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BICYCLIC METHYLENE AZIRIDINE IN REACTIONS WITH C- AND N-NUCLEOPHILES

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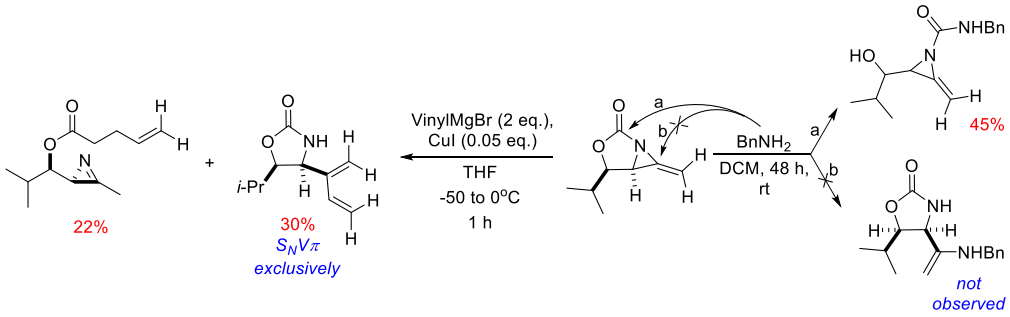
Abstract



In recent years, various catalytic synthetic methods, starting with allenes, have been developed to produce a wide range of bicyclic methylene aziridines (MA). MA are valuable intermediates for the preparation of complex amine-containing stereotriads, tetrads, and heterocycles potentially useful in the synthesis of natural products and pharmaceuticals. This work reports the possibilities of using ring opening reactions of MA in the synthesis of biologically relevant heterocyclic motifs such as aziridineurea, 2*H*-azirine and 4,5-disubstituted oxazolidin-2-one. We performed detailed studies on the reaction between model MA with vinylmagnesium bromide and found that along with formal nucleophilic vinylic substitution product minor fraction of 2-methyl-1-(3-methyl-2*H*-azirin-2-yl)propyl pent-4-enoate was isolated. We showed that investigated reactions are stereoretentive, ruling out a S_NV_π pathway, but the detailed mechanism remains open to speculation. Thus, reactivity patterns shown here for MA reactions can be useful in predicting reaction paths with other C- and N-nucleophiles. 2D NMR spectra of the key products were studied in detail including COSY, NOESY and HSQC experiments.

Keywords: azaheterocycles; 1,4-vinylation; vinylmagnesium bromide; aminolysis.

БІЦИКЛІЧНИЙ МЕТИЛЕНАЗИРИДИН В РЕАКЦІЯХ З С- ТА N-НУКЛЕОФІЛАМИ

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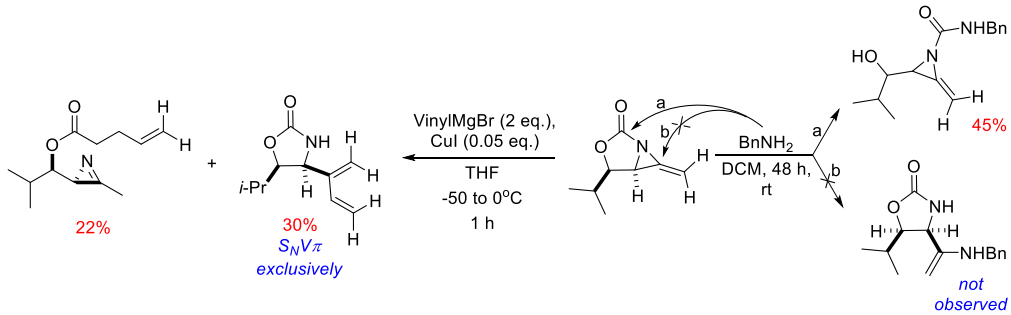
Анотація



У цій роботі повідомляється про можливості використання реакцій розкриття циклу біциклічного метиленазиридину в синтезі біологічно значущих гетероциклічних сполук, таких як азиридиносечовина, 2Н-азирин і 4,5-дизаміщений оксазолідин-2-он. Детально досліджено 2D ЯМР спектри продуктів.

Ключові слова: азагетероцикли; 1,4-вінілювання; вінілмагній бромід; аміноліз.

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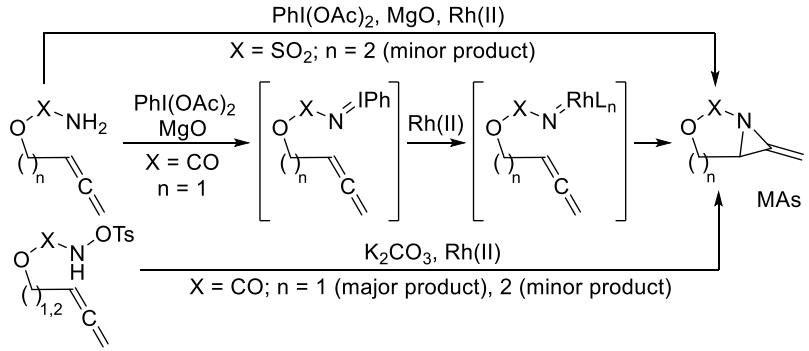
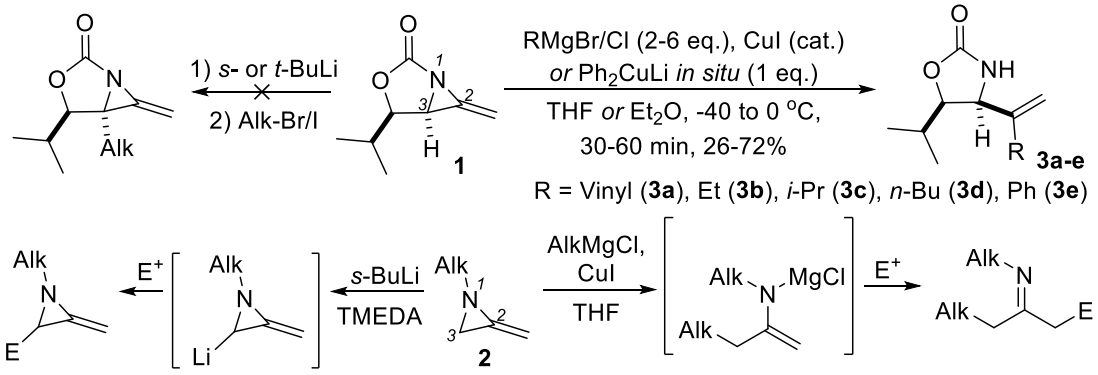
Introduction

Various catalytic synthetic methods starting from allenes have been developed in recent years to prepare wide range of bicyclic methylene aziridines (MAs) [1–7] on the basis on first report (Scheme 1) [8; 9]. MAs, prepared via intramolecular allene aziridination (isolated or *in situ*), are valuable intermediates for the preparation of complex amine-containing stereotriads, tetrads, and heterocycles potentially useful in the synthesis of natural products and pharmaceuticals. Most of these attempts are summarized in [10].



Scheme 1. Access to bicyclic MAs *via* allenic intermediates developed by Robertson [8; 9].

In [8] Robertson and co-workers described the preliminary reactivity profile of this type MAs, including the overall S_NV-mode ring-opening with organometallic reagents and found some unexpected reactivity of MA 1. Whereas carbon nucleophiles (Grignard reagents) open monocyclic MAs 2 at C-3 position [11–17], in our hands we obtained a formal S_NV products 3a-e via C-2 nucleophilic attack of MA 1. On the other hand, in reactions with AlkLi (commonly *s*-BuLi) MAs 2 readily produce aziridinyl anions by deprotonation. The anions can be alkylated with a wide variety of electrophiles (E^+), suggesting that the neighboring exocyclic double bond plays an important role in increasing the acidity of the C-3 hydrogens [18; 19] (Scheme 2).



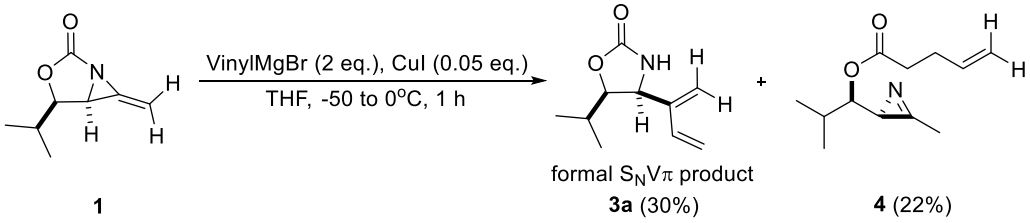
Scheme 2. Literature insights into the reactivity of mono- and bicyclic MAs with C-nucleophiles

The purpose of this work is to test the possibility of using ring opening reactions of bicyclic methylene aziridine with C- and N-nucleophiles in the synthesis of biologically relevant heterocyclic motifs.

Results and discussion

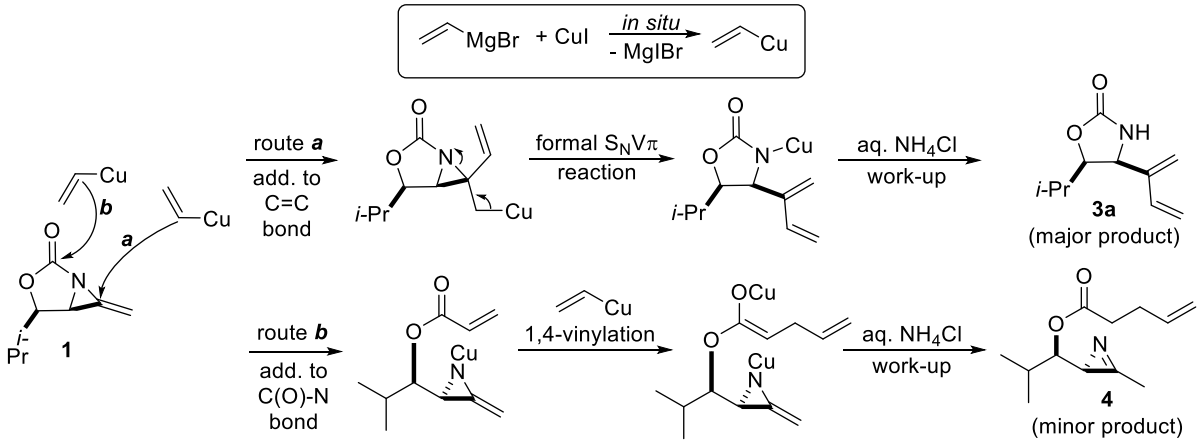
An S_N1 type reaction between MAs and C-nucleophiles can be ruled out on the basis of the conditions of the reaction (aprotic solvent) and electronic considerations (poor leaving group and high energy vinyl cation intermediate). Of the remaining alternative mechanisms, it could be a concerted process, whereby the nucleophile attacks the C-N σ* orbital (S_NV_σ) in-plane, which would be expected to proceed with inversion of configuration at the sp^2 centre. Alternatively, a carbometallation-elimination process could be involved. By this mechanism, the nucleophile would out-of-plane attack the π* orbital. This could be accompanied by some electron delocalisation into the exocyclic double bond in a concerted breaking of the C-N bond (S_NV_π). In our very recent work [20] using deuterium labeled MA-d_1 we showed that this S_NV reaction is stereoretentive, ruling out an S_NV_π pathway, but the detailed mechanism remains open to speculation. Here we performed detailed studies on the reaction between model MA 1 with

vinylmagnesium bromide and found that along with formal S_NV_π product 3a minor fraction of 2-methyl-1-(3-methyl-2*H*-azirin-2-yl)propyl pent-4-enoate 4 was isolated. The use of one equivalent of vinylmagnesium bromide led to no reaction, whilst the double excess of this reagent gave the by-product 4 (Scheme 3).



Scheme 3. The reaction of MA 1 with the double excess of vinylmagnesium bromide

Plausible mechanisms for the formation of different types of products are shown on Scheme 4. It includes the generation in situ vinylcupper species on the initial stages of the reaction and their competitive addition to MA double bond (route a) or to the carbonyl group of MA (route b). A copper-catalysed Grignard reaction with vinylmagnesium bromide afforded 4-(buta-1,3-dien-2-yl)-5-isopropyloxazolidin-2-one 3a as the major product. Formation of the azirine 4 may be explained by competing addition at the carbonyl followed by 1,4-vinylation of the so-formed *γ,δ*-unsaturated ester [21].



Scheme 4. Plausible mechanism of the formation of compounds 3a and 4 starting from MA 1.

Next, we studied the aminolysis of MA 1 with benzylamine. Under these conditions, the oxazolidinone fragment proved to be more labile. The conclusion about formation of the compound 5 (route a) instead of alternative enamine product 6 (route b) was made according to the decrease in the frequency of the stretching vibration of carbonyl group (1785→1672 cm^{-1}) (Fig. 1).

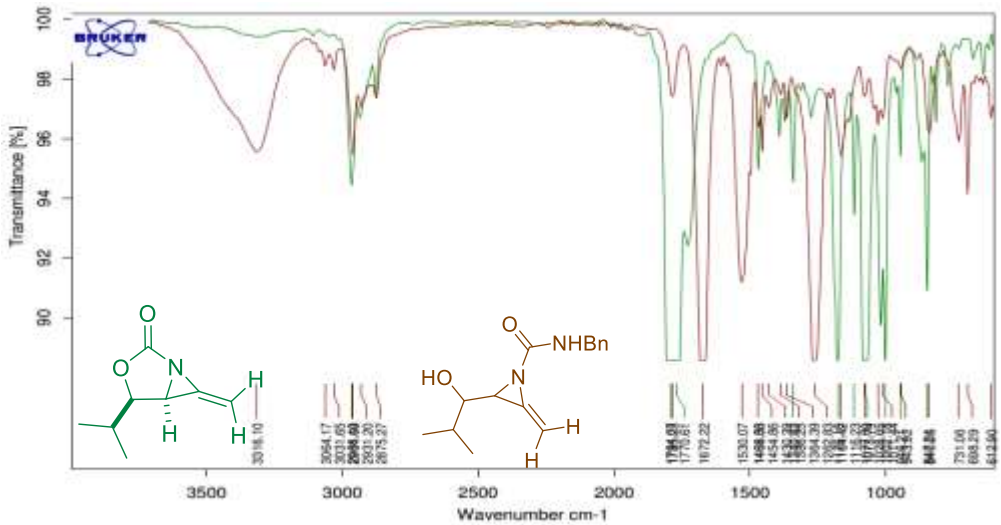


Fig. 1. IR spectra of MA 1 (*green*) and aziridineurea 5 (*red-brown*)

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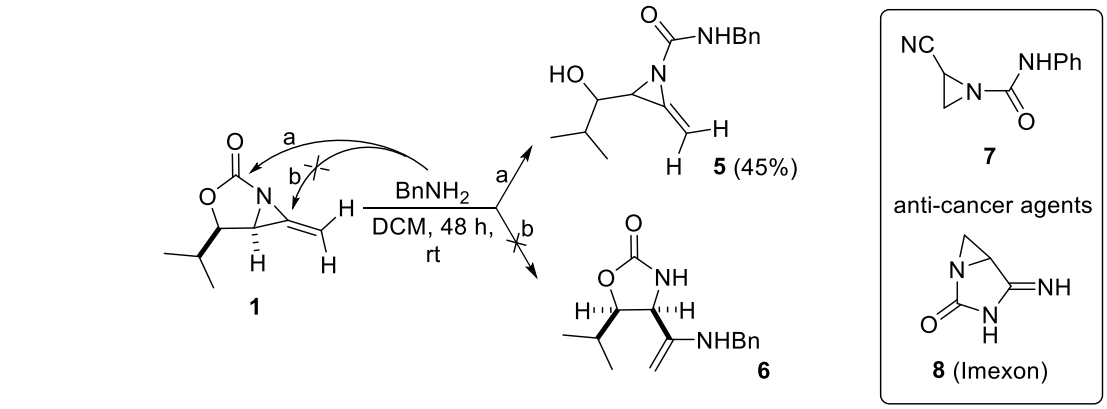
Obviously, in oxazolidin-2-one 6 stretching vibration of carbonyl fragment would not change much compared to starting MA 1. Also, a broad absorption band at 3316 cm^{-1} corresponds exactly to hydroxyl group. In the alternative structure 6, the enamine fragment stretching vibrations should be placed about 1540-1650 cm^{-1}. NMR chemical shifts and key COSY correlations to support the structure of products 4 and 5 are shown on Fig. 2. Structural similarity of the new aziridineurea 5 to known anticancer agents 7 and 8 [22–24] may have some great advantages for further investigations of the biological activity of this type of aziridines easily available from bicyclic MAs (Scheme 5).



Scheme 5. Aminolisys of MA 1 with benzylamine and examples of known strong anti-cancer aziridineureas 7, 8.

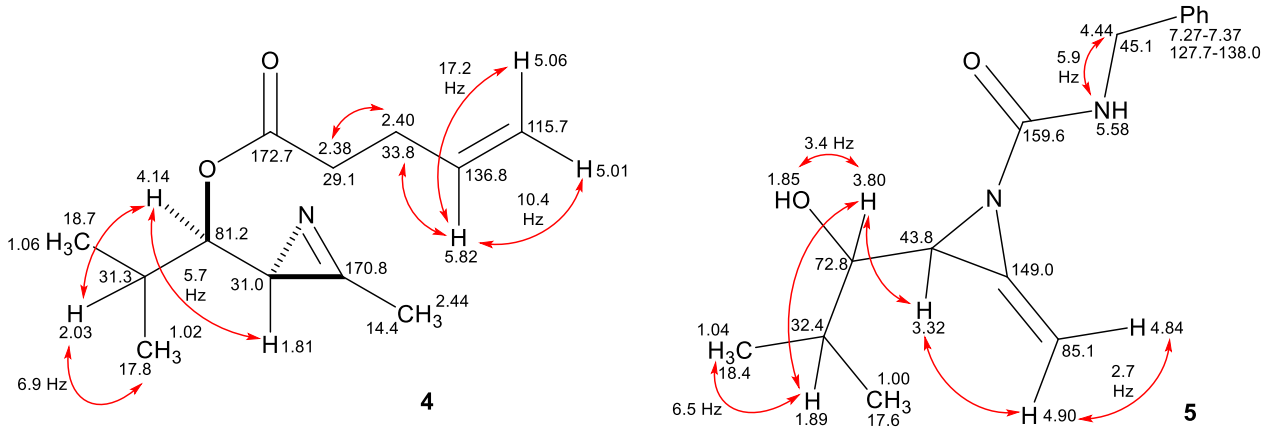
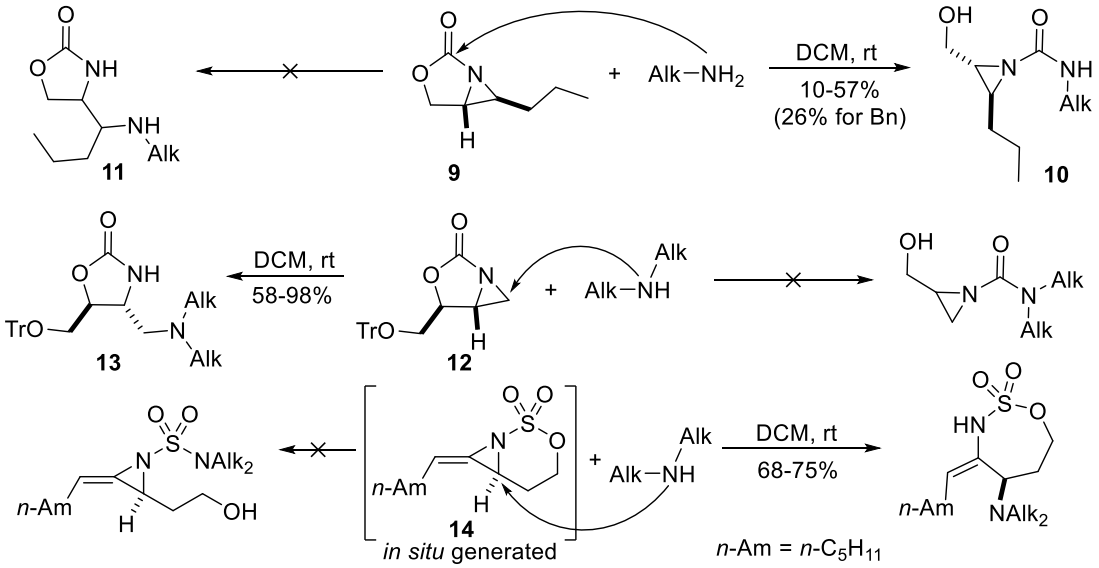


Fig. 2. NMR chemical shifts and key COSY correlations to support the structure of products 4 and 5.

Our results are in good correlation with previous work [25; 26], which reported similar regioselectivity for oxazolidinone aziridines. The papers mentioned show that presence of a substituent (n-propyl group) on the aziridine ring of 9 promote the formation of compounds 10 instead of alternative oxazolidinones 11. In the case of compounds 12, without sterically hindered substituents on the aziridine fragment, corresponding oxazolidinones 13 was synthesized in high yields. In contrast, aminolysis of the bicyclic MA 14 led to the breaking "internal" C-N bond followed by ring expansion [27; 28] (Scheme 6).



Scheme 6. Literature insights into the aminolysis of bicyclic aziridines 9, 12 and 14.

Conclusions

In summary, starting from easily available bicyclic methylene aziridine (MA) we have developed valuable routes for the synthesis of new biologically relevant aziridineurea, 2*H*-azirine and 4,5-disubstituted oxazolidin-2-one. Reactivity patterns shown by us in MA reactions can be useful in predicting reaction paths with other C- and N-nucleophiles.

Experimental

General information All solvents for anhydrous reactions were obtained dry from Grubbs solvent dispenser units after being passed through an activated alumina column under argon. THF was additionally distilled from sodium/benzophenone ketyl under argon. Commercially available reagents were used as supplied unless otherwise specified. Triethylamine was distilled from CaH_2 and stored over KOH pellets under argon. 'Petrol' refers to the fraction of light petroleum ether boiling between 30 and 40 °C. All reactions were carried out in oven-dried glassware and under an atmosphere of argon unless otherwise specified. Thin layer chromatography (TLC) was carried out using Merck aluminium backed DC60 F_{254} 0.2 mm precoated plates. Spots were then visualised by the quenching of ultraviolet light fluorescence (λ_{max} 254 nm) and then stained and heated with either anisaldehyde or $KMnO_4$ solutions as appropriate. Retention factors (R_f) are reported along with the solvent system used in parentheses. Flash column chromatography was performed using Merck 60 silica gel (particle size 40–63 μm) and the solvent system used is reported in parentheses. Infrared spectra were recorded using a Bruker Tensor 27 FT-IR fitted with a diamond ATR module. Absorption maxima (ν_{max}) are reported in wavenumbers (cm^{-1}) and are described as strong (s), medium (m), weak (w) or broad (br). Proton (^1H) and carbon-13 (^{13}C) spectra were recorded on Bruker AVIII HD 500, AVII 500, or AVIII HD 400 spectrometers. Chemical shifts (δ_H or δ_C) are reported in parts per million (ppm) downfield of tetramethylsilane, internally referenced (in MestReNova) to the appropriate solvent peak: $CDCl_3$, 7.26/77.16 ppm. Peak multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), octet (oct), multiplet (m), and broad (br) or a combination thereof. Coupling constants (J) are rounded to the nearest 0.5 Hz. Assignments are made on the basis of chemical shifts, integrations, and coupling constants, using COSY and HSQC experiments. High Resolution Mass Spectra (HRMS) were recorded by the staff at the Chemistry Research Laboratory (University of Oxford, UK) using a Waters GC-TOF spectrometer (EI/FI).

Reaction of (4R,5S)-4-isopropyl-6-methylene-3-oxa-1-azabicyclo[3.1.0]hexan-2-one 1 with vinylmagnesium bromide. Synthesis of (4S,5R)-4-(buta-1,3-dien-2-yl)-5-isopropyloxazolidin-2-one 3a and 2-methyl-1-(3-methyl-2H-azirin-2-yl)propyl pent-4-enoate 4. Vinylmagnesium bromide (0.25 mL of a 1.0 M solution in THF, 0.25 mmol) was added dropwise to a stirred suspension of CuI (1.2 mg, 0.0125 mmol) in THF (1 mL) in a pear-shaped flask at − 50 °C. After 10 min, a solution of methylene aziridine 1 (19 mg, 0.124 mmol) in THF (1 mL) was added via cannula. The mixture was allowed to warm to − 20 °C over 1 h and was then quenched with saturated aqueous NH_4Cl solution (1 mL), stirred for 30 min, and then warmed to

room temperature. The organic components were extracted with diethyl ether (3×20 mL), the combined organic extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (petrol/diethyl ether 7:1→1:1, SiO2 40-63μm, 5×60 mm) to afford the (4S,5R)-4-(buta-1,3-dien-2-yl)-5-isopropyloxazolidin-2-one 3a (7 mg, 30%, major product) as an off-white solid (second fraction). R_f 0.12 (petrol/diethyl ether 1:1); m.p. 81°C; ν_{max}/cm^{-1} (thin film) 3266br, 2362m, 1745s, 1403m, 1249s; δH (500 MHz, $CDCl_3$): 0.90 (3H, d, J 6.8Hz, CH_3), 1.01 (3H, d, J 6.8Hz, CH_3), 1.90 (1H, oct, J 6.8, $CH(CH_3)_2$), 4.45 (1H, dd, J 8.0, 6.8Hz, CHO), 4.65 (1H, d, J 8.0Hz, CHN), 5.13 (1H, br.s, NH), 5.19 (1H, d, J 11.3Hz, CH=CHH'), 5.29 (1H, s, C=CHH), 5.31 (1H, d, J 17.5Hz, CH=CHH'), 5.43 (1H, s, C=CHH'), 6.38 (1H, dd, J 17.5, 11.3Hz, $CH=CH_2$); δC (125 MHz, $CDCl_3$): 17.8, 19.8, 28.4, 57.1, 84.8, 115.5, 117.9, 135.9, 141.9, 159.3; HRMS (ESI^+) found 204.0997, $C_{10}H_{15}NNaO_2$ (MNa^+) requires 204.0995. These data are consistent with those described [8]. As the first fraction 2-methyl-1-(3-methyl-2H-azirin-2-yl)propyl pent-4-enoate 4 was isolated as a colorless oil (6 mg, 22%, minor product). R_f 0.74 (petrol/diethyl ether 1:1), ν_{max}/cm^{-1} (thin film) 2966m, 1731s, 1439m, 1369m, 1250m, 1175m, 984m, 915m; δ_H (500 MHz, $CDCl_3$): 1.02 (3H, d, $CH(CH_3)CH_3$, J 6.9 Hz), 1.06 (3H, d, $CH(CH_3)CH_3$, J 6.9 Hz), 1.81 (1H, d, H5, J 5.7 Hz), 2.03 (1H, oct, $CH(CH_3)_2$, J 6.9 Hz), 2.38 (2H, m, CH_2CH_2-Vinyl), 2.40 (2H, m, CH_2CH_2-Vinyl), 2.44 (3H, s, C_4-CH_3), 4.14 (1H, t, H_6, J 5.7 Hz), 5.01 (1H, dd, –CH=CHH, J 10.4, 1.5 Hz), 5.06 (1H, dd, –CH=CHH, J 17.2, 1.5 Hz), 5.82 (1H, m, –CH=CHH); δ_C (125 MHz, CDCl3): 14.4 (C_4-CH_3), 17.8 ($CH(CH_3)CH_3$), 18.7 ($CH(CH_3)CH_3$), 29.1 (CH_2CH_2-Vinyl), 31.0 (C_5), 31.3 ($CH(CH_3)_2$), 33.8 (CH_2CH_2-Vinyl), 81.2 (C_6), 115.7 (–CH=CH_2), 136.8 (–CH=CH_2), 170.8 (C=N), 172.7 (C=O); HRMS (ESI^+) found 232.1302, $C_{12}H_{19}NNaO_2$ (MNa^+) requires 232.1308.

N-benzyl-2-(1-hydroxy-2-methylpropyl)-3-methyleneaziridine-1-carboxamide 5. To a stirring solution of (4*R*,5*S*)-4-isopropyl-6-methylene-3-oxa-1-azabicyclo[3.1.0]hexan-2-one 1 (13 mg, 0.085 mmol) in 1 mL DCM benzylamine (9 mg, 0.094 mmol) was added and stirred at room temperature for 48 h. Reaction mixture was evaporated *in vacuo*. Purification by flash chromatography (diethyl ether-petrol 1:1, SiO_2 40-63μm, 5×60 mm) afforded the title compound as a colorless oil (9 mg, 45%). R_f 0.67 (diethyl ether). ν_{max}/cm^{-1} (thin film): 3316m, 2962m, 1785w, 1672s, 1530s, 1263s, 1164m, 840m, 731m, 698m. δ_H (400 MHz, $CDCl_3$): 1.00 (3H, d, J 6.5Hz, CH_3), 1.04 (3H, d, J 6.5Hz, CH_3), 1.85 (1H, d, J 3.4Hz, OH), 1.89 (1H, m, $CH(CH_3)_2$), 3.32 (1H, m, CHN), 3.80 (1H, m, CHO), 4.44 (2H, d, JH,NH 5.9Hz, CH_2Ph), 4.84 (1H, dd, J 2.7, 0.5Hz, =CHH), 4.90 (1H, m, =CHH), 5.58 (1H, t, JH,NH 5.9Hz, NH), 7.27-7.37 (5H, m, Ph). δ_C (100 MHz, $CDCl_3$): 17.6 (CH_3), 18.4 (CH_3), 32.4 ($CH(CH_3)_2$), 43.8 (CHN), 45.1 (CH_2Ph), 72.8 (CHO), 85.1 ($C=CH_2$), 127.7 (Ar), 127.9 (Ar), 128.9 (Ar), 130.9 (Ar), 138.0 (Ar), 149.0 ($C=CH_2$), 159.6 (C=O). HRMS (FI^+) Found: 283.1408; $C_{15}H_{20}N_2NaO_2$ (MNa^+) requires 283.1417.

Acknowledgements

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