, 5.5 mmol) in THF (20 ml) was added diethyl azodicarboxylate (1.0 g, 5.5 mmol) at 0°C. The mixture was allowed to warm to ambient temperature, and further stirred for 2 h. The solvent was evaporated to leave a residue which was subjected to column chromatography on silica gel. Elution with hexane-dichloromethane (8:1 v/v) afforded the azide (**6**)(870 mg, 77.2%) as a colorless oil; ir ($CHCl_3$) 2120 and 1735 cm^{-1}; nmr ($CDCl_3$) δ 1.02 (3H, d, J=6.1 Hz, Me), 1.65 and 1.73 (each 3H, each m, 2×C=CMe), 2.13-2.51 (5H, m, 2-H_2, 3-H, and 5-H_2), 3.22-3.29 (1H, m, 4-H), 3.68 (3H, s, OMe), 5.14-5.20 (1H, m, C=CH); $[\alpha]_D$ +51.88° (c=1.0, $CHCl_3$).

(4*R*,5*S*)-5-Dimethylallyl-4-methyl-2-pyrrolidone (**7**)

To a stirred solution of the azide (**6**)(18 mg, 0.7 mmol) in methanol (0.5 ml) was added Mg powder (35 mg, 0.16 mmol) at 0°C, and the resulting solution was further stirred for 3 h at the same temperature. The solvent was evaporated off and a residue was treated with ice-water and ether. The resulting solution was filtered through a pad of Celite to remove insoluble materials and the filtrate was washed with brine and concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with dichloromethane-ethyl acetate (1:1 v/v) afforded the lactam (**7**)(13 mg, 94.3%) as a colorless oil; ir ($CHCl_3$): 3400 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.13 (3H, d, J=6.7 Hz, Me), 1.63 and 1.72 (each 3H, each m, 2×C=CMe), 1.95-2.57 (5H, m, 3-H_2, 4-H, and C=CH_2), 3.20 (1H, dt, J=5.5 and 7.9 Hz, 5-H), 5.07-5.12 (1H, m, C=CH), 5.77 (1H, br s, NH); ms m/z $C_{10}H_{17}NO$ requires: 167.1308 (M^+). Found: 167.1305 (M^+); $[\alpha]_D$ -38.3 °(c=3.7, $CHCl_3$); Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.59; H, 10.41; N, 8.25.

(4*R*,5*S*)-5-Formylmethyl-4-methyl-2-pyrrolidone (**8**)

A stream of ozone was bubbled through a stirred solution of **7** (1.0 g, 6.0 mmol) in methanol (100 ml) at -78 °C until disappearance of the starting material on tlc. The reaction mixture was flushed with argon and treated with triphenylphosphine (2.4 g, 10.0 mmol). The resulting solution was allowed to warm to room temperature and further stirred for 2 h at the same temperature. After removal of the solvent, a residue was subjected to column chromatography on silca gel. Elution with ethyl acetate-methanol (10:1 v/v) afforded the aldehyde (**8**)(840 mg, 100%) as a colorless oil; ir ($CHCl_3$) 3400, 1725 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (3H, d, J=6.1 Hz, Me), 2.01 (1H, dd, J=7.9 and 15.9 Hz, 3-H), 2.52 (1H, dd, J=7.9 and 15.9 Hz, 3-H), 2.08-2.13 (1H, m, 4-H), 2.59 (1H, dd, J=9.8 and 18.3 Hz, COCH), 2.93 (1H, dd, J=3.1 and 18.3 Hz, COCH), 3.57-3.63 (1H, m, 5-H), 5.95 (1H, br s, NH), 9.83 (1H, m, CHO); ms m/z $C_7H_{11}NO_2$ requires:141.0789 (M^+). Found:141.0794 (M^+); $[\alpha]_D$ -88.7° (c=0.9, $CHCl_3$); Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.12; H, 8.07; N, 9.62.

(4*R*,5*S*)-5-(*E*/*Z*)-5-(3-Methoxypropen-2-yl)-4-methyl-2-pyrrolidone (**9**)

To a stirred solution of methoxymethyltriphenylphosphonium chloride (290 mg, 0.85mmol) in THF (1.0 ml) was added *n*-BuLi (1.56M *n*-hexane solution)(0.53 ml, 0.83 mmol) at ambient temperature and the mixture was further stirred for 15 min. To this solution was added a solution of the aldehyde (**8**) (50 mg, 0.4 mmol) in THF (1 ml) at the same temperature. After being stirred for 30 min, brine was added and the mixture was extracted with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:7 v/v) afforded the enol ether (**9**) as an oily mixture of *E*/*Z* stereoisomers; ir ($CHCl_3$) 3450, 1690 and 1660 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (1.5H, d, J=6.7, Me), 1.13 (1.5H, d, J=6.7, Me) , 1.94-2.56 (5H, m, 3-H_2, 4-H, C=CCH_2), 3.12-3.24 (each 0.5H, each m, 5-H), 3.53 and 3.60 (each 1.5H, each s, OMe), 4.28-4.36 (0.5 H, m, OC=CH), 4.64 (0.5H, ddd, J=6.7, 8.6, and 12.8 Hz, OC=CH), 5.91 (1H, br s, NH), 6.00-6.03 (0.5H, m, OCH=C), 6.33-6.37 (0.5H, m, OCH=C); ms m/z $C_9H_{15}NO_2$ requires:169.1103 (M^+). Found 169.1103 (M^+). Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 63.90; H, 9.14; N, 7.98. The enol ether was used in the next reaction without separation.

(4*R*,5*S*)-8-Hydroxy-4-methyl-1-azabicyclo[3.3.0]octan-2-one (**10**)

A solution of the enol ether (**9**)(990 mg, 5.9 mmol) in AcOH-H_2O-THF (3:1:1 $^v/_v$)(30 ml) was stirred for 1 h at 80°C. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with dichloromethane-ethyl acetate (1:5 v/v) afforded the alcohol (**10**)(227 mg, 24.3%, 2 steps overall yield from **8**) as a colorless oil; ir ($CHCl_3$) 3350 and 1680 cm^{-1}; nmr ($CDCl_3$) δ 1.14-1.16 (3H, m, Me), 1.26-1.48 (1H, m, 4-H), 1.90-2.63 (6H, m, 3-H_2, 6-H_2, and 7-H_2), 3.66-3.81 (1H, m, 5-H), 4.50 (1H, br s, OH), 5.55-5.59 (1H, m, 8-H); ms m/z $C_8H_{13}NO_2$ requires 155.0944 (M^+). Found 155.0939 (M^+).

(4*R*,5*S*)-4-Methyl-1-azabicyclo[3.3.0]octan-2-one (**11**)

To a stirred solution of **10** (0.2 g, 1.27 mmol) in trifluoroacetic acid (12 ml) was added triethylsilane (1 ml, 6 mmol) dropwise at room temperature and the resulting mixture was further stirred for 1 h at the same temperature. The solution was cooled to 0°C and methanol (4 ml) was added slowly to this solution and further

stirred for 30 min. The solution was neutralized by addition of ammonium hydroxide and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (1:5 v/v) gave the lactam (**11**)(102 mg, 56.9%) as a colorless oil; ir ($CHCl_3$) 1670 cm^{-1}; nmr ($CDCl_3$) δ 1.16 (3H, d, J=6.7 Hz, Me), 1.34-1.42 (1H, m, 4-H), 1.97-2.20 (4H, m, 6-H_2 and 7-H_2), 2.40 (1H, dd, J=11.0 and 16.5 Hz, 3-H), 2.55 (1H, dd, J=8.5 and 11.0 Hz, 3-H) ; 3.00-3.09 (1H, m, 5-H), 3.45-3.60 (2H, m, 8-H_2); ms m/z $C_8H_{13}NO$ requires 139.0996 (M^+). Found 139.1001 (M^+). $[\alpha]_D$ -63.5° (c=1.0, $CHCl_3$) .

Isopropyl (1*S*,2*S*,3*S*,5*S*)-3-Hydroxy-5-isopropenyl-2-methylcyclopentane-1-carboxylate (**13**)
To a stirred solution of the acid (**12**)(3.0 g, 16 mmol) and potassium carbonate (4.5 g, 33 mmol) in DMF (30 ml) was added isopropyl iodide (8.3 g, 49 mmol) at ambient temperature and the resulting mixture was further stirred for 3 h at the same temperature. The mixture was poured into water and extracted with ethyl acetate. The extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (3:1 v/v) afforded the ester (**13**)(2.9 g, 78.8%) as a colorless oil; ir ($CHCl_3$) 3500 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (3H, d, J=6.7 Hz, Me), 1.22 and 1.24 (each 3H, each d, J=4.9 Hz, 2×OCH*Me*), 1.71 (3H, s, C=CMe), 1.18-1.94 (1H, m, 2-H), 2.04-2.28 (3H, m, 1-H, 4-H_2), 3.08 (1H, q, J=9.2 Hz, 5-H), 3.83-3.85 (1H, m, 3-H), 4.72-4.75 (2H, m, C=CH_2), 5.03 (1H, quint, J=6.1 Hz OCH); $[\alpha]_D$= +31.0° (c=1.1, $CHCl_3$); Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found:C, 69.03; H, 10.01.

Isopropyl (1*S*, 2*S*, 3*R*, 5*S*)-3-Benzoyloxy-5-isopropenyl-2-methylcyclopentane-1-carboxylate (**14**)
To a stirred solution of the ester (**13**)(100 mg, 0.44 mmol) in THF (3 ml) were added triphenylphosphine (130 mg, 0.49 mmol), benzoic acid (70 mg, 0.58 mmol) and diethyl azodicarboxylate (80 mg, 0.49 mmol) at 0°C and the resulting solution was further stirred for 10 min at the same temperature. After removal of the solvent, a residue was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (9:1 v/v) afforded the benzoate (**14**)(140 mg, 98.6%) as a colorless oil; ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.09 (3H, d, J=6.7 Hz, Me), 1.23 and 1.25 (each 3H, each d, J=5.5 Hz, 2×OCH*Me*), 1.74 (3H, m, Me), 1.76-1.82 (1H, m, 2-H), 2.39-2.60 (2H, m, 4-H_2), 2.69 (1H, t, J=11.0 Hz, 1-H), 2.98 (1H, dt, J=8.6 and 9.8 Hz, 5-H), 4.74-4.80 (2H, m, C=CH_2), 5.08 (1H, quint, J=6.1 Hz, 3-H), 5.43-5.46 (1H, m, OCH), 7.45 (2H, t, J=7.3 Hz, ArH), 7.57 (1H, t, J=7.3 Hz, ArH), 8.05 (2H, d, J=7.3 Hz, ArH) ; ms m/z $C_{20}H_{26}O_4$ requires: 330.1830 (M^+). Found: 330.1824 (M^+); $[\alpha]_D$ -33.6° (c=3.3, $CHCl_3$); Anal. Calcd for $C_{20}H_{26}O4$: C, 72.70; H, 7.93. Found: C, 72.92; H, 8.05.

Isopropyl (1*S*,2*S*,3*R*, 5*S*)-3-Hydroxy-5-isopropenyl-2-methylcyclopentane-1-carboxylate (**15**)
To a stirred solution of the benzoate (**14**)(3.0 g, 9.1 mmol) in methanol (30 ml) was added potassium carbonate (3.8 g, 27 mmol) and the mixture was further stirred overnight at ambient temperature. After treatment with ammonium chloride, the mixture was extracted with ethyl acetate, and the extract was washed with water and dride over Na_2SO_4. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1 v/v) afforded the alcohol (**15**)(1.7 g, 84.7%) as a colorless oil ; ir ($CHCl_3$) 3500 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3H, d, J=7.3 Hz, Me), 1.20 and 1.22 (each 3H, each

d, J=6.1 Hz, 2×OCH*Me*), 1.53-1.63 (1H, m, 2-H), 1.74 (3H, s, C=CMe), 2.04-2.41 (2H, m, 4-H_2), 2.55 (1H, t, J=11.0 Hz, 1-H), 2.86 (1H, dt, J=8.6 and 9.8 Hz, 5-H), 4.18 (1H, dt, J=2.4 and 5.5 Hz, 3-H), 4.71-4.77 (2H, m, C=CH_2), 5.04 (1H, quint, J=6.1 Hz, OCH); $[\alpha]_D$ -13.2° (c=2.0, $CHCl_3$); Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.21; H, 10.10.

Isopropyl (1*S*,2*S*,3*R*,5*S*)-5-(2-Chloroethyl)-3-hydroxy-2-methylcyclopentane-1-carboxylate (**16**)
Hydrogen chloride gas was bubbled into a stirred solution of the alcohol (**15**)(1.5 g, 6.6 mmol) in ether (60 ml) at 0°C for 1 h. The solution was allowed to warm to ambient temperature, and further stirred for 1 day. The solution was poured into ice-water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue,which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (4:1 v/v) afforded the chloride (**16**)(1.6 g, 92.4 %) as a colorless oil; ir ($CHCl_3$) 3500 and 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.07 (3H, d, J=7.3 Hz, Me), 1.24 and 1.26 (each 3H, each d, J=6.1 Hz, 2×OCH*Me*), 1.53 and 1.56 (each 3H, each s, 2×C=CMe), 1.76-1.83 (1H, m, 2=H), 2.01-2.38 (2H, m, 4-H_2), 2.60 (1H, dd, J=9.2 and 11.6 Hz, 1-H), 2.75 (1H, ddd, J=5.5, 9.2 and 11.0 Hz, 5-H), 4.06 (1H, m, 3-H), 5.06 (1H, quint, J=6.1 Hz, OCH); $[\alpha]_D$ -5.3° (c=5.2, $CHCl_3$).

Isopropyl (1*S*,2*S*,3*R*,5*S*)-5-(2-Chloroethyl)-3-triethylsiloxy-2-methylcyclopentane-1-carboxylate (**17**)
A solution of the chloride (**16**)(13.7 g, 52 mmol), imidazole (8.2 g, 120 mmol) and triethylsilyl chloride (8.7 g, 57 mmol) in DMF (150 ml) was stirred at ambient temperature for 1 h. The mixture was treated with brine and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (20:1 v/v) afforded the silyl ether (**17**)(19.6 g, 100%) as a colorless oil; ir ($CHCl_3$) 1720 cm^{-1}; nmr ($CDCl_3$) δ 0.54-0.63 (6H, m 3×SiCH_2), 0.92-0.99 (9H, m, 3×SiCMe), 1.24 (6H, t, J=6.1 Hz, 2×OCH*Me*), 1.52 (3H, d, J=1.8 Hz, Me), 1.69 (1H, ddd, J=2.4, 6.7, and 13.4 Hz, 1-H), 1.99-2.21 (2H, m, 4-H_2), 2.54 (1H, t, J=9.8 Hz, 1-H), 2.77 (1H, dt, J=6.7 and 9.8 Hz, 5-H), 4.07-4.12 (1H, m, 3-H), 5.05 (1H, quint, J=6.1 Hz OCH); $[\alpha]_D$ -30.0° (c=2.6, $CHCl_3$); Anal. Calcd for $C_{19}H_{37}O_3ClSi$: C, 60.53; H, 9.89. Found: C, 60.83; H, 10.19.

Isopropyl (3*S*,4*R*)-3,7-Dimethyl-4-triethylsiloxy-6-octanoate (**18**)
A solution of the γ-halo ester (**17**)(6.3 g, 17 mmol) was treated with 3 equiv. of samarium diiodide (prepared from samarium metal and 1,2-diiodoethane) in THF-HMPA (310 ml, 20:1 v/v) at ambient temperature for 5 min. The mixture was treated with saturated sodium hydrogen carbonate solution and then diluted with ether. The insoluble material was removed off by filtration and the filtrate was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (40:1 v/v) afforded the olefin (**18**)(5.24 g, 91.7%) as a colorless oil; ir ($CHCl_3$) 1730 cm^{-1}; nmr ($CDCl_3$) δ 0.54-0.63 (6H, m, 3×SiCH_2), 0.92-0.98 (12H, m, 3×SiCMe and Me), 1.22 and 1.23 (each 3H, each d, J=6.1 Hz, 2×OCH*Me*), 1.60 and 1.70 (each 3H, each s, 2×C=CMe), 1.99-2.46 (5H, m, 2-H_2, 3-H and 5-H_2), 3.52-3.58 (1H, m, 4-H), 5.01 (1H, q, J=6.1 Hz, OCH), 5.12-5.15 (1H, m, 6-H); ms m/z $C_{17}H_{33}O_3Si$ requires:313.2199 (M^+-29). Found: 313.2204 (M^+-29); $[\alpha]_D$ -8.1° (c=1.2 $CHCl_3$); Anal. Calcd for $C_{19}H_{38}O_3Si$: C, 66.61 H,11.18. Found: C, 66.60; H, 11.48.

Isopropyl (3*S*,4*R*)-3,7-Dimethyl-4-hydroxy-6-octanoate (**19**)

A solution of the olefin (**18**)(0.5 g, 1.5 mmol) in AcOH-H_2O-THF (3:1:1 v/v)(1.5 ml) was stirred for 10 h at 0°C. The mixture was extracted with ethyl acetate and the extract was washed with water, dried over Na_2SO_4 and concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (7:1 v/v) afforded the alcohol (**19**) as a colerless oil; ir ($CHCl_3$) 1725 and 3500 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (3H, d, J=6.7 Hz, Me), 1.22 and 1.25 (each 3H, each s, 2×OCH*Me*), 1.64 and 1.74 (each 3H, each s, 2×OCMe), 1.86 (1H, br s, OH), 2.04-2.59 (5H, m, 2-H_2, 3-H and 5-H), 3.39 (1H, m, 3-H), 5.03 (1H, quint, J=6.1 Hz, OCH), 5.18 (1H, m, 5-H); $[\alpha]_D$ -8.1° (c=0.6, $CHCl_3$), which without further purification was used in the next reaction.

Isopropyl (3*S*,4*S*)-4-Azido-3,7-dimethyl-6-octanoate (**20**)

To a stirred solution of the alcohol (**19**)(2.0 g, 8.8 mmol) in THF (40 ml) were added triphenylphosphine (2.8 g, 11 mmol), diethyl azodicarboxylate (1.7 ml, 11 mmol) and diphenylphosphoryl azide (3.6 g, 13 mmol) at 0°C and the resulting mixture was further stirred for 30 min. Evaporation of the solvent gave a residue, which was subjected to column chromatography on silica gel. Elution with hexane-ethyl acetate (30:1 v/v) afforded the azide (**20**)(1.3 g, 57.7%) as a colorless oil; ir ($CHCl_3$) 1730 and 2125 cm^{-1}; nmr ($CDCl_3$) δ 0.94 (3H, d, J=6.1 Hz, Me), 1.23 and 1.25 (each 3H, each s, 2×OCH*Me*), 1.66 and 1.73 (each 3H, each s, 2×OCMe), 2.13-2.42 (5H, m, 2-H_2, 3-H and 5-H_2), 3.37 (1H, ddd, J=3.1, 5.5 and 7.9 Hz, 4-H), 5.02 (1H, quint, J=6.1 Hz, CH), 5.12-5.18 (1H, m, C=CH); $[\alpha]_D$ +47.8° (c=2.5, $CHCl_3$).

(4*S*,5*S*)-5-Dimethylallyl-4-methyl-2-pyrrolidone (**23**)

To a stirred solution of the azide (**20**)(0.2 g, 0.8 mmol) in methanol (3 ml) was added magnesium powder (0.1 g, 4 mmol) at 0°C, and the mixture was further stirred for 5 h at ambient temperature. After evaporation of the solvent, a residue was treated with water and extracted with ether. The ethereal layer was washed with brine, dried over Na_2SO_4, and concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with dichloromethane-ethyl acetate (1:1 v/v) afforded the lactam (**23**)(0.1 g, 98.9%) as a colorless oil; ir ($CHCl_3$) 3450 and 1700 cm^{-1}; nmr ($CDCl_3$) δ 1.05 (3H, d, J=6.7 Hz, Me), 1.63 and 1.72 (each 3H, each s, 2×OCMe), 2.01 (1H, dd, J=6.1 and 15.8 Hz, allylic CH), 2.09-2.15 (2H, m, 3-H_2), 2.45 (1H, dd, J=7.9 and 15.8 Hz, allylic CH), 2.58 (1H, quint, J=7.3 Hz, 4-H), 3.54-3.62 (1H, m, 5-H), 5.04-5.09 (1H, m, C=CH), 5.82 (1H, br s, NH); $[\alpha]_D$ -66.0° (c=0.9, $CHCl_3$); Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.69; H, 10.42; N, 8.35.

(4*S*,5*S*)-5-Formylmethyl-4-methyl-2-pyrroridone (**24**)

A stream of ozone was bubbled through a stirred solution of **23** (0.5 g, 3.0 mmol) in methanol(50 ml) at -78 °C until disappearance of the starting material on tlc. The reaction mixture was flushed with argon and treated with triphenylphosphine(1.2 g, 5.0 mmol). The resulting solution was allowed to warm to room temperature and further stirred for 2 h at the same temperature. After removal of the solvent, a residue was subjected to column chromatography on silca gel. Elution with ethyl acetate-methanol (10:1 v/v) afforded the aldehyde (**24**)(0.4 g, 100%) as a colorless oil; ir ($CHCl_3$) 1685, 1720, and 3425 cm^{-1}; nmr ($CDCl_3$) δ 1.04 (3H, d, J=6.7 Hz, Me), 2.00 (1H, dd, J=7.9 and 16.5 Hz, 3-H), 2.47 (1H, dd, J=7.9 and 16.5 Hz, 3-H), 2.62 (1H, dd, J=9.8 and 18.3 Hz, OCCH), 2.65-2.68 (1H, m, 4-H), 2.76 (1H, dd, J=3.7 and 18.3 Hz, OCCH), 4.02-4.16 (1H, m, 5-H), 5.98 (1H,

br s, NH), 9.87 (1H, s, COH); $[\alpha]_D$ -84.6° (c=0.9, $CHCl_3$); Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.61; H, 7.95; N, 9.88.

(4*S*,5*S*)-5-(*E*/*Z*)-3-Methoxypropen-2-yl -4-methyl-2-pyrroridone (**25**)

To a stirred solution of methoxymethytriphenylphosphonium chloride (0.8 g, 2.2 mmol) in THF (15 ml) was added *n*-BuLi (1.71M *n*-hexane solution)(1.2 ml, 2.1 mmol) at ambient temperature and the mixture was further stirred for 15 min. To this solution was added a solution of the aldehyde (**24**)(0.14 g, 1 mmol) in THF (5 ml) at the same temperature. After being stirred for 30 min, the mixture was treated with brine and extracted with ethyl acetate. The extract was dried over Na_2SO_4 and concentrated to leave a residue which was subjected to column chromatography on silica gel. Elution with ethyl acetate-acetone (5:1 v/v) gave the enol ether (**25**) as a mixture of E/Z stereoisomers; nmr ($CDCl_3$) δ 1.04 (3H, d, J=6.8 Hz, Me); 1.92-2.62 (5H, m, 3-H_2, 4-H and allylic CH_2), 3.45 and 3.52 (each 1.5 H, each s, OMe), 4.27-4.35 (0.5H, m, OC=CH(*E*-)), 4.59-4.69 (0.5H, m, OC=CH(*Z*-)), 5.99 (0.5H, d, J=6.7 Hz, OCH=C(*Z*-)), 6.34 (0.5H, d, J=12.8 Hz, OCH=C(*E*-)); ms m/z $C_9H_{15}NO_2$ requires: 169.1103 (M^+). Found: 169.1093 (M^+).

(4*S*,5*S*)-8-Hydroxy-4-methyl-1-azabicyclo[3.3.0]octan-2-one (**26**)

A solution of the enol ether (**25**)(170 mg, 0.99 mmol) in AcOH-H_2O-THF (3:1:1 $^v/_v$)(5 ml) was stirred for 1 h at 80°C. The mixture was extracted with ethyl acetate, and the organic layer was wash with water and brine, and dried over Na_2SO_4. Evaporation of the solvent gave a residue which was subjected to column chromatography on silica gel. Elution with dichloromethane-ethyl acetate (1:5 v/v) afforded the alcohol (**26**)(45 mg, 29.2%, 2 steps overall yield from **24**) as colorless needles, mp 76-78°C; ir ($CHCl_3$) 3350 and 1660 cm^{-1}; nmr ($CDCl_3$) δ 0.96 (3H, d, J=7.3 Hz, Me), 1.55-1.66 (1H, m, 4-H), 1.82-2.05 (2H, m, 6-H_2), 2.02 (1H, dd, J=3.1 and 16.5 Hz, 3-H), 2.33-2.62 (2H, m, 7-H_2), 2.88 (1H, dd, J=7.9 and 16.5 Hz, 3-H), 3.03 (1H, d, J=3.7 Hz, OH), 4.25 (1H, dt, J=6.1 and 9.8 Hz, 5-H), 5.54-5.59 (1H, m, 8-H); ms m/z Calcd for $C_8H_{13}NO_2$ requires 155.0944 (M^+). Found 155.0941 (M^+).

(4*S*,5*S*)-4-Methyl-1-azabicyclo[3.3.0]octan-2-one (**27**)

To a stirred solution of **26** (0.425 g, 2.74 mmol) in trifluoroacetic acid (15 ml) was added triethylsilane (5 ml, 31 mmol) dropwise at room temperature and the resulting mixture was further stirred for 1 h at the same temperature. The solution was cooled to 0°C and methanol (20 ml) was added slowly to this solution and further stirred for 30 min. The solution was neutralized by addition of ammonium hydroxide and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated to leave a residue, which was subjected to column chromatography on silica gel. Elution with ethyl acetate-methanol (10:1 v/v) gave the lactam (**27**)(190mg, 50.2%) as a colorless oil; ir ($CHCl_3$) 1670 cm^{-1}; nmr ($CDCl_3$) δ 0.98 (3H, d, J=7.3 Hz, Me), 1.51-1.62 (1H, m, 4-H), 1.67-1.76 (1H, m, 7-H), 1.97-2.11 (2H, m, 6-H_2), 2.05 (1H, dd, J=2.4 and 16.5 Hz, 3-H), 2.51-2.60 (1H, m, 7-H), 2.91 (1H, dd, J=7.9 and 16.5 Hz, 3-H), 3.03-3.1 (1H, m, 8-H), 3.53 (1H, dt, J=7.9 and 11.6 Hz, 8-H), 3.97 (1H, dt, J=6.1 and 9.8 Hz, 5-H); ms m/z $C_8H_{13}NO$ requires 139.0996(M^+). Found 139.0991(M^+). $[\alpha]_D$ -57.63° (c=1.9, $CHCl_3$).

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