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CONCISE HIGHLY ENANTIOSELECTIVE CASCADE SYNTHESIS OF AZACYCLOOCTENE ALKALOIDS WITH A QUATERNARY STEREOCENTER

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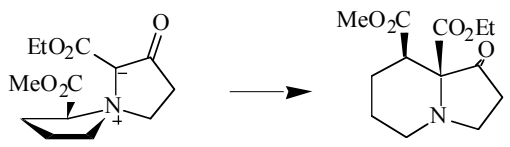
Abstract –Enantiopure azabicyclo[6.3.0]undecene ring systems bearing a quaternary stereocenter were prepared by a cascade process.

INTRODUCTION

Syntheses of enantiopure quaternary asymmetric carbon atoms are always of remarkable value; here we report a method for a very rapid construction of quaternary stereocenters.[1]

Optically active alkaloids have been prepared starting from cyclic amine templates by catalytic diazo-decomposition-cyclization reaction in tandem with [1,2]-[2] or [2,3]- rearrangements[3] of the supposed ammonium ylide intermediates;[4] in few cases, acceptable stereoselectivities have been reached.[5] Recently, isolation of stable spirocyclic ammonium ylide intermediates enabled us to probe the stereochemistry of the complete cascade process, unambiguously.[6] [5,5]-Spirocyclic ylide (**1**) (Scheme 1), formed by cyclization of the carbenoid species generated by transition metal catalytic diazo-decomposition, was obtained as pure diastereomer.



1 **2**

Scheme 1

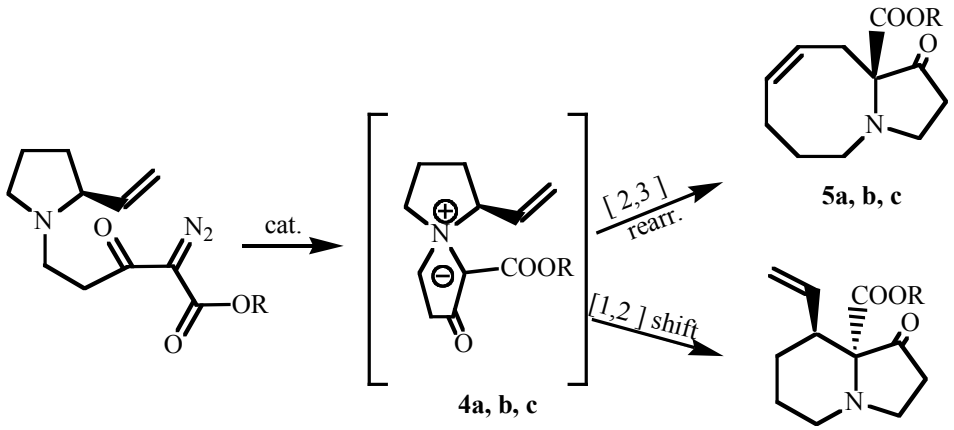
By heating without catalyst, this ylide undergoes the Stevens [1,2]shift, with ring enlargement, affording the [6.5]-bicyclic swansonine-type alkaloid (**2)** with high diastereoselectivity. Moreover, an excellent

chirality transfer from the obliterate nitrogen spiranic stereocenter of the ylide (**1)** to the newly formed quaternary carbon of **2** was obtained.

Given this achievment, we were interested in utilizing the cascade approach for a rapid construction of enantiopure azabicyclo[6.3.0]undecene ring systems bearing a quaternary stereocenter. These heterocycles are precursors of the corresponding polyhydroxy derivatives with potential therapeutical activity.

RESULT AND DISCUSSION

Our strategy, depicted in Scheme 2, was based upon a three carbons homologation possibility of the chiral 2-vinylpyrrolidine template moiety of diazo compound (**3)**. Catalytic decomposition of this compound would generate a metal-carbenoid species which attack to the pyrrolidine nitrogen was expected to diastereoselectively generate the ylide intermediates (**4)**. The process would proceed in cascade with [2,3]shift across the pendant vinyl group situated at 2-position of the pyrrolidine ring. This reaction has been previously published by J. S. Clark *et al.* which reported the formation of the azacyclooctene alkaloid ring system.[5a] For our purposes, we modified this method by using a β-keto ester rather than a ketone in the carbene precursor.



Scheme 2

We selected this protocol with the aim of obtaining high "chirality transfer" in the generation of quaternary carbon stereocenter of the target (**5)**: stereocontrol of [2,3]sigmatropic concerted rearrangements is well documented.[7] Due to migratory aptitude of the carbon atom situated in α position to the spirocyclic ammonium group, assisted by a stabilizing allylic function, the undesirable ylide Stevens [1,2]shift with one carbon ring expansion, to afford the [6.5]-bicyclic alkaloid (**6)**, as the secondary product, would not be avoided, in principle.[8]

The cyclization precursors (**3)** were efficiently prepared in two steps by conjugate addition of the enantiopure (*S*)-2-vinylpyrrolidine[9] to ethyl[10], benzyl[11] and (-)-menthyl 3-keto-pent-4-enoate,[12] followed

by diazo-transfer reaction with tosyl azide.

^{1}H NMR spectral analysis of diazocompounds (**3a-c)** using the chiral reagent Eu(hfc)$_3$ indicated its enantiomeric purity, excluding racemization during the N-alkylation step.

Two transition metal catalysts were studied (Table 1). The Cu(acac)$_2$ catalyzed diazodecomposition of **3a-c**, carried out in refluxing toluene, gave mixtures of azacyclooctenes (**5a-c**) and indolizidines (**6a-c**) approximately in the 90/10 ratio (NMR spectrometry).[13] The same reaction, performed by using Rh$_2$(OAc)$_4$ as the catalyst in refluxing toluene, afforded the same product mixtures. In spite of data previously reported, the copper-based catalysis for generation of ammonium ylides has been shown not to be more effective.[14]

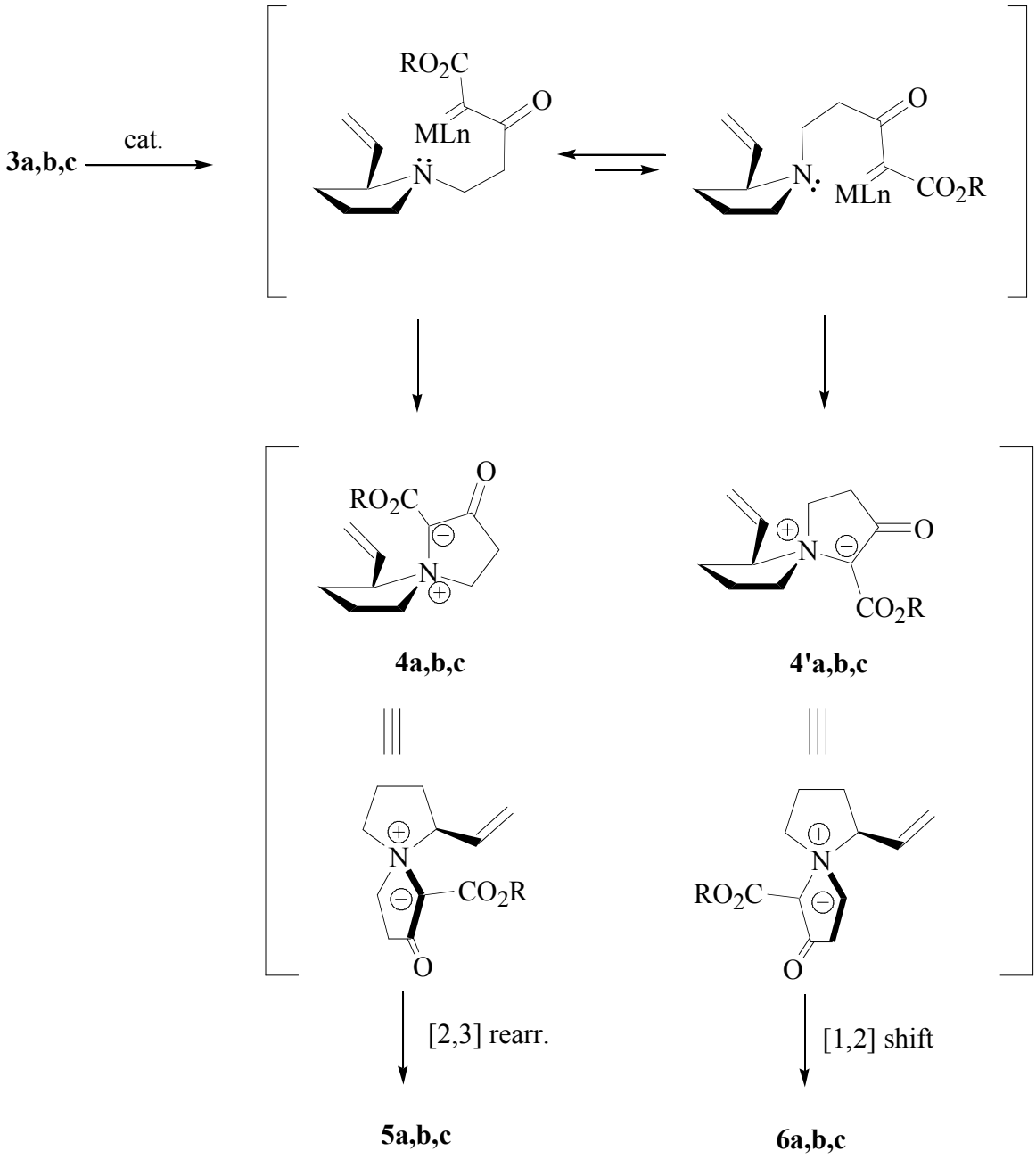
Table 1

3a, b, c $\xrightarrow[\text{toluene /reflux}]{\text{diazodecomposition}}$ **5a, b, c** **6a, b, c**

Substrate	Cat	**yield (%)**	**5a, b, c : 6a, b, c**	**ee 5a, b, c**
3a	Cu(acac)$_2$	60	93 : 7	97.9
3a	Rh$_2$(OAc)$_4$	54	93 : 7	96.6
3b	Cu(acac)$_2$	40	90 : 10	96.9
3b	Rh$_2$(OAc)$_4$	54	85 : 15	97.2
3c	Cu(acac)$_2$	65	92 : 8	96.9
3c	Rh$_2$(OAc)$_4$	72	90 : 10	97.7

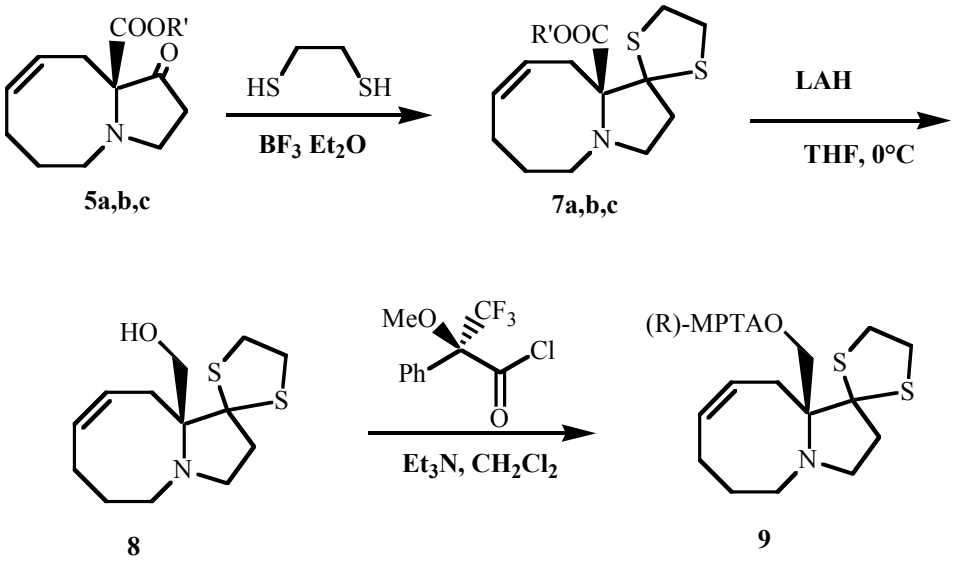
However all the compounds obtained could be rationalized in terms of the initial formation of the spirocyclic ammonium ylides (**4**) and (**4'**). A rationale could be proposed for both the rearrangements caused by the [2,3]- and [1,2]-shifts (Scheme 3) confirming our findings[6] and those of West[15] and Clark.[3b] Attack of the electrophilic metallo-carbenoid center to the nitrogen lone pair may form both the ylides (**4**) and (**4'**) in different amounts with preference by the metallocarbene intermediate from the β-face of the 5-membered heterocycle**.** The ylides (**4**) presents orientation of the nucleophilic carbon with a properly disposition to attack to the pendant pyrrolidine olefine, giving the derivatives (**5**) through a [2,3]

sigmatropic rearrangement. The ylides (**4'**), generated by the less preferred face attack, are more suitable to undergo the Stevens [1,2] shift rearrangement, affording compounds (**6**).



Scheme 3

Compounds (**5a-c**) were obtained in 96-98% ee. The enantiomeric excess was determined by ^{19}F NMR spectral analysis of the dithiolane ester (**9**) produced upon reaction of excess (*R*)-Mosher's acid chloride with dithiolane alcohol (**8**), obtained according to Scheme 4. In order to confirm that the observed resonances in the ^{19}F NMR spectrum correnspondedto the two diastereoisomers, the Mosher's esters were also prepared from racemic mixtures of alcohols (**8**).



5a,b,c 7a,b,c 8 9

Scheme 4

The configuration of the newly formed quaternary stereocenter of compounds (**6**) was tentatively assigned according to the proposed mechanism. The 2D NOESY correlation studies does not rule out these conclusions. Thus, for compounds (**6**), the NOESY trace of the ethyl ester methylene protons not showed positive NOE effect for the proton at C-8.

CONCLUSIONS

The [2,3]sigmatropic rearrangement of ylide intermediates affording cyclic systems by ring expansions, since the relevant work of Vedejs and his group, has been shown to be a versatile synthetic tool.[16] In this contest, the present synthesis represents one of the more efficient and concise routes to construct enantiopure bicyclic amine ring systems bearing quaternary asymmetric carbon atoms from precursors of the convenient "chiral pool approach".

EXPERIMENTAL

General

^{1}H NMR (300 MHz) and ^{13}C NMR (75MHz) were recorded on a Varian VXR-300 spectrometer with TMS as internal standard. COSY, NOESY, HSQC and USQC-TOSCY spectra were recorded with a Broker Avance 600 equipped with inverse detection probe. IR spectra were measured on a FT/IR-480plus JASKO spectrophotometer. The optical rotations were measured by a polarimeter P-1010 JASKO in a 1 dm tube. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

2-Diazo-3-oxo-5-[(2*S*)-2-vinylpyrrolidin-1-yl]pentanoic acid ethyl ester (3a)

TFA (1.17 mL, 15 mmol) was added dropwise under nitrogen atmosphere to N-BOC-vinylpyrrolidine (1.0 g, 5 mmol) at 0 °C. The mixture was stirred at rt until the disappearance of substrate at NMR spectrum and formation of trifluoroacetate of the amine (about 1 h), afterwards the excess of TFA was evaporated in vacuum at rt. To a stirred solution of the residue and 3-oxo-pent-4-enoic acid ethyl ester (790 mg, 5.5 mmol) in CH_2Cl_2 (10 mL) a solution of Et_3N (0.76 mL, 5.5 mmol) in CH_2Cl_2 (10 mL) was added dropwise and stirred for 30 min. To the reaction mixture tosyl azide (1.1 g, 5.5 mol) and a solution of Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (10 mL) were added dropwise at 0 °C. After the addition was complete, the solution was stirred overnight at rt. The solvent was evaporated and the residue was purified by flash chromatography (Et_2O/petroleum ether/Et_3N, 8:2:0,1) to give the diazo compound (**3a**) (950 mg, 70%) as a yellow oil: $[\alpha]^{25}_D$= -36.8° (c 1.5 , $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.33 (t, 3H, J=7.1 Hz), 1.52-1.69 (m, 1H), 1.69-1.85 (m, 2H), 1.85-2.02 (m, 1H), 2.17 (q, 1H, J= 8.7 Hz), 2.33-2.45 (m, 1H), 2.72 (q, 1H, J= 8.1 Hz), 3.00-3.11 (m, 2H), 3.11-3.26 (m, 2H), 4.30 (q, 2H, J=7.1 Hz), 5.09 (dd, 1H, J=1.8, 10.2 Hz), 5.16 (dd, 1H, J=1.8, 17.4 Hz), 5.68 (ddd, 1H, J=8.1, 10.2, 17.4 Hz); ^{13}C NMR ($CDCl_3$): δ 14.3, 22.1, 31.5, 39.1, 48.5, 53.4, 61.3, 68.7, 76.2, 116.5, 140.5, 161.2, 191.7; IR (neat) 3076, 2965, 2795, 2133, 1719, and 1655 cm^{-1}; Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.61; H, 7.30; N, 16.08.

2-Diazo-3-oxo-5-[(2*S*)-2-vinyl-pyrrolidin-1-yl]-pentanoic acid benzyl ester (3b)

Following the above procedure, treatment of N-BOC-vinylpyrrolidine (670 mg, 3.4 mmol) with TFA (0.79 mL, 10 mmol), 3-oxopent-4-enoic acid benzyl ester (1.0 g, 3.8 mmol), tosyl azide (750 mg, 3.8 mmol) and Et_3N (1.4 mL, 10 mmol), gave, after flash chromatography (Et_2O/petroleum ether/Et_3N, 4:6:0,1), the diazo compound (**3b**) (810 mg, 77%) as a yellow oil: $[\alpha]^{25}_D$= -26.0° (c 1.0 , $CHCl_3$); ^{1}H NMR: δ 1.49-1.66 (m, 1H), 1.66-1.85 (m, 2H), 1.85-2.00 (m, 1H), 2.15 (q, 1H, J=8.7 Hz), 2.30-2.43 (m, 1H), 2.71 (q, 1H, J=8.1 Hz), 2.97-3.10 (m, 2H), 3.10-3.25 (m, 2H), 5.07 (dd, 1H, J=1.8, 10.2 Hz), 5.14 (dd, 1H, J=1.8, 17.4 Hz), 5.26 (br s, 2H), 5.66 (ddd, 1H, J=8.1, 10.2, 17.4 Hz), 7.37 (br s, 5H); ^{13}C NMR ($CDCl_3$): δ 22.1, 31.5, 39.2, 48.4, 53.4, 66.8, 68.7, 116.5, 128.3, 128.6, 128.7, 135.2, 140.6, 161.1, 191.5; IR (neat): 3067, 3033, 2961, 2798, 2133, 1718 and 1655 cm^{-1}. Anal. Calcd for $C_{18}H_{21}N_3O_3$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.21; H, 6.47; N, 12.59.

2-Diazo-3-oxo-5-[(2*S*)-2-vinylpyrrolidin-1-yl]pentanoic acid (-)-menthyl ester (3c)

Following the above procedure, treatment of N-BOC-vinylpyrrolidine (750 mg, 3.8 mmol) with TFA (0.9 mL, 10.2 mmol), 3-oxopent-4-enoic acid (-)-menthyl ester (1.1 g, 4 mol), tosyl azide (850 mg, 4 mmol) and Et_3N (1.4 mL, 10 mmol) gave, after flash chromatography (ether petroleum/Et_2O, 8:2), the diazo compound (**3c**) (850 mg, 60 %) as a yellow oil: $[\alpha]^{25}_D$= -89.4° (c 0.35, $CHCl_3$); ^{1}H NMR: δ 0.79 (d, 3H,

J=6.9 Hz), 0.92 (dd, 6H, J=4.8, 6.9 Hz), 0.84-1.26 (m, 3H), 1.36-2.00 (m, 9H), 2.00-2.10 (m, 1H), 2.17 (q, 1H, J=8.7 Hz), 2.30-2.43 (m, 1H), 2.71 (q, 1H, J=8.1 Hz), 2.96-3.15 (m, 2H), 3.15-3.24 (m, 2H), 4.82 (dt, 1H, J=4.5, 10.8 Hz), 5.08 (dd, 1H, J=1.8, 10.2 Hz), 5.15 (dd, 1H, J=1.8, 17.4 Hz), 5.26 (br s, 2H), 5.68 (ddd, 1H, J=8.1, 10.2, 17.4 Hz); ^{13}C NMR ($CDCl_3$): δ 16.4, 20.6, 21.9, 22.1, 23.5, 26.4, 31.3, 31.5, 33.9, 39.1, 41.0, 46.9, 48.5, 53.3, 68.6, 75.5, 76.2, 116.4, 140.5, 160.7, 191.7; IR (neat): 3077, 2957, 2870, 2793, 2363, 2130, 1710 and 1656 cm^{-1}. Anal. Calcd for $C_{21}H_{33}N_3O_3$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.30; H, 8.61; N, 11.02.

General procedure for the diazo decomposition

To a refluxing solution of catalyst $Rh_2(OAc)_4$ (13 mg, 3 mol%) or $Cu(acac)_2$ (13 mg, 5 mol%) in 30 mL of dry toluene, a solution of diazo compound (1 mmol) in 20 mL of dry toluene was added dropwise over 30 min. After stirring for another 30 min at reflux, the mixture was cooled, concentrated and purified by flash chromatography (petroleum ether/ Et_2O, 8:2). The results are shown in Table 1.

Azocine Alkaloids

(10a*R*)-1-Oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-*a*]azocine-10a-carboxylic acid ethyl ester (5a): colorless oil; $[\alpha]^{25}_D$= +97° (c 0.96, $CHCl_3$), 97.9% ee; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, 3H, J=7.2 Hz), 1.31-1.46 (m, 1H), 1.75 (ddt, 1H, J=4.8, 8.4 and 18.3 Hz), 2.11-2.80 (m, 1H), 2.20-2.40 (m, 2H), 2.40-2.62 (m, 2H), 2.68-2.90 (m, 3H), 3.32-3.42 (m, 2H), 4.16 (dq, 1H, J= 0.9, 7.2 Hz), 5.60-5.84 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 14.3, 25.0, 28.2, 32.5, 36.4, 48.1, 48.5, 61.1, 76.2, 125.6, 133.0, 169.9; IR (neat): 3020, 2977, 2929, 2851, 2360, 2335, 1761 and 1726 cm^{-1}; Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.54; H, 8.33; N, 5.71.

(10a*R*)-1-Oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-*a*]azocine-10a-carboxylic acid benzyl ester (5b): colorless oil; $[\alpha]^{25}_D$= +63.8° (c 0.6, $CHCl_3$), 97.2% ee; ^{1}H NMR ($CDCl_3$): δ 1.30-1.46 (m, 1H), 1.66-1.82 (m, 1H), 1.96-2.11 (m, 1H), 2.22-2.42 (m, 2H), 2.42-2.62 (m, 2H), 2.69-2.91 (m, 3H), 3.22-3.42 (m, 2H), 5.13 (s, 2H), 5.60-5.82 (m, 2H), 7.25-7.45 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 25.0, 28.2, 32.5, 36.4, 48.1, 48.5, 66.8.1, 76.3, 125.4, 127.9, 128.2, 128.5, 133.1, 135.6, 169.9, 210.8; IR (neat): 3024, 2928, 2850, 2127, 1760 and 1728 cm^{-1}; Anal Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 71.98; H, 7.22; N, 4.40.

(10a*R*)-1-Oxo-2,3,5,6,7,10-hexahydro-1*H*-pyrrolo[1,2-*a*]azocine-10a-carboxylic acid (-)-menthyl ester (5c): colorless oil; $[\alpha]^{25}_D$= -2.6° (c 1,1, $CHCl_3$), 97.7% ee; ^{1}H NMR ($CDCl_3$): δ 0.71 (d, 3H, J=6.9 Hz), 0.75-1.12 (m, 9H), 1.30-1.58 (m, 3H), 1.60-1.84 (m, 3H), 1.84-2.10 (m, 3H), 2.30-2.40 (m, 2H), 2.40-2.60 (m, 2H), 2.71-2.88 (m, 2H), 3.22-3.38 (m, 2H), 4.65 (dt, 1H, J=4.2, 10.8 Hz), 5.60-5.82 (m,

2H); ^{13}C NMR ($CDCl_3$): δ 15.7, 20.8, 21.9, 22,9 24.9, 25.8, 28.4, 31.3, 32.4, 34.1, 36.4, 40.5, 46.9, 48.1, 48.4, 75.5, 76.2, 125.7, 132.9, 169.9, 211.1; IR (neat): 3027, 2927, 2859, 2721, 1757, 1707 and 1456 cm^{-1}; Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.86; H, 9.80; N, 4.26.

Data for Indolizidine alkaloids

The optical rotations of the minor and secondary compounds (**6a-c**) are not reported since they could not be obtained totally free of **5a-c**.

(8*S*, 8a*S*)-1-Oxo-8-vinylhexahydroindolizine-8a-carboxylic acid ethyl ester (6a): yellow oil; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, 3H, J=7.2 Hz), 1.34-1.46 (m, 1H), 1.60-1.90 (m, 3H), 2.32-2.44 (m, 2H), 2.84-2.94 (m, 1H), 3.05 (dt, 1H, J=3.3, 11.7 Hz), 3.12-3.28 (m, 2H), 3.41 (q, 1H, J= 7.8 Hz), 4.10-4.30 (m, 2H), 5.08 (dd, 1H, J=0.9, 10.2 Hz), 5.16 (dd, 1H, J=0.9, 17.4 Hz), 5.97 (ddd, 1H, J=8.7, 10.2, 17.4 Hz); ^{13}C NMR ($CDCl_3$): δ 14.2, 19.7, 27.8, 36.5, 41.1, 46.7, 47.1, 61.3, 75.5, 117.2, 136.6, 169.4, 210.0; IR (neat): 3078, 2928, 2855, 2364, 1762 and 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65,80; H, 8,07; N, 5,90. Found: 65,97; H, 8,16; N, 5,72.

(8*S*, 8a*S*)-1-Oxo-8-vinylhexahydroindolizine-8a-carboxylic acid benzyl ester (6b): yellow oil; ^{1}H NMR ($CDCl_3$): δ 1.34-1.50 (m, 1H), 1.50-1.94 (m, 3H), 2.20-2.50 (m, 2H), 2.83-2.96 (m, 1H), 3.03 (dt, 1H, J=3.3, 11.7 Hz), 3.12-3.30 (m, 2H), 3.39 (q, 1H, J= 7.8 Hz), 5.00-5.10 (m, 4H), 5.95 (ddd, 1H, J=8.7, 10.2, 17.4 Hz); ^{13}C NMR ($CDCl_3$): δ 19.7, 27.8, 36.5, 41.1, 46.7, 47.1, 66.9, 75.6, 117.3, 128.1, 128.3, 128.6, 135.5, 136.5, 169.3, 209.7; IR (neat): 3068, 3032, 2933, 2855, 2360, 1762 and 1724 cm^{-1}. Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72,22; H, 7,07; N, 4,68. Found: C, 72,37; H, 7,24; N, 4,51.

(8*S*, 8a*S*)-1-Oxo-8-vinylhexahydroindolizine-8a-carboxylic acid menthyl ester (6c): yellow oil; ^{1}H NMR: δ 0.79 (d, 3H, J=6.9 Hz), 0.78-1.16 (m, 9H), 1.30-1.55 (m, 3H), 1.55-2.00 (m, 7H), 2.36 (dd, 2H, J=5.4 and 7.5 Hz), 2.84-2.95 (m, 1H), 3.04 (dt, 1H, J=3.3, 11.7 Hz), 3.12-3.30 (m, 2H), 3.42 (q, 1H, J= 7.8 ßHz), 4.73 (dt, 1H, J=4.5, 10.8 Hz), 5.07 (d, 1H, J=10.5 Hz), 5.16 (d, 1H, J=17.4 Hz), 5.68 (ddd, 1H, J=8.4, 10.5, 17.4 Hz); ^{13}C NMR ($CDCl_3$): δ 15.6, 19.9, 20.9, 21.9, 22.8, 26.0, 27.8, 31.4, 34.1, 36.5, 40.8, 40.9, 46.7, 46.8, 47.1, 75.5, 75.7, 117.1, 136.7, 169.1, 209.9; IR (neat): 3076, 2952, 2866, 2360, 1763, and 1718 cm^{-1}. Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.30; H, 9.71; N, 3.88.

Determination of optical purity of 5a-c

General procedure for protection of carbonyl group with dithiolane

To a solution of **5** (1 mmol) in 1 mL of 1,2 ethanedithiol was added dropwise 1 mL of $BF_3 \cdot Et_2O$ and the resulting mixture was stirred for 2 days. The reaction mixture was poured in an ice cold saturated

$NaHCO_3$ (15 mL) and extracted with CH_2Cl_2 (2X15 mL). The organic phase was dried with anhydrous Na_2SO_4, evaporated and the residue purified by flash chromatography (petroleum ether/ Et_2O, 9:1) to give a colorless oil in 60-70% yield.

(10a'*S*)-2',3',5',6',7',10'-Hexahydro-10a'*H*-spiro[1,3-dithiolane-2,1'-pyrrolo[1,2-*a*]azocine]-10a'-carboxylic acid ethyl ester (7a) : $[\alpha]^{25}_D$= -53° (c 0.4, $CHCl_3$), 97.9% ee ; ^{1}H NMR ($CDCl_3$): δ 1.31 (t, 3H, J=7.2 Hz), 1.74-1.90 (m, 1H), 1.90-2.04 (m, 1H), 2.27-2.46 (m, 2H), 2.56-2.91 (m, 6H), 2.91-3.06 (m, 3H), 3.27 (s, 4H), 3.29-3.41 (m, 1H), 4.07-4.26 (m, 2H), 5.57-5.71 (m, 1H), 5.71-5.87 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 14.3, 23.9, 28.5, 34.2, 39.1, 39.4, 43.0, 48.6, 51.9, 60.6, 77.3, 78.8, 127.9, 131.7, 173.6; IR (neat): 3019, 2973, 2928, 2855, 2360 and 1720 cm^{-1}; Anal. Calcd for $C_{15}H_{23}NO_2S_2$: C, 63.96; H, 6.71; N, 3.73. Found: C, 64.21; H, 6.33; N, 3.50.

(10a'*S*)-2',3',5',6',7',10'-Hexahydro-10a'*H*-spiro[1,3-dithiolane-2,1'-pyrrolo[1,2-*a*]azocine]-10a'-carboxylic acid benzyl ester (7b) : $[\alpha]^{25}_D$= -55° (c 0.56, $CHCl_3$), 97.2% ee; ^{1}H NMR ($CDCl_3$): δ 1.10-1.30 (m, 1H), 1.74-1.87 (m, 1H), 1.87-2.04 (m, 1H), 2.24-2.48 (m, 2H), 2.50-2.64 (m, 1H), 2.64-2.90 (m, 4H), 2.90-3.06 (m, 1H), 3.10-3.27 (m, 4H), 3.27-3.39 (m, 1H), 5.16 (s, 2H), 5.57-5.68 (m, 1H), 5.68-5.80 (m, 1H), 7.28-7.46 (m, 5H);); ^{13}C NMR ($CDCl_3$): δ 23.9, 28.5, 34.5, 39.1, 39.5, 43.0, 48.4, 51.4, 66.6, 77.2, 79.3, 127.7, 128.1, 128.3, 128.4, 131.9, 135.9; IR (neat): 3020, 2980, 2927, 2855, 2360 and 1722 cm^{-1}; Anal. Calcd for $C_{20}H_{25}NO_2S_2$: C, 65.20; H, 8.80; N, 3.31. Found: C, 65.44; H, 8.52; N, 3.12.

(10a'*S*)-2',3',5',6',7',10'-Hexahydro-10a'*H*-spiro[1,3-dithiolane-2,1'-pyrrolo[1,2-*a*]azocine]-10a'-carboxylic acid menthyl ester (7c) : $[\alpha]^{25}_D$= -61° (c 0.6, $CHCl_3$), 97.7% ee; ^{1}H NMR ($CDCl_3$): δ 0.65-1.09 (m, 11H), 1.09-1.24 (m, 1H), 1.32-1.54 (m, 1H), 1.60-1.87 (m, 4H), 1.90-2.24 (m, 2H), 2.24-2.54 (m, 2H), 2.54-3.02 (m, 10H), 3.28-3.35 (m, 3H), 3.35-3.50 (m, 1H), 4.70 (dt, 1H, J=4.2 and 10.8 Hz) 5.56-5.72 (m, 1H), 5.72-5.94 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 15.5, 21.0, 22.1, 22.7, 23.9, 25.4, 28.7, 31.4, 34.2, 38.9, 39.5, 40.8, 42.2, 43.0, 47.1, 49.0, 53.0, 75.6, 77.5, 78.9, 128.3, 131.0, 173.5; IR (neat): 3020, 2927, 2855, 2360 and 1721 cm^{-1}; Anal. Calcd for $C_{23}H_{37}NOS_2$: C, 65.20; H, 8.80; N, 3.31; S, 15.14. Found: C, 65.44; H, 8.52; N, 3.12.

General procedure for reduction of ester group

To a suspension of $LiAlH_4$ (19 mg, 0.5 mmol) in THF (5 mL) was added a solution of **7** (0.5 mmol) in THF (5 mL). The mixture was stirred at rt until disappearing of the ester function (IR). The mixture was diluted with ethyl acetate (20 mL), quenched with NaOH 10% (1 mL), filtrated, dried over Na_2SO_4 and concentrated to give yellow oil. Flash cromatography (petroleum ether/ ethyl acetate, 8:2) provided **8** (108-122 mg, 80-90 %) as a colorless oil.

(10a'*S*)-2',3',5',6',7',10'-Hexahydro-10a'*H*-spiro[1,3-dithiolane-2,1'-pyrrolo[1,2-*a*]azocin]-10a'-ylmethanol (8): $[\alpha]^{25}_{D}$= +15° (c 0.54, $CHCl_3$), 97.9% ee; ^{1}H NMR ($CDCl_3$): δ 1.33-1.50 (m, 1H), 1.88-2.04 (m, 1H), 2.04-2.27 (m, 2H), 2.27-2.46 (m, 3H), 2.46-2.62 (m, 2H), 2.73-3.03 (m, 4H), 3.11-3.21 (m, 1H), 3.21-3.45 (m, 4H), 3.73 (q, 2H, J= 11.4 Hz), 5.63-5.89 (m, 1H); ^{13}C NMR ($CDCl_3$): δ 23.9, 29.6, 33.3, 38.0, 38.6, 42.8, 45.4, 64.0, 72.2, 78.0, 127.9, 132.1; IR (neat): 3419, 3012, 2926, 2851, 1758, and 1722 cm^{-1}; Anal. Calcd for $C_{13}H_{21}NOS_2$: C, 57.52; H, 7.80; N, 5.16. Found: C, 57.80; H, 7.59; N, 5.31.

Preparation of Mosher's ester

To a solution of **8** (25 mg, 0.1 mmol) and DMAP (1 mg) in dry CH_2Cl_2 (5 mL), Et_3N (0.04 mL, 0.3 mmol) was added dropwise at 0 °C. The mixture was stirred for 10 min and then a solution *R*-(+)-MTPA chloride (46 mg, 0.2 mmol) in dry CH_2Cl_2 (0.5 mL) was added dropwise. The resulting solution was stirred at 0 °C for 1 h and at rt for 24 h; the solvent was then removed in vacuo, and the residue purified by flash chromatography (petroleum ether/ ethyl acetate /Et_3N, 9:1:0.1). The Mosher's ester (**9**) was analysed by ^{19}F NMR spectrum in $CDCl_3$ on a Varian VXR-400.

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3-Hydroxy-pent-4-enoic acid (-)-menthyl ester: racemic mixture at C(3)**;** ^{1}H NMR ($CDCl_3$): δ 0.67-1.13 (m, 12H), 1.30-1.58 (m, 2H), 1.60-1.75 (m, 2H), 1.75-1.93 (m, 1H), 1.93-2.08 (m, 1H), 2.50 (dd, 1H, J=8.1 and 16.2 Hz), 2.59 (dd, 1H, J=4.5 and 16.2 Hz), 3.08 (br d, 1H, J=17.1 Hz), 4.45-4.60 (m, 1H), 4.74 (dt, 1H, J=4.5, 11.1 Hz), 5.16 (d, 1H, J=10.5 Hz), 5.32 (d, 1H, J=17.1 Hz), 5.88 (ddd, 1H, J=5.4, 10.5, 17.1 Hz); ^{13}C NMR ($CDCl_3$ average values): δ 16.2, 20.7, 21.9, 23.3, 26.2, 31.3, 34.1, 40.8, 41.2, 46.9, 68.9, 74.8, 115.3, 138.7 and 171.9; IR (neat): 3448, 3082, 2955,

2928, 2361, 1732 cm^{-1}; Anal. Calcd for $C_{15}H_{26}O_3$: C, 70.83; H, 10.30. Found: C. 71.01; H, 9.93: **3-Oxo-pent-4-enoic acid (-)-menthyl ester:** keto enol mixture; ^1H NMR ($CDCl_3$): δ 0.68-1.22 (m, 12H), 1.26-1.60 (m, 2H), 1.60-1.78 (m, 2H), 1.78-1.95 (m, 1H), 1.95-2.10 (m, 1H), 3.43 and 3.63 (s, ketonic 2H at C(2)), 4.60-4.95 (m or overlapping dt, 1H), 5.06 (s, enolic 1H at C(2)), 5.53 (t, ketonic 1H at C(4), J=6.3 Hz), 5.94 (d, enolic 1H at C(5), J=10.2 Hz), 6.10 (d, ketonic 2H at C(5), J=6.3 Hz), 6.27 (d, enolic 1H at C(5), J=17.7 Hz), 6.35-6.60 (m, enolic 1H at C(5)), 11.89 (s, enol OH); IR (neat): 3103, 2956, 2929, 2870, 2361, 1736, 1656, 1588 cm^{-1}; Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.89; H, 9.59. Found: C. 71.61; H, 9.52.

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