

O-(2-Oxopyrrolidin-5-yl)trichloroacetimidates as Amidoalkylating Agents – Synthesis of (+)-Lentiginosine

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Keywords: Amidoalkylation / Trichloroacetimidate / Synthesis / Indolizidines / Glycosidase Inhibitor / Lentiginosine

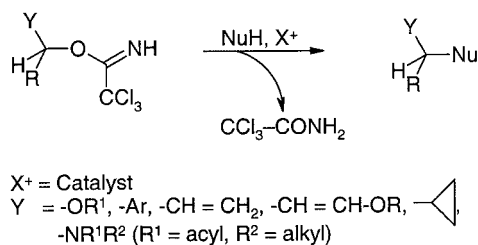
N- α -Hydroxyalkylamides **6a,b**, readily available from L-tartarate, with trichloroacetonitrile furnish *O*-(2-oxopyrrolidin-5-yl)trichloroacetimidates **3a,b**. α -Amido-alkylation studies of **3a,b** with allyl-trimethylsilane and electron-rich benzene derivatives as *C*-nucleophiles afforded 5-allyl- and 5-aryl-2-pyrrolidinones **2a,b**, **7a,b**, and **8–10**. The target compound

(+)-**1** and its epimer **15** were readily obtained from 1,5-diallyl-2-pyrrolidinones **2b** and **7b**, respectively, via ring-closing metathesis, amide group reduction, and CC-double bond hydrogenation.

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Introduction

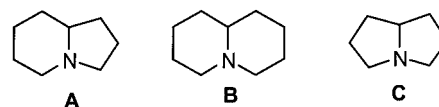
The transformation of *O,O*- and *N,O*-halfacetals into trichloroacetimidoyl derivatives and their acid-catalyzed activation has proven to be a highly attractive and powerful alternative to the classical glycosylation methods. It is currently one of the most frequently applied strategies for glycoside bond formation (Scheme 1, Y = OR, NR¹R²).^[1–5] Other systems supporting carbonium ion generation such as benzyl, allyl, oxyallyl, cyclopropylmethyl (i.e., Y = –Ar, –CH=CH₂, –CH=CH–OR, cyclopropyl, etc.) can also be transformed into the corresponding trichloroacetimidate (TCAI) and then employed in these valuable acid-catalyzed alkylation reactions.^[6–9]



Scheme 1. Acid-catalyzed alkylation of nucleophiles with *O*-alkyl trichloroacetimidate derivatives

The *N*-acyl-*N*- α -hydroxyalkyl systems, out of the various possibilities for extension of this reaction principle, seemed to be of considerable interest for various reasons: (i) structurally different starting materials are readily available, (ii) they can be conveniently transformed into the required trichloroacetimidates; (iii) activation of these *O,N*-acetal derivatives in order to perform α -amidoalkylations^[10,11] can be carried out under mild conditions with catalytic amounts of acid, and (iv) thus, also access to sensitive target molecules is permitted. α -Amidoalkylation has been extensively investigated^[10] and the intermediates thereof have been employed in polar cycloadditions.^[11]

After a specific application of this reaction principle to the synthesis of *C*-glycosides of glucosidase inhibitor nojirimycin,^[12] we would like to demonstrate the general usefulness of this concept in the synthesis of the indolizidine ring system (Scheme 2, **A**). Quinolizidine (Scheme 2, **B**) and pyrrolizidine (Scheme 2, **C**) skeleton based compounds should be equally accessible. The target compound in this paper is (+)-lentiginosine [Scheme 3, (+)-**1**] which is also an efficient glucosidase inhibitor.^[13] Different synthetic routes towards **1** have been reported previously.^[14–19] The retrosynthesis in Scheme 3 exhibits that 1,5-diallylpyrrolidinone intermediate **2** which should be readily available from *O*-(2-oxopyrrolidin-5-yl)trichloroacetimidate will provide this compound in an efficient manner. The designed ring-clos-

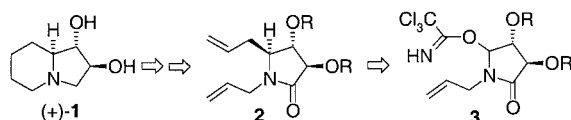


Scheme 2. Important nitrogen-fused bicyclic systems

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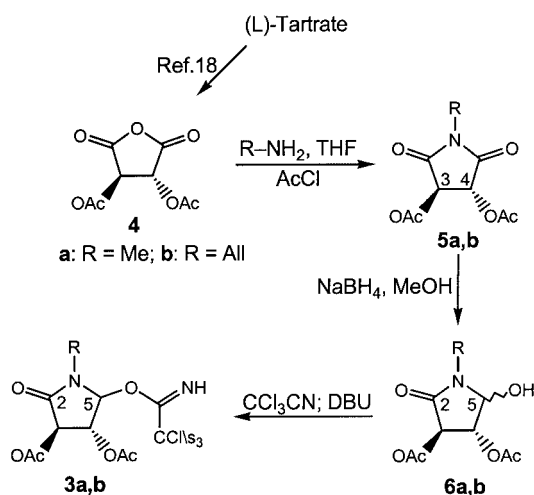
ing metathesis to attach a cyclohexene ring to the pyrrolidinone ring has been already successfully probed.^[19–21]



Scheme 3. Structure of (+)-Lentiginosine (**1**); retrosynthesis with **2** and **3** as intermediates

Results and Discussion

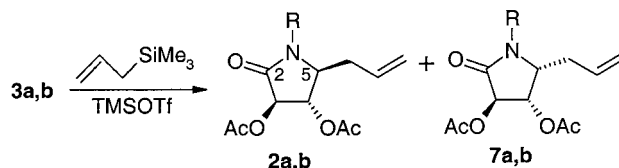
Cheap L-tartrate was transformed into anhydride **4** (Scheme 4) and then with methyl and allylamine into imides



Scheme 4. Synthesis of *O*-(2-oxopyrrolidin-5-yl)trichloroacetimidates **3a,b**

5a^[22] and **5b**, respectively. Reduction with sodium borohydride in methanol afforded 5-hydroxypyrrolidinone derivatives **6a,b**. Treatment with trichloroacetonitrile in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base furnished trichloroacetimidates **3a,b** in high yields. Only one diastereoisomer was obtained, which based on the $J_{4,5}$ -coupling constant of 2.4 Hz seems to be the (5*S*)-isomer, as will be shown below.

Trichloroacetimidates **3a,b** were employed for the α -amidoalkylation studies with different *C*-nucleophiles. Reaction of trichloroacetimidate **3a** with allyl-trimethylsilane as *C*-nucleophile in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst afforded a 1:2 ratio of 5-*C*-allyl derivatives **2a** and **7a** (Scheme 5). Similarly, from **3b** the desired 1,5-diallyl-2-pyrrolidinones **2b** and **7b** were obtained in a 1:1 ratio in almost quantitative yield (96%). Separation of the diastereomers **2a/7a** and **2b/7b** was readily accomplished by silica gel chromatography. The structural assignment was based on the ¹H NMR spectroscopic data of the ring protons ($J_{4,5} \approx 8$ Hz for **2a,b** and $J_{4,5} \approx 5$ Hz for **7a,b**, see Table 1) and the final transformation of **2b** into known target compound (+)-**1** and **7b** into its epimer.



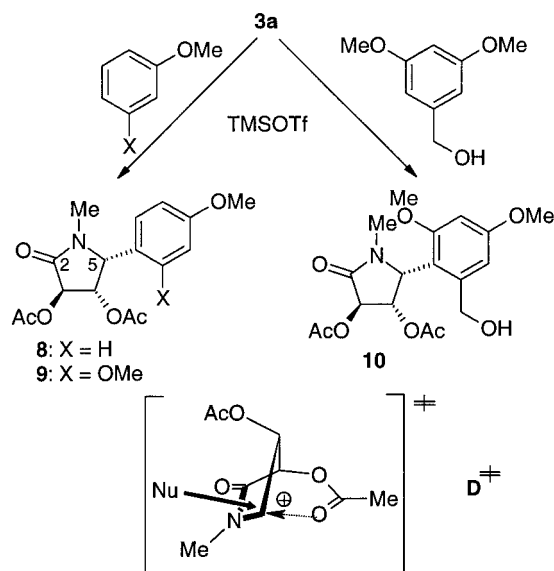
Scheme 5. Allylation of **3a,b** with allyltrimethylsilane

Reaction of trichloroacetimidate **3a** with electron-rich phenyl ethers as potential *C*-nucleophiles led to 5-aryl-2-pyrrolidinones **8–10** (Scheme 6). Even with 3,5-dimethoxybenzyl alcohol as nucleophile *C*-amidoalkylation, presumably via *O*-amidoalkylation,^[23] was observed. In all cases

Table 1. ¹H NMR spectroscopic data of compounds **2a,b**, **7a,b**, **8–15**, and (+)-**1**

No.	3-H	4-H	5-H
2a	5.58 (d, $J = 8.0$ Hz, 1 H)	5.40 (dd, $J = 8.0, 8.0$ Hz, 1 H)	3.91 (ddd, $J = 4.0, 8.0, 10.1$ Hz, 1 H)
2b	5.61 (d, $J = 8.1$ Hz, 1 H)	5.37 (dd, $J = 8.0, 8.1$ Hz, 1 H)	3.99 (ddd, $J = 4.4, 8.0, 9.8$ Hz, 1 H)
7a	5.36 (d, $J = 5.0$ Hz, 1 H)	5.13 (dd, $J = 5.0, 5.0$ Hz, 1 H)	3.52 (ddd, $J = 3.7, 5.0, 8.2$ Hz, 1 H)
7b	5.38 (d, $J = 5.0$ Hz, 1 H)	5.14 (dd, $J = 5.0, 5.0$ Hz, 1 H)	3.60 (ddd, $J = 3.4, 5.0, 8.5$ Hz, 1 H)
8	5.48 (d, $J = 5.0$ Hz, 1 H)	5.40 (dd, $J = 5.0, 4.9$ Hz, 1 H)	4.69 (d, $J = 5.0$ Hz, 1 H)
9	5.49 (d, $J = 5.0$ Hz, 1 H)	5.42 (dd, $J = 5.0, 5.0$ Hz, 1 H)	4.62 (d, $J = 5.0$ Hz, 1 H)
10	5.58 (d, $J = 4.6$ Hz, 1 H)	5.45 (dd, $J = 4.6, 4.6$ Hz, 1 H)	4.82 (d, $J = 4.6$ Hz, 1 H)
	2-H	1-H	8a-H
11	5.48 (d, $J = 7.3$ Hz, 1 H)	5.45 (dd, $J = 7.3, 6.6$ Hz, 1 H)	4.02 (ddd, $J = 4.4, 7.3, 11.4$ Hz, 1 H)
12	5.45 (d, $J = 5.0$ Hz, 1 H)	5.07 (dd, $J = 5.0, 5.0$ Hz, 1 H)	3.50 (dt, $J = 5.0, 4.5$ Hz, 1 H)
13	4.03 (ddd, $J = 1.8, 3.9, 7.4$ Hz, 1 H)	3.61 (dd, $J = 4.0, 8.1$ Hz, 1 H)	2.19 (dt, $J = 1.9, 4.0$ Hz, 1 H)
14	4.02 (ddd, $J = 1.5, 6.8, 8.2$ Hz, 1 H)	3.91 (dd, $J = 1.5, 5.3$ Hz, 1 H)	2.48 (dt, $J = 4.7, 5.3$ Hz, 1 H)
(+)- 1	4.03 (ddd, $J = 1.8, 4.0, 7.4$ Hz, 1 H)	3.61 (dd, $J = 4.0, 8.8$ Hz, 1 H)	1.85, m, 1 H)
15	3.97 (dd, $J = 6.8, 6.9$ Hz, 1 H)	3.83 (d, $J = 5.0$ Hz, 1 H)	2.12, m, 1 H)

only one stereoisomer was obtained in good yield. Because of the $J_{4,5}$ -coupling constant of ca. 5 Hz (see Table 1) (*S*)-configuration was assigned at C-5. This result is unexpected, since neighboring group participation of the 4-*O*-acetyl group in the stereocontrol does not seem to be effective; but



Scheme 6. Arylation of **3b** with electron-rich aromatic compounds

it is rather the 3-*O*-acetyl group that provides anchimeric assistance (see $D^\ddagger$ in Scheme 6), which leads to products **8–10**.

Transformation of **2b** into the target molecule (+)-**1** could be performed as indicated in Scheme 7. Ring-closing metathesis of **2b** with the Grubbs catalyst^[24,25] afforded indolizinone derivative **11** in 78% yield. Similarly, from **7b** epimeric indolizinone **12** was obtained. Treatment of **11** and **12** with lithium aluminium hydride in THF led to the reduction of the amide group to the corresponding amine and to concomitant removal of the *O*-acetyl groups, thus affording 1,2-dihydroxyindolizines **13** and **14**, respectively. The CC-double bond in **13** and **14** was hydrogenated under standard conditions, furnishing target compound (+)-**1** and its epimeric indolizidine derivative **15** in good overall yields. The physical data of these compounds (m.p., $[\alpha]_D$, and NMR) are in agreement with those reported in the literature [(+)-**1**,^[14] **15**^[26]].

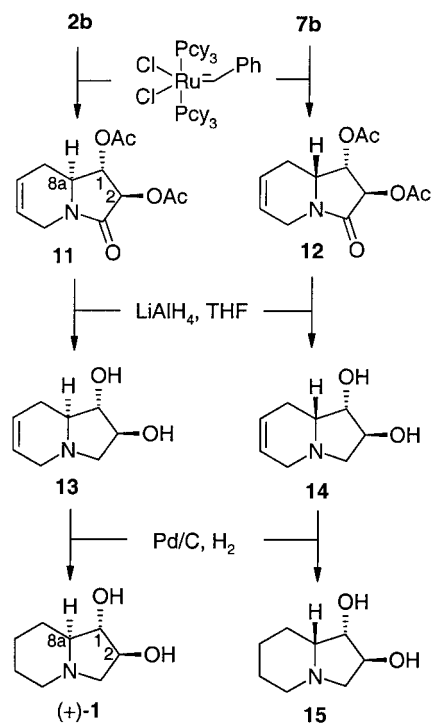
Conclusion

Readily available trichloroacetimidates **3** are excellent precursors for α -amidoalkylation reactions, for instance, of various *C*-nucleophiles. As the corresponding *O*-glycosyl trichloroacetimidates, these precursors require only catalytic amounts of acid for activation. This concept can be employed in the synthesis of nitrogen fused bicyclic systems. This is exhibited in efficient syntheses of indolizidine derivatives (+)-**1** and **15**.

Experimental Section

General Remarks: All air-sensitive and/or water-sensitive reactions were carried out under argon with dry solvents under anhydrous conditions. Reactions were monitored by TLC carried out on Merck silica gel-coated plastic sheets (60 F₂₅₄) by using UV light as visualizing agent and 5% (NH₄)₂MoO₄, 0.1% Ce(SO₄)₂ in 10% H₂SO₄ and heat as developing agents. Baker silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. NMR spectra were recorded with Bruker DRX 600 (600 MHz) and AC 250 (250 MHz) instruments and calibrated using tetramethylsilane as internal standard. Optical rotations were recorded with a Perkin–Elmer 241 MC polarimeter in a 1-dm cell at 22 °C. FAB mass spectra were recorded with a Finnigan MAT 312/AMD 5000 spectrometer with 3-nitrobenzyl alcohol matrix. EI mass spectra were recorded on a Finnigan MAT 312.

(3*R*,4*R*)-4-(Acetyloxy)-1-methyl-2,5-dioxypyrrolidin-3-yl Acetate (5a):^[22] A mixture of L-tartaric acid (26.64 g, 177.6 mmol) and acetyl chloride (90 mL, 1.27 mol) was stirred under reflux for 30 h during which the solution became homogeneous. Excess acetyl chloride was removed by distillation at 1 atm, and trace amounts were removed under vacuum. The crude anhydride **4** was dissolved in THF (120 mL) and methylamine (14.5 mL, 470 mmol) was slowly added. After the solution was stirred for 2 h, it was concentrated in vacuo and the residue was refluxed with acetyl chloride (90 mL, 1.27 mol) for another 5 h. After concentration of the reaction mixture in vacuo, the residue was purified by using column chromatography (petroleum ether/ethyl acetate, 1:1) to give **5a** (yield 24.89 g, 88%) as a pale yellow oil. $[\alpha]_D = +53.4$ ($c = 4$,



Scheme 7. Synthesis of target molecule (+)-**1** and its epimer **15**

MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.06 (s, 6 H, Ac), 2.94 (s, 3 H, NCH_3), 5.42 (s, 2 H, CHOAc) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): δ = 19.9, 24.9, 72.4, 169.4, 169.7 ppm. EI-FAB: m/z (%) = 229 (10) [M^+], 187 (69), 169 (100), 145 (62), 127 (60), 116 (25), 102 (90). $\text{C}_9\text{H}_{11}\text{NO}_6$ (229.2): calcd. C 47.16, H 4.83, N 6.11; found C 47.20, H 4.90, N 6.12.

(3R,4R)-4-(Acetyloxy)-1-allyl-2,5-dioxopyrrolidin-3-yl Acetate (5b): Allylamine (0.34 mL, 4.6 mmol) in acetic acid (30 mL) was added to a solution of anhydride **4** (0.99 g, 4.6 mmol). The mixture was stirred under reflux for 3 h. The residue after solvent evaporation was subjected to flash chromatography (petroleum ether/ethyl acetate, 20:1) to give **5b** (yield 1.0 g, 87%) as a pale yellow solid m.p. 53–54 °C [α]_D = +98.3 (c = 1.7, MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.14 (s, 3 H, Ac.), 2.17 (s, 3 H, Ac.), 4.16 (dd, J = 5.8, 9.3 Hz, 2 H, N-CH_2), 5.24 (m, 2 H, $\text{NCH}_2\text{CH=CH}_2$), 5.50 (s, 2 H, CHOAc), 5.80 (m, 1 H, $\text{NCH}_2\text{CH=CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): δ = 20.3, 41.4, 72.7, 119.1, 129.4, 168.8, 169.8 ppm. EI-FAB: m/z (%) = 255.2 (15) [M^+], 153 (37), 136 (45), 102 (57), 69 (80), 60 (100). $\text{C}_{11}\text{H}_{13}\text{NO}_6$ (255.2): calcd. C 51.76, H 5.13, N 5.49; found C 51.65, H 5.11, N 5.50.

(3R,4R)-4-(Acetyloxy)-5-hydroxy-1-methyl-2-oxopyrrolidin-3-yl Acetate (6a): Sodium borohydride (875 mg, 23.1 mmol) was added in one portion to a stirred solution of **5a** (4.57 mmol) in methanol (125 mL), cooled to –7 °C in an ice-salt bath, and the resulting solution was stirred for 12 min. The reaction mixture was partitioned between 200 mL of CH_2Cl_2 , 100 mL of saturated aqueous sodium bicarbonate and water (50 mL). The layers were separated and the aqueous phase was extracted with three 150 mL portions of CH_2Cl_2 . The combined organic phases were dried (MgSO_4) and concentrated in vacuo to give **6a** as a white solid (yield 0.98 g, 89%), m.p. 75 °C, which was isolated by column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1). [α]_D = –25.4 (c = 1.6, MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.05 (s, 3 H, Ac.), 2.06 (s, 3 H, Ac.), 2.83 (s, 3 H, NCH_3), 4.90 (br.s, 1 H, OH), 5.01 (d, J = 2.9 Hz, 1 H, CHOAc), 5.04–5.15 (m, 2 H, CHOAc and NCHO) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): δ = 20.3, 20.5, 26.5, 73.8, 78.7, 84.9, 167.0, 170.1, 170.2 ppm. EI-FAB: m/z (%) = 231 (5) [M^+], 171 (65), 129 (100), 112 (30), 102 (80), 71 (32), 60 (86). $\text{C}_9\text{H}_{13}\text{NO}_6$ (231.2): calcd. C 46.75, H 5.67, N 6.05; found C 46.51, H 5.56, N 6.00.

(3R,4R)-4-(Acetyloxy)-1-allyl-5-hydroxy-2-oxopyrrolidin-3-yl Acetate (6b): Preparation was performed as described for **6a** furnishing a pale yellow oil which was chromatographed on silica gel (petroleum ether/ethyl acetate, 2:1) to give **6b** (yield 1.169 g, 89%). [α]_D = +8.1 (c = 1.5, MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.12 (s, 3 H, Ac.), 2.14 (s, 3 H, Ac.), 3.60 (dd, J = 7.3, 15.2 Hz, 1 H, $\text{NCH}_2\text{CH=CH}_2$), 4.10 (m, 1 H, $\text{NCH}_2\text{CH=CH}_2$), 4.90–5.30 (m, 6H), 5.70 (m, 1 H, $\text{NCH}_2\text{CH=CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): δ = 21.2, 21.3, 42.7, 74.9, 79.6, 84.2, 119.5, 131.7, 167.4, 171.0, 171.2 ppm. EI-FAB: m/z (%) = 257 (15) [M^+], 197 (35), 155 (70), 138 (30), 86 (40), 94 (100). $\text{C}_{11}\text{H}_{15}\text{NO}_6$ (257.2): calcd. C 51.36, H 5.88, N 5.44; found C 51.30, H 5.56, N 4.99.

Trichloroacetimidate 3a: A stirred solution of **6a** (1.28 g, 5 mmol) in dry CH_2Cl_2 (15 mL) and trichloroacetonitrile (5 mL, 50 mmol) was treated with DBU (71 μL) at 0 °C and then left for 10 min. The solvent was evaporated and the product purified by column chromatography (5% triethylamine in toluene) to give **3a** as a pale yellow oil (yield 1.48 g, 72%). [α]_D = +50.9 (c = 1.8, MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.01 (s, 3 H, Ac.), 2.03 (s, 3 H, Ac.), 2.91 (s, 3 H, NCH_3), 5.30 (m, 2 H, 3-H, 4-H), 6.19 (d, J = 2.4 Hz, 1 H, 5-H), 8.60 (br.s, 1 H, NH) ppm. ^{13}C NMR (CDCl_3 ,

62.8 MHz): δ = 20.4, 20.5, 26.9, 74.1, 78.6, 85.1, 162.2, 167.9, 170.1, 170.3 ppm.

Trichloroacetimidate 3b: Preparation was performed as described for **3a** from **6b** furnishing **3b** as a pale yellow oil (yield 1.49 g, 75%). [α]_D = +72 (c = 1.8, MeOH). ^1H NMR (CDCl_3 , 250 MHz): δ = 2.08 (s, 3 H, Ac.), 2.09 (s, 3 H, Ac.), 3.67 (dd, J = 7.4, 15.3 Hz, 1 H, $\text{NCH}_2\text{CH=CH}_2$), 4.30 (m, 1 H, $\text{NCH}_2\text{CH=CH}_2$), 5.27 (m, 4 H, 3-H, 4-H, $\text{NCH}_2\text{CH=CH}_2$), 5.68 (m, 1 H, $\text{NCH}_2\text{CH=CH}_2$), 6.13 (d, J = 2.4 Hz, 1 H, 5-H), 8.57 (br.s, 1 H, NH) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): δ = 21.0, 21.2, 44.0, 73.6, 75.3, 89.0, 120.2, 131.2, 161.2, 168.6, 169.6, 169.9 ppm. EI-FAB: m/z (%) = 401 (10) [M^+], 342 (12), 257 (15), 240 (17), 197 (30), 155 (55), 138 (100), 117 (60).

General Procedure for the Reaction of Trichloroacetimidates with Nucleophiles: A solution of trichloroacetimidate **3a** or **3b** (1.4 mmol) and the nucleophiles allyltrimethylsilane, anisol, dimethylresorcin, and 3,5-dimethoxybenzyl alcohol (1.4 mmol), respectively, in dry dichloromethane (15 mL) was treated with TMSOTf (0.15 mL) and then stirred for 30–120 min. The reaction was quenched by addition of solid sodium bicarbonate, diluted with dichloromethane, filtered, and concentrated. The crude residue was purified by column chromatography on silica gel to give **2a,b**, **7a,b**, **8**, **9**, and **10**, respectively.

(3R,4S,5S)-4-(Acetyloxy)-5-allyl-1-methyl-2-oxopyrrolidin-3-yl Acetate (2a) and (3R,4S,5R)-4-(Acetyloxy)-5-allyl-1-methyl-2-oxopyrrolidin-3-yl Acetate (7a): Reaction of **3a** with allyltrimethylsilane afforded **2a** and **7a**.

2a: Column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) afforded **2a** as a colorless oil (yield 114 mg, 32%). [α]_D = +82.7 (c = 0.7, MeOH). ^1H NMR (CDCl_3 , 600 MHz): δ = 2.11 (s, 3 H, Ac.), 2.16 (s, 3 H, Ac.), 2.27 (dt, J = 4.9, 5.6 Hz, 1 H, $\text{CH}_2\text{CH=CH}_2$), 2.40 (dt, J = 6.6, 6.7 Hz, 1 H, $\text{CH}_2\text{CH=CH}_2$), 2.87 (s, 3 H, NCH_3), 3.91 (ddd, J = 4.0, 8.0, 10.1 Hz, 1 H, 5-H), 5.16 (dd, J = 0.9, 8.7 Hz, 2 H, $\text{CH}_2\text{CH=CH}_2$), 5.40 (dd, J = 8.0, 8.0 Hz, 1 H, 4-H), 5.58 (d, J = 8.0 Hz, 1 H, 3-H), 5.72 (m, 1 H, $\text{CH}_2\text{CH=CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): δ = 20.7, 28.8, 32.5, 58.5, 72.4, 73.2, 119.9, 132.3, 166.7, 169.9, 170.3 ppm. EI-FAB: m/z (%) = 214 (30) [M^+ – allyl], 154 (40), 112 (100). $\text{C}_{12}\text{H}_{17}\text{NO}_5$ (255.3): calcd. C 56.46, H 6.71, N 5.49; found C 56.60, H 6.54, N 5.70.

7a: Column chromatography on silica gel (petroleum ether/ethyl acetate, 2:1) afforded **7a** as a colorless oil (yield 67 mg, 16%). [α]_D = +38.7 (c = 1.6, MeOH). ^1H NMR (CDCl_3 , 600 MHz): δ = 2.07 (s, 3 H, Ac.), 2.13 (s, 3 H, Ac.), 2.40 (dt, J = 6.7, 7.6 Hz, 1 H, $\text{CH}_2\text{CH=CH}_2$), 2.52 (m, 1 H, $\text{CH}_2\text{CH=CH}_2$), 2.87 (s, 3 H, NCH_3), 3.52 (ddd, J = 3.7, 5.0, 8.2 Hz, 1 H, 5-H), 5.13 (dd, J = 5.0, 5.0 Hz, 1 H, 4-H), 5.19 (m, 2 H, $\text{CH}_2\text{CH=CH}_2$), 5.36 (d, J = 5.0 Hz, 1 H, 3-H), 5.67 (m, 1 H, $\text{CH}_2\text{CH=CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): δ = 20.6, 20.7, 28.9, 34.8, 60.9, 74.3, 119.9, 120.0, 130.9, 167.5, 170.0 ppm. EI-FAB: m/z (%) = 214 (30) [M^+ – allyl], 154 (38), 112 (100). $\text{C}_{12}\text{H}_{17}\text{NO}_5$ (255.3): calcd. C 56.46, H 6.71, N 5.49; found C 56.68, H 6.45, N 5.80.

(3R,4S,5S)-4-(Acetyloxy)-1,5-(diallyl)-2-oxopyrrolidin-3-yl Acetate (2b) and (3R,4S,5R)-4-(Acetyloxy)-1,5-(diallyl)-2-oxopyrrolidin-3-yl Acetate (7b): Reaction of **3b** with allyltrimethylsilane afforded **2b** and **7b**.

2b: Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) afforded **2b** as a colorless oil (yield 0.17 g, 48%) [α]_D = +69.8 (c = 0.5, MeOH). ^1H NMR (CDCl_3 , 600 MHz): δ = 2.11

(s, 3 H, Ac.), 2.15 (s, 3 H, Ac.), 2.25 (dd, $J = 5.2$, 14.7 Hz, 1 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 2.40 (dd, $J = 7.8$, 14.0 Hz, 1 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 3.49 (dd, $J = 7.7$, 15.2 Hz, 1 H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 3.99 (ddd, $J = 4.4$, 8.0, 9.8 Hz, 1 H, 5-H), 4.42 (dd, $J = 4.6$, 15.2 Hz, 1 H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.15–5.25 (m, 4 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.37 (dd, $J = 8.0$, 8.1 Hz, 1 H, 4-H), 5.61 (d, $J = 8.1$ Hz, 1 H, 3-H) 5.69 (m, 2 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$, $\text{NCH}_2\text{CH}=\text{CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 20.7$, 32.4, 43.9, 55.3, 72.7, 73.2, 119.4, 119.9, 131.2, 132.4, 166.4, 169.9, 170.3 ppm. EI-FAB: m/z (%) = 281 (10) [M^+], 240 (35), 181 (48), 138 (100), 55 (20). $\text{C}_{14}\text{H}_{19}\text{NO}_5$ (281.3): calcd. C 59.78, H 6.81, N 4.98; found C 60.03, H 6.96, N 4.55.

7b: Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) afforded **7b** as a colorless oil (yield 170 mg, 48%). $[\alpha]_{\text{D}} = +177$ ($c = 1.0$, MeOH). ^1H NMR (CDCl_3 , 600 MHz): $\delta = 2.07$ (s, 3 H, Ac.), 2.13 (s, 3 H, Ac.), 2.37 (dd, $J = 7.2$, 14.3 Hz, 1 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 2.51 (m, 1 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$), 3.51 (dd, $J = 7.5$, 15.5 Hz, 1 H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 3.60 (ddd, $J = 3.4$, 5.0, 8.5 Hz, 1 H, 5-H), 4.42 (dd, $J = 4.5$, 15.5 Hz, 1 H, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.14 (dd, $J = 5.0$, 5.0 Hz, 1 H, 4-H), 5.18–5.23 (m, 4 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$, $\text{NCH}_2\text{CH}=\text{CH}_2$), 5.38 (d, $J = 5.0$ Hz, 1 H, 3-H), 5.67 (m, 2 H, $\text{CHCH}_2\text{CH}=\text{CH}_2$, $\text{NCH}_2\text{CH}=\text{CH}_2$) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 20.7$, 20.8, 34.8, 43.1, 58.6, 74.4, 118.9, 119.9, 131.1, 131.4, 167.3, 169.9 ppm. EI-FAB: m/z (%) = 281 (10) [M^+], 240 (32), 181 (50), 138 (100), 55 (20). $\text{C}_{14}\text{H}_{19}\text{NO}_5$ (281.3): calcd. C 59.78, H 6.81, N 4.98; found C 59.38, H 6.78, N 4.78.

(3R,4S)-4-(Acetyloxy)-5-(4-methoxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl Acetate (8): Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) afforded **8** as a colorless oil (310 mg, 68%). $[\alpha]_{\text{D}} = -21.68$ ($c = 1.9$, MeOH). ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.02$ (s, 3 H, Ac.), 2.10 (s, 3 H, Ac.), 2.61 (s, 3 H, NCH_3), 3.79 (s, 6 H, OCH_3), 4.69 (d, $J = 5.0$ Hz, 1 H, 5-H), 5.40 (dd, $J = 5.0$, 4.9 Hz, 1 H, 4-H), 5.48 (d, $J = 5.0$, 1 H, 3-H), 6.90–7.30 (m, 4 H, Ph-H) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): $\delta = 20.6$, 27.9, 55.3, 62.2, 74.6, 76.5, 111.0, 114.4, 120.8, 123.6, 128.8, 130.2, 157.6, 167.8, 169.6, 169.8 ppm. EI-FAB: m/z (%) = 321 (20) [M^+], 261 (55), 219 (100), 202 (20), 150 (40), 91 (20). $\text{C}_{16}\text{H}_{19}\text{NO}_6$ (321.3): calcd. C 59.81, H 5.96, N 4.35; found C 59.89, H 6.29, N 4.33.

(3R,4S)-4-(Acetyloxy)-5-(2,4-dimethoxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl Acetate (9): Column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) afforded **9** as a colorless oil (yield 350 mg, 70%). $[\alpha]_{\text{D}} = -40.8$ ($c = 1.0$, MeOH). ^1H NMR (CDCl_3 , 250 MHz): $\delta = 2.03$ (s, 3 H, Ac.), 2.13 (s, 3 H, Ac.), 2.61 (s, 3 H, NCH_3), 3.79 (s, 6 H, OCH_3), 4.62 (d, $J = 5.0$ Hz, 1 H, 5-H), 5.42 (dd, $J = 5.0$, 5.0 Hz, 1 H, 4-H), 5.49 (d, $J = 5.0$, 1 H, 3-H), 6.46 (m, 2 H, Ph-H), 7.04 (d, $J = 8.5$ Hz, 1 H, Ph-H) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): $\delta = 20.8$, 28.0, 55.5, 55.6, 62.0, 74.9, 76.7, 99.1, 104.2, 104.9, 116.1, 130.1, 159.0, 162.0, 167.7, 169.9, 170.1 ppm. EI-FAB: m/z (%) = 351 (7) [M^+], 291 (55), 249 (100), 232 (37), 180 (47), 149 (17). $\text{C}_{17}\text{H}_{21}\text{NO}_7$ (351.3): calcd. C 58.11, H 6.02, N 3.99; found C 58.54, H 6.41, N 3.83.

(3R,4S)-4-(Acetyloxy)-5-(6-hydroxymethyl-2,4-dimethoxyphenyl)-1-methyl-2-oxopyrrolidin-3-yl Acetate (10): Column chromatography on silica gel (petroleum ether/ethyl acetate, 1:1) afforded **10** as a colorless oil (yield 350 mg, 65%). $[\alpha]_{\text{D}} = -15.9$ ($c = 2.2$, MeOH). ^1H NMR (CDCl_3 , 250 MHz): $\delta = 1.97$ (s, 3 H, Ac.), 2.10 (s, 3 H, Ac.), 2.40 (br s, 1 H, OH), 2.48 (s, 3 H, NCH_3), 3.72 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.54 (2d, $J = 12.0$ Hz, 2 H, CH_2OH), 4.82 (d, $J = 4.6$ Hz, 1 H, 5-H), 5.45 (dd, $J = 4.6$, 4.6 Hz, 1 H, 4-H), 5.58 (d, $J = 4.6$ Hz, 1 H, 3-H), 6.36 (d, $J = 2.4$ Hz, 1 H,

Ph-H), 6.43 (d, $J = 2.4$ Hz, 1 H, Ph-H) ppm. ^{13}C NMR (CDCl_3 , 62.8 MHz): $\delta = 20.6$, 20.7, 27.4, 55.3, 55.4, 60.4, 63.3, 74.8, 75.0, 98.4, 106.0, 114.1, 142.0, 159.7, 160.9, 168.1, 170.0, 170.4 ppm. EI-FAB: m/z (%) = 351 (10) [$\text{M}^+ - \text{CHO}$], 291 (35), 249 (100), 232 (30), 180 (45), 149 (35), 91 (20), 77 (25). $\text{C}_{18}\text{H}_{23}\text{NO}_8$ (381.4): calcd. C 56.68, H 6.08, N 3.67; found C 56.69, H 6.51, N 3.92.

General Procedure for Olefin Metathesis

Synthesis of Dehydroindolizinones 11 and 12: A solution of {bis(tricyclohexylphosphane)benzylidene}ruthenium(IV) dichloride (Grubbs') catalyst (0.003 g, 0.004 mmol) in CH_2Cl_2 (5 mL) was added to a solution of **2b** or **7b** (281 mg, 1 mmol) in CH_2Cl_2 (10 mL), under an argon atmosphere. The mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the oily residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate, 5:1) to give dehydroindolizinones **11** or **12**, respectively.

(1S,2R,8aS)-1,2-Diacetyloxy-1,2,3,5,8,8a-hexahydro-3-indolizinone (11): Colorless oil (196 mg, 78%). $[\alpha]_{\text{D}} = +26.2$ ($c = 0.9$, MeOH). ^1H NMR (CDCl_3 , 600 MHz): $\delta = 2.05$ (m, 1 H, 8-H), 2.15 (s, 3 H, Ac.), 2.17 (s, 3 H, Ac.), 2.22 (m, 1 H, 8-H), 3.61 (br d, $J = 18.4$ Hz, 1 H, 5-H), 4.02 (ddd, $J = 4.4$, 7.3, 11.4 Hz, 1 H, 8a-H), 4.39 (dd, $J = 2.4$, 18.8 Hz, 1 H, 5-H), 5.45 (dd, $J = 7.3$, 6.6 Hz, 1 H, 1-H), 5.48 (d, $J = 7.3$ Hz, 1 H, 2-H), 5.71 (dd, $J = 3.0$, 10.3 Hz, 1 H, 6-H), 5.83 (m, 1 H, 7-H) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 20.7$, 30.4, 40.6, 65.6, 74.8, 78.1, 122.6, 123.8, 166.4, 169.9, 170.3 ppm.

(1S,2R,8aR)-1,2-Diacetyloxy-1,2,3,5,8,8a-hexahydro-3-indolizinone (12): Colorless oil (196 mg, 78%). $[\alpha]_{\text{D}} = +17$ ($c = 1$, MeOH). ^1H NMR (CDCl_3 , 600 MHz): $\delta = 2.13$ (s, 3 H, Ac.), 2.15 (s, 3 H, Ac.), 2.20 (m, 1 H, 8-H), 2.55 (br d, $J = 16.8$ Hz, 1 H, 8-H), 3.50 (dt, $J = 5.0$, 4.5 Hz, 1 H, 8a-H), 3.64 (br d, $J = 18.7$ Hz, 1 H, 5-H), 4.34 (dd, $J = 2.4$, 18.8 Hz, 1 H, 5-H), 5.07 (dd, $J = 5.0$, 5.0 Hz, 1 H, 1-H), 5.45 (d, $J = 5.0$ Hz, 1 H, 2-H), 5.72 (dd, $J = 2.6$, 10.3 Hz, 1 H, 7-H), 5.82 (t, $J = 7.9$ Hz, 1 H, 6-H) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 20.7$, 20.9, 25.4, 40.9, 52.7, 73.1, 74.1, 123.8, 123.9, 167.3, 169.8 ppm. EI-FAB: m/z (%) = 252 (40) [$\text{M}^+ - 1$], 211 (20), 193 (40), 151 (100), 134 (20), 82 (25). $\text{C}_{12}\text{H}_{15}\text{NO}_5$ (253.2): calcd. C 56.91, H 5.97, N 5.53; found C 56.66, H 6.35, N 5.23.

(1S,2S,8aS)-(-)-1,2-Dihydroxy-1,2,3,5,8,8a-hexahydroindolizine (13): A solution of **11** (267 mg, 1.13 mmol) dissolved in THF (10 mL) was added under argon to a suspension of LiAlH_4 in THF (0.088 g, 2.3 mmol in 5 mL) and heated at reflux for 4 h. Excess hydride was destroyed at 0 °C with 10% aq. NH_4Cl (0.3 mL), the solid was filtered and washed with ethyl acetate (30 mL). The organic phase was dried (MgSO_4) and after solvent evaporation, the crude material was purified by column chromatography on silica gel ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 10:1) to give **13** (yield 117 mg, 73%) as a white solid, m.p. 92–93 °C. $[\alpha]_{\text{D}} = +88.2$ ($c = 2.4$, MeOH). ^1H NMR (D_2O , 600 MHz): $\delta = 1.97$ (m, 1 H, 8-H), 2.19 (dt, $J = 1.9$, 4.0 Hz, 1 H, 8a-H), 2.26 (dd, $J = 4.2$, 7.1 Hz, 1 H, 8-H), 2.60 (dd, $J = 7.5$, 11.3 Hz, 1 H, 3-H), 2.71 (dt, $J = 2.2$, 1.7 Hz, 1 H, 5-H), 2.88 (dd, $J = 1.7$, 11.3 Hz, 1 H, 3-H), 3.19 (ddt, $J = 2.2$, 4.2, 2.2 Hz, 1 H, 5-H), 3.61 (dd, $J = 4.0$, 8.1 Hz, 1 H, 1-H), 4.03 (ddd, $J = 1.8$, 3.9, 7.4 Hz, 1 H, 2-H), 5.59 (dd, $J = 1.4$, 10.1 Hz, 1 H, 6-H), 5.68 (m, 1 H, 7-H) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 28.2$, 51.3, 63.3, 74.9, 83.1, 123.8, 124.1 ppm. EI-FAB: m/z (%) = 155 (40) [M^+], 95 (100), 82 (35), 67 (65), 54 (45). $\text{C}_8\text{H}_{13}\text{NO}_2$ (155.2): calcd. C 61.91, H 8.44, N 9.02; found C 61.69, H 8.54, N 8.62.

(1S,2S,8aR)-(-)-1,2-Dihydroxy-1,2,3,5,8,8a-hexahydroindolizine (14): Preparation was performed from **12** as described for **13** fur-

nishing a white solid (yield 149 mg, 75%) m.p. 86–87 °C. $[\alpha]_D = +6.1$ ($c = 1.3$, MeOH). ^1H NMR (D_2O , 600 MHz): $\delta = 1.94$ (dd, $J = 4.3$, 7.4 Hz, 1 H, 8-H), 2.01 (dd, $J = 6.4$, 10.5 Hz, 1 H, 3-H), 2.16 (ddd, $J = 2.2$, 4.5, 6.5 Hz, 1 H, 8-H), 2.48 (dt, $J = 4.7$, 5.3 Hz, 1 H, 8a-H), 2.74 (dd, $J = 2.4$, 16.2 Hz, 1 H, 5-H), 3.23 (tt, $J = 2.4$, 2.4 Hz, 1 H, 5-H), 3.37 (dd, $J = 6.9$, 10.5 Hz, 1 H, 3-H), 3.91 (dd, $J = 1.5$, 5.3 Hz, 1 H, 1-H), 4.02 (ddd, $J = 1.5$, 6.8, 8.2 Hz, 1 H, 2-H), 5.58 (m, 1 H, 6-H), 5.72 (dt, $J = 2.2$, 2.3 Hz, 1 H, 7-H) ppm. ^{13}C NMR (CDCl_3 , 150.9 MHz): $\delta = 23.7$, 51.4, 59.0, 61.2, 76.1, 77.4, 123.5, 124.7 ppm. EI-FAB: m/z (%) = 155 (40) $[\text{M}^+]$, 95 (100), 82 (30), 67 (65), 54 (45). $\text{C}_8\text{H}_{13}\text{NO}_2$ (155.2): calcd. C 61.91, H 8.44, N 9.02; found C 61.78, H 8.61, N 8.98.

(+)-Lentiginosine [(1S,2S,8aS)-(+)-1,2-Dihydroxyindolizidine] [(+)-1]: Conc'd HCl (8 drops) was added to a solution of **13** (92 mg, 0.596 mmol, in 10 mL MeOH) and the mixture was hydrogenated at 3.4 bar (0.07 g of 10% Pd on carbon). TLC monitoring indicated the reaction was complete after 14 h. NaOH soln (1.5 mL, 3 M) was added followed by filtration through Celite and column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{aq. NH}_3$, 80:18:2). The title compound **(+)-1** was obtained as a white solid (yield 69 mg, 75%), m.p. 106–107 °C (ref.^[14] 106–107 °C). $[\alpha]_D = +4.0$ ($c = 0.3$, MeOH) {ref.^[14] $[\alpha]_D = +3.2$ ($c = 0.21$, MeOH)}. ^1H NMR (D_2O , 600 MHz): $\delta = 1.13$ –1.69 (m, 5 H, 2 7-H, 2 6-H, 1 8-H), 1.81–1.85 (m, 2 H, 1 8-H, 8a-H), 2.07 (ddd, $J = 2.9$, 11.8, 16.7 Hz, 1 H, 5-H), 2.59 (dd, $J = 7.6$, 11.3 Hz, 1 H, 3-H), 2.78 (br d, $J = 11.3$ Hz, 1 H, 3-H), 2.91 (br d, $J = 11.1$ Hz, 1 H, 5-H), 3.61 (dd, $J = 4.0$, 8.8 Hz, 1 H, 1-H), 4.03 (ddd, $J = 1.8$, 4.0, 7.4 Hz, 1 H, 2-H) ppm. ^{13}C NMR (D_2O , 150.9 MHz): $\delta = 24.4$, 25.2, 29.1, 54.1, 62.1, 70.2, 78.2, 84.6 ppm. EI-FAB: m/z (%) = 157 (15) $[\text{M}^+]$, 97 (100), 84 (20), 69 (30), 55 (20). $\text{C}_8\text{H}_{15}\text{NO}_2$ (157.2): calcd. C 61.12, H 9.62, N 8.91; found C 61.16, H 9.48, N 8.58.

(1S,2S,8aR)-(–)-1,2-Dihydroxyindolizidine (15): Preparation was performed as described for **(+)-1**. The title compound was obtained as a white solid (yield 75 mg, 81%), m.p. 137–138 °C (ref.^[26] 137–138 °C). $[\alpha]_D = -5.3$ ($c = 0.3$, MeOH) {ref.^[26] $[\alpha]_D = -5.8$ ($c = 0.885$, MeOH)}. ^1H NMR (D_2O , 600 MHz): $\delta = 1.19$ –2.12 (m, 9 H, 2 7-H, 2 6-H, 2 8-H, 1 5-H, 1 8a-H, 1 3-H), 2.92 (br d, $J = 11.3$ Hz, 1 H, 5-H), 3.28 (dd, $J = 7.1$, 10.4 Hz, 1 H, 3-H), 3.83 (d, $J = 5.0$ Hz, 1 H, 1-H), 3.97 (dd, $J = 6.8$, 6.9 Hz, 1 H, 2-H) ppm. ^{13}C NMR (D_2O , 150.9 MHz): $\delta = 23.9$, 24.4, 24.8, 53.3, 61.6, 66.8, 77.7, 80.6 ppm. EI-FAB: m/z (%) = 157 (15) $[\text{M}^+]$, 97 (100), 84 (22), 69 (37), 55 (20). $\text{C}_8\text{H}_{15}\text{NO}_2$ (157.2): calcd. C 61.12, H 9.62, N 8.91; found C 60.99, H 9.62, N 8.75.

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