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One-pot synthesis of chiral multifunctionalized aziridines

Stefania Fioravanti *, Sara Morea, Alberto Morreale, Lucio Pellacani *, Paolo A. Tardella *

Dipartimento di Chimica, Università degli Studi 'La Sapienza', P.le Aldo Moro 2, I-00185 Roma, Italy

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ABSTRACT

A direct synthetic procedure to obtain chiral aziridines is reported, involving a diastereoselective aza-MIRC (Michael Initiated Ring Closure) reaction. Multifunctionalized aziridines are obtained in high overall yields (82–92%) and with a diastereomeric ratio up to 99:1. Further synthetic elaboration can lead to the formation of interesting biochemical molecules, such as amino glycosides. The diastereomeric induction seems to be strongly controlled both by the choice of chiral moiety and by the electron withdrawing groups (EWG) present on the starting alkenes.

1. Introduction

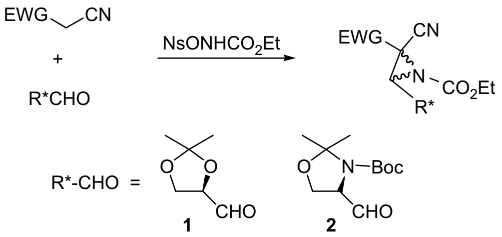
The development of procedures leading to the stereocontrolled formation of carbon–nitrogen bonds is considered a challenging research topic. The aza-Michael reaction is a very simple tool to synthesize chiral nitrogen-containing compounds, owing to its simplicity and usefulness. The most successful strategies to achieve asymmetric induction include the use of a chiral amine or Michael acceptor or catalyst.[1] The aza-MIRC (Michael Initiated Ring Closure) reaction represents an intriguing approach to obtain in one synthetic step the formation of small or medium sized nitrogen-containing ring systems. However, this approach has not been investigated fully.

During the last years, we found that *N*-protected *O*-sulfonyl hydroxylamine derivatives in the presence of inorganic bases give a highly regio- and stereoselective aza-Michael initiated aziridination reaction on functionalized alkenes.[2]

This reaction has been applied with success also to the chiral synthesis of different substituted aziridines either by using chiral auxiliaries on the alkenes or on the aminating agents but also by using chiral catalysts.

Recently, we reported the synthesis of diastereomerically pure nitro aziridines by a stereoselective aza-MIRC reaction performed on optically active (*E*)-nitro alkenes carrying a 1,3-dioxolane or 1,3-oxazolidine residue, useful precursors of important chemical functionality.[3]

Continuing our studies on the stereoselective aza-MIRC reactions, here we report the two step one-pot synthesis of highly functionalized chiral aziridines, starting from cyano methylene compounds and (*R*)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde[4] (**1**) or Garner's aldehyde[5] (**2**) (Scheme 1).



Scheme 1. Two step one-pot synthesis of chiral cyano functionalized aziridines.

2. Results and discussion

For the synthesis of the intermediate chiral cyano acrylates **6** and **7** and oxo acrylonitriles **8**–**11**, classical condensation reaction conditions (piperidine/toluene, reflux) failed because of uncontrolled decomposition and/or polymerization reactions favored by the high temperatures. Consequently, an Al_2O_3 induced Knoevenagel reaction was attempted.[6] Under these conditions the target products were obtained in unsatisfactory yields (<30%).

Finally, a synthetic strategy involving the use of catalytic piperidine in an equimolar CH_2Cl_2 solution of reactants at room temperature was successfully performed (Scheme 2) and the

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* Corresponding authors. Tel.: +39 0649913673; fax: +39 06490631.
E-mail address: lucio.pellacani@uniroma1.it (L. Pellacani).

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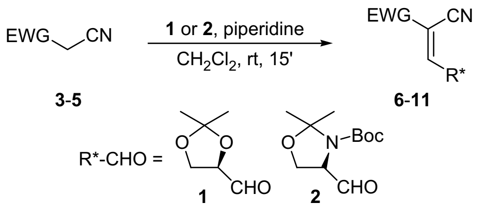


Scheme 2. Mild conditions to synthesize chiral cyano alkenes.

Table 1
Synthesis of (*E*)-chiral alkenes

Substrate	EWG	R*CHO	Alkene	Yield[a] (%)
3	CO_2Et	**1**	**6**	76
		2	**7**	65
4	COPh	**1**	**8**	72
		2	**9**	80
5	CO*t*-Bu	**1**	**10**	68
		2	**11**	75

[a] After fast filtration of reaction mixtures on short plugs filled with silica gel using 200 mL of a hexane/ethyl acetate 8:2 mixture.

Table 2
Results of aziridination reactions

Entry	Aziridine	R*CHO	EWG	Time (h)	Yield[a] (%)	dr[b]
1	**12/12′**	**1**	CO_2Et	1	82	8:2
2	**13/13′**	**2**	CO_2Et	4	85	7:3
3	**14/14′**	**1**	COPh	1	90	8:2
4	**15**	**2**	COPh	2	87	>99:1
5	**16/16′**	**1**	CO*t*-Bu	4	92	6:4
6	**17**	**2**	CO*t*-Bu	4	83	>99:1

[a] After purification, calculated on the starting aldehydes.
[b] Determined by HPLC–UV.

desired alkenes were obtained after 15 min stirring in very high yields and purities (Table 1).

Chiral alkenes were obtained as pure *E* isomers[7] in high purity as showed by ^1H NMR spectra and HPLC–UV analyses performed on the crude filtrates. Longer reaction times give rise to lower product yields.

The optimal reaction conditions to obtain alkenes **6**–**11** suggested a two step one-pot aziridination reaction starting directly from methylene active compounds and chiral aldehydes.

Therefore, catalytic piperidine (5 mol %) was added at room temperature to an equimolar solution of methylene active compounds **3**–**5** and optically active aldehydes in CH_2Cl_2. After 15 min, a two-fold excess of CaO and a four-fold excess of $NsONHCO_2Et$ were added at room temperature (Scheme 3).

The aziridination step was monitored by TLC analysis and the results are reported in Table 2.

As reported in Table 2, in all cases the aziridines were obtained in high overall yields and in moderate to high diastereoselectivities (up to 99:1 dr) with retention of the starting alkene configurations, according to the previous results we reported for the synthesis of *N*-protected cyano aziridines by the same aza-MIRC reaction on several (*E*)-2-cyano acrylates.[8] Flash chromatography on silica gel (eluent: hexane/ethyl acetate 80:20) allowed to obtain the aziridines (entries 1–3 and 5) directly as pure diastereomers.

Using a carboxylic group as EWG comparable results were obtained in the yields and in the drs even by changing the chiral moiety (entries 1 and 2). On the other hand, interesting differences on the stereoselective induction were observed when the EWG was an acyl group (entries 3–6).

Starting from **4** and **5**, the stereochemical aziridination outcome was found to be strongly influenced by the choice of the chiral aldehyde. In fact, using the chiral aldehyde **1** (entries 3 and 5) a moderate stereoselective induction was observed, especially in the presence of the *tert*-butyl group. In contrast, a very high diastereomeric purity was obtained using Garner's aldehyde **2** regardless of the group on the carbonyl function (entries 4 and 6).

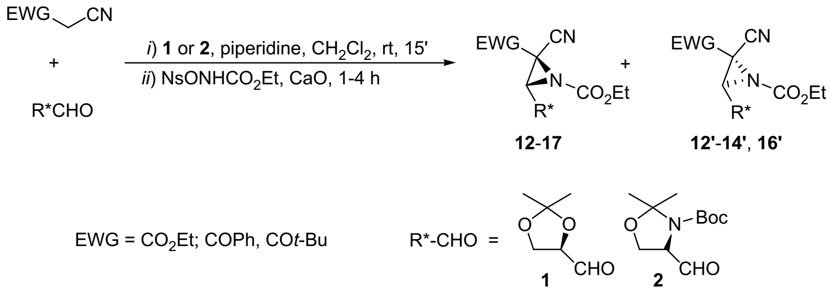
The cyano acyl aziridines **14**–**17** were found to be stable compounds, rearranging slowly into the isomeric 2,3-dihydrooxazoles, in contrast to the behavior previously reported for analogous heterocycles.[9] ^1H NMR spectra performed on a sample of aziridines **16** and **16′** stored at room temperature in $CDCl_3$ for two months showed the presence of two doublets at δ 5.95 attributable to the isomeric 2,3-dihydrooxazoles. As determined by integration analyses, the initial dr of the corresponding aziridines was maintained.

The absolute configuration of the new chiral centers of the major aziridine diastereomers was tentatively assigned according to the data reported for the same diastereoselective aza-MIRC reaction performed on chiral nitro alkenes. The major diastereomer obtained by using **1** as the chiral residue can be explained by the coordination of the nucleophilic reagent by the dioxolane oxygen,[10] while the absolute configuration of the major aziridine diastereomers **13**, **15**, and **17** was assigned according to the results of X-ray analysis we performed on a similar chiral substrate.[3]

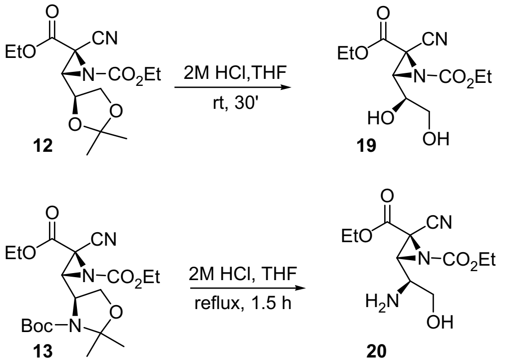
Finally, our attention turned toward chemoselective ring opening reactions of the 1,3-dioxolane and the 1,3-oxazolidine ring, leading to chiral multifunctionalized aziridines, useful scaffolds in the construction of interesting structures, like amino glycosides.

Starting from **12**, the dioxolane ring was hydrolyzed at room temperature with HCl to form the diol derivative **19**, in quantitative yield after 30 min[11] (Scheme 4).

The deprotection reaction of the acetonide function of **13** was attempted in the presence of Montmorillonite K10 clay (20% w/w),[12] but the starting material was quantitatively recovered after 48 h. The desired hydrolysis took place using HCl in THF at reflux for 1.5 h, giving β-amino alcohol **20** as main product. The presence of aziridine **13** and of diethyl (2*R*,3*R*)-2-cyano-3-[(4*S*)-2,2-dimethyl-

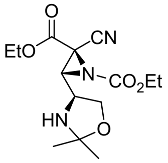


Scheme 3. Direct synthesis of chiral functionalized cyano aziridines.



Scheme 4. Chemoselective ring opening reactions of the 1,3-dioxolane and the 1,3-oxazolidine ring.

1,3-oxazolidin-4-yl]aziridine-1,2-dicarboxylate (**21**) were detected by ESI-MS spectra performed on the crude mixture.



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Longer reaction times led to a complex reaction mixture, due to uncontrolled opening reactions of aziridine ring. Interestingly in both cases the aziridine ring was unaffected.

3. Conclusions

In summary, a direct synthetic procedure to obtain aziridines was reported, involving a diastereoselective aza-MIRC reaction. The functional groups and the chiral moieties present on the aziridine ring allow further chemical transformation addressed to multi-step syntheses of different biomolecular targets, by ring opening reactions and focused elaborations of the carbonyl[13] and the cyano functions.[14]

4. Experimental section

4.1. General

GC–MS analyses were performed with a HP G1800A gas chromatograph equipped with a capillary column (phenyl methyl silicone, 30 m×0.25 mm). IR spectra were recorded on a PERKIN ELMER 1600 FT/IR spectrophotometer in $CHCl_3$ as the solvent, and reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz or at 200 and 50 MHz with a Varian XL-300 or Gemini 200 NMR spectrometer, respectively, and reported in δ units. $CDCl_3$ was used as the solvent and $CHCl_3$ as the internal standard. ESI-MS analyses were performed using a Micromass Q-TOF Micro quadrupole-time of flight (TOF) mass spectrometer equipped with an ESI source and a syringe pump. The experiments were conducted in the positive ion mode. Optical rotations were determined with a JASCO DIP-370 polarimeter at 20 °C. HPLC analyses were performed with a VARIAN 9002 instrument using an analytical column (3.9×300 mm, flow rate 1.3 mL/min; detector: 254 nm) equipped with a VARIAN 9040 differential refractometer, or a VARIAN 9050 UV/VIS detector. Eluents were HPLC grade. Analytical thin-layer chromatography (TLC) was carried out on precoated silica gel plates. Silica gel 230–400 mesh was used for column chromatography.

4.2. Synthesis of chiral (*E*)-cyano alkenes 6–11. General procedure

To a solution of cyano methylene compounds **3**–**5** (3 mmol) in CH_2Cl_2 (3.0 mL), chiral aldehyde **1** or **2** (3 mmol) and catalytic piperidine (0.15 mmol) were added. The reaction mixture was stirred for 15 min at room temperature (TLC) and purified by flash chromatography (hexane/ethyl acetate 8:2).

*4.2.1. Ethyl (2E)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]prop-2-enoate **6***

Yellow oil (0.52 g, 76%). $[\alpha]_D$ +12.3 (*c* 1.0, $CHCl_3$). IR: 2234, 1733, 1634 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.20–1.41 (m, 9H), 3.76 (d, *J* 5.8 Hz, 1H), 3.80 (d, *J* 5.8 Hz, 1H), 4.20–4.42 (m, 2H), 4.86–5.24 (m, 1H), 7.55 (d, *J* 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 25.3, 26.3, 62.8, 68.2, 73.6, 93.3, 110.3, 112.6, 135.8, 160.3. HRMS (ES Q-TOF) calcd for $C_{11}H_{15}NNaO_4$ $(M+Na)^+$: 248.0899; found: 248.0907.

*4.2.2. tert-Butyl (4S)-4-[(1E)-2-cyano-3-ethoxy-3-oxoprop-1-en-1-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate **7***

Yellow oil (0.62 g, 65%). $[\alpha]_D$ +8.8 (*c* 1.0, $CHCl_3$). IR: 2235, 1731, 1632 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08–1.84 (m, 18H), 3,74 (d, *J* 5.8 Hz, 1H), 3.79 (d, *J* 5.8 Hz, 1H), 4.16–4.32 (m, 2H), 4.80 (m, 1H), 7.43 (d, *J* 10.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 25.8, 26.2, 28.2, 62.7, 66.7, 72.1, 81.2, 94.5, 110.0, 112.7, 137.9, 156.3, 160.6. HRMS (ES Q-TOF) calcd for $C_{16}H_{24}N_2NaO_5$ $(M+Na)^+$: 347.1583; found: 347.1580.

*4.2.3. (2E)-3-[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-(phenylcarbonyl)prop-2-enenitrile **8***

Yellow oil (0.54 g, 72%). $[\alpha]_D$ +16.4 (*c* 1.0, $CHCl_3$). IR: 2204, 1705, 1610 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.02–1.68 (m, 6H), 3.38–3.82 (m, 2H), 4.83–5.10 (m, 1H), 7.43–7.85 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.4 (2C), 69.5, 74.2, 95.1, 111.8, 115.0, 128.0, 129.6, 134.6, 136.7, 152.8, 182.3. HRMS (ES Q-TOF) calcd for $C_{15}H_{15}NNaO_3$ $(M+Na)^+$: 280.0950; found: 280.0943.

*4.2.4. tert-Butyl (4S)-4-[(1E)-2-cyano-3-oxo-3-phenylprop-1-en-1-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate **9***

Yellow oil (0.85 g, 80%). $[\alpha]_D$ +18.3 (*c* 1.0, $CHCl_3$). IR: 2169, 1698, 1598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96–1.72 (m, 15H), 3.35–3.80 (m, 2H), 4.93–5.18 (m, 1H), 7.23 (d, *J* 9.5 Hz, 1H), 7.13–7.55 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 23.3 (2C), 27.1, 67.6, 73.4, 81.2, 92.4, 113.8, 117.0, 127.5, 128.0, 132.9, 136.2, 154.7, 156.3, 197.3. HRMS (ES Q-TOF) calcd for $C_{20}H_{24}N_2NaO_4$ $(M+Na)^+$: 379.1634; found: 379.1643.

*4.2.5. (2E)-2-{[(4S)-2,2-Dimethyl-1,3-dioxolan-4-yl]methylidene}-4,4-dimethyl-3-oxopentanenitrile **10***

Yellow oil (0,48 g, 68%). $[\alpha]_D$ +11.0 (*c* 1.0, $CHCl_3$). IR: 2200, 1702 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.97–1.74 (m, 15H), 3.36–3.79 (m, 2H), 4.92–5.16 (m, 1H), 7.48 (d, *J* 8.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1 (2C), 28.5, 69.7, 75.8, 79.6, 94.6, 110.1, 115.2, 154.5, 193.2. HRMS (ES Q-TOF) calcd for $C_{13}H_{19}NNaO_3$ $(M+Na)^+$: 260.1263; found: 260.1270.

*4.2.6. tert-Butyl (4S)-4-[(1E)-2-cyano-4,4-dimethyl-3-oxopent-1-en-1-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate **11***

Yellow oil (0.76 g, 75%). $[\alpha]_D$ +6.2 (*c* 1.0, $CHCl_3$). IR: 2169, 1711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.96–1.86 (m, 24H), 3.56–3.93 (m, 2H), 4.63–5.01 (m, 1H), 7.42 (d, *J* 9.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.4, 26.2, 28.3, 29.5, 67.1, 73.2, 79.8, 81.1, 99.3, 115.4, 116.8, 135.0, 157.2, 192.6. HRMS (ES Q-TOF) calcd for $C_{18}H_{28}N_2NaO_4$ $(M+Na)^+$: 359.1947; found: 359.1940.

4.3. One-pot synthesis of chiral functionalized aziridines. General procedure

To a stirred solution of cyano methylene compounds **3**–**5** (3 mmol) in CH_2Cl_2 (3.0 mL), chiral aldehyde **1** or **2** (3 mmol) and a catalytic amount of piperidine (0.15 mmol), after 15 min a two-fold excess of CaO and a four-fold excess of $NsONHCO_2Et$ were added at room temperature. After the time reported in Table 2, the crude mixtures were purified by flash chromatography (hexane/ethyl acetate 8:2), giving directly the optically pure diastereomeric aziridines.

4.3.1. Diethyl (2R,3S)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1,2-dicarboxylate ***12***

Pale yellow oil (0.62 g, 66%). $[\alpha]_D$ +2.2 (*c* 1.0, $CHCl_3$). IR: 2256, 1757, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.15–1.51 (m, 6H), 1.47 (s, 6H), 3.24 (d, *J* 8.1 Hz, 1H), 3.86–4.09 (m, 2H), 4.11–4.26 (m, 4H), 4.30–4.44 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 14.0, 24.8, 26.5, 37.9, 50.7, 63.9, 64.1, 67.5, 74.2, 86.1, 111.2, 156.6, 162.3. HRMS (ES Q-TOF) calcd for $C_{14}H_{20}N_2NaO_6$ $(M+Na)^+$: 335.1219; found: 335.1225.

4.3.2. Diethyl (2S,3R)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]aziridine-1,2-dicarboxylate ***12′***

Pale yellow oil (0.15 g, 16%). $[\alpha]_D$ +3.9 (*c* 1.0, $CHCl_3$). IR: 2256, 1757, 1735 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.02–1.62 (m, 6H), 1.45 (s, 6H), 3.23 (d, *J* 6.7 Hz, 1H), 3.94 (d, *J* 3.6 Hz, 1H), 3.98 (d, *J* 3.6 Hz, 1H), 4.03–4.15 (m, 4H), 4.22–4.59 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.8, 14.0, 25.1, 26.5, 36.2, 50.4, 63.8, 64.5, 66.6, 74.2, 87.2, 111.3, 157.2, 162.4. HRMS (ES Q-TOF) calcd for $C_{14}H_{20}N_2NaO_6$ $(M+Na)^+$: 335.1219; found: 335.1228.

4.3.3. Diethyl (2R,3R)-2-cyano-3-[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]aziridine-1,2-dicarboxylate ***13***

Yellow oil (0.73 g, 59%). $[\alpha]_D$ +3.4 (*c* 1.0, $CHCl_3$). IR: 2254, 1756, 1698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.93–1.72 (m, 21H), 3.31 (d, *J* 8.8 Hz, 1H), 3.49–3.98 (m, 2H), 4.02–4.27 (m, 4H), 4.30–4.42 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.8, 14.1, 25.1, 25.9, 28.1, 51.1, 57.0, 63.6, 64.4, 65.1, 74.8, 80.6, 94.7, 115.7, 156.5, 158.3, 162.3. HRMS (ES Q-TOF) calcd for $C_{19}H_{29}N_3NaO_7$ $(M+Na)^+$: 434.1903; found: 434.1917.

4.3.4. Diethyl (2S,3S)-2-cyano-3-[(4S)-3-(tert-butoxycarbonyl)-2,2-dimethyl-1,3-oxazolidin-4-yl]aziridine-1,2-dicarboxylate ***13′***

Pale yellow oil (0.20 g, 16%). $[\alpha]_D$ +2.2 (*c* 1.0, $CHCl_3$). IR: 2254, 1756, 1698 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.95–1.72 (m, 21H), 3.27 (d, *J* 5.5 Hz, 1H), 3.78–4.05 (m, 2H), 4.10–4.36 (m, 4H), 4.40–4.56 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 14.8, 25.6 (2C), 28.1, 51.3, 57.5, 62.8, 64.8, 67.8, 73.5, 81.8, 95.1, 113.2, 155.8, 157.1, 161.6. HRMS (ES Q-TOF) calcd for $C_{19}H_{29}N_3NaO_7$ $(M+Na)^+$: 434.1903; found: 434.1920.

4.3.5. Ethyl (2R,3S)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(phenylcarbonyl)aziridine-1-carboxylate ***14***

Pale yellow oil (0.74 g, 72%). $[\alpha]_D$ +15.1 (*c* 1.0, $CHCl_3$). IR: 2203, 1740, 1697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.01–1.76 (m, 9H), 3.23 (d, *J* 8.5 Hz, 1H), 3.96–4.34 (m, 5H), 7.50–7.94 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.8, 24.8, 25.3, 53.1, 57.0, 63.7, 67.9, 74.5, 94.2, 115.0, 127.6, 128.6, 129.3, 134.2, 157.3, 199.0. HRMS (ES Q-TOF) calcd for $C_{18}H_{20}N_2NaO_5$ $(M+Na)^+$: 367.1270; found: 367.1258.

4.3.6. Ethyl (2S,3R)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(phenylcarbonyl)aziridine-1-carboxylate ***14′***

Pale yellow oil (0.19 g, 18%). $[\alpha]_D$ +11.1 (*c* 1.0, $CHCl_3$). IR: 2203, 1740, 1697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.98–1.74 (m, 9H), 3.12 (d, *J* 5.6 Hz, 1H), 4.03–4.44 (m, 5H), 7.32–7.78 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.2, 25.6, 26.1, 52.8, 57.6, 64.4, 68.2, 72.5, 98.0, 113.2, 128.1, 128.9, 129.5, 134.4, 156.1, 201.0. HRMS (ES Q-TOF) calcd for $C_{18}H_{20}N_2NaO_5$ $(M+Na)^+$: 367.1270; found: 367.1268.

4.3.7. tert-Butyl (4S)-4-[(2R,3R)-3-cyano-1-(ethoxycarbonyl)-3-(phenylcarbonyl)aziridin-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate ***15***

Pale yellow oil (1.16 g, 87%). $[\alpha]_D$ +19.0 (*c* 1.0, $CHCl_3$). IR: 2217, 1738, 1694, 1598 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.00–1.79 (m, 18H), 3.05 (d, *J* 7.3 Hz, 1H), 4.00–4.32 (m, 5H), 7.60–8.00 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.0, 26.2 (2C), 27.4, 38.3, 58.2, 63.7, 64.6, 65.1, 79.7, 93.7, 114.3, 127.2, 127.7, 128.3, 133.5, 156.9, 159.0, 198.2. HRMS (ES Q-TOF) calcd for $C_{23}H_{29}N_3NaO_6$ $(M+Na)^+$: 466.1954; found: 466.1966.

4.3.8. Ethyl (2R,3S)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(2,2-dimethylpropanoyl)aziridine-1-carboxylate ***16***

Pale yellow oil (0.53 g, 55%). $[\alpha]_D$ +8.2 (*c* 1.0, $CHCl_3$). IR: 2201, 1744, 1716 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.03–1.79 (m, 12H), 1.36 (s, 3H), 1.37 (s, 3H), 3.07 (d, *J* 7.3 Hz, 1H), 3.43–4.06 (m, 2H), 4.12–4.36 (m, 2H), 4.43–4.64 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 14.1, 25.4, 26.5, 28.0, 39.4, 57.1, 63.4, 66.2, 74.4, 80.3, 96.3, 110.8, 157.5, 199.3. HRMS (ES Q-TOF) calcd for $C_{16}H_{24}N_2NaO_5$ $(M+Na)^+$: 347.1583; found: 347.1581.

4.3.9. Ethyl (2S,3R)-2-cyano-3-[(4S)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-(2,2-dimethylpropanoyl)aziridine-1-carboxylate ***16′***

Pale yellow oil (0.36 g, 37%). $[\alpha]_D$ +12.0 (*c* 1.0, $CHCl_3$). IR: 2201, 1744, 1716 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.99–1.86 (m, 12H), 1.36 (s, 3H), 1.37 (s, 3H), 3.02 (d, *J* 8.0 Hz, 1H), 3.76–4.34 (m, 4H), 4.40–4.63 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.9, 24.6 (2C), 28.4, 38.4, 56.8, 64.1, 68.3, 76.0, 82.2, 98.3, 113.1, 155.9, 202.3. HRMS (ES Q-TOF) calcd for $C_{16}H_{24}N_2NaO_5$ $(M+Na)^+$: 347.1583; found: 347.1576.

4.3.10. tert-Butyl (4S)-4-[(2R,3R)-3-cyano-3-(2,2-dimethyl propanoyl)-1-(ethoxycarbonyl)aziridin-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate ***17***

Pale yellow oil (1.05 g, 83%). $[\alpha]_D$ +16.4 (*c* 1.0, $CHCl_3$). IR: 2222, 1744, 1697 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.99–1.85 (m, 27H), 3.05 (d, *J* 8.7 Hz, 1H), 3.86–4.32 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 25.5 (2C), 28.2, 28.6, 39.3, 53.7, 63.4, 68.5, 73.6, 78.9, 80.2, 94.3, 116.0, 157.2, 158.3, 201.7. HRMS (ES Q-TOF) calcd for $C_{21}H_{33}N_3NaO_6$ $(M+Na)^+$: 446.2267; found: 446.2272.

4.4. Synthesis of diethyl (2*R*,3*S*)-2-cyano-3-[(1*R*)-1,2-dihydroxyethyl]aziridine-1,2-dicarboxylate (19)

To a solution of **12** (0.2 mmol) in THF (2.0 mL) was added 2 M hydrochloric acid (4 mL). The reaction mixture was stirred for 30 min at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$, the mixture was extracted with ethyl acetate, the organic layer washed with brine, dried over Na_2SO_4, and the solvents evaporated under reduced pressure. Purification by short plugs filled with silica gel (ethyl acetate/methanol 95:5, 100 mL) gave **19** as a white wax (0.05 g, 87%). $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$). IR: 3585, 3391, 2256, 1748 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.12–1.38 (m, 6H), 3.36 (d, *J* 8.1 Hz, 1H), 3.74–4.00 (m, 2H), 4.12–4.26 (m, 4H), 4.30–4.47 (m, 1H), 6.69 (br, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.8, 14.1, 36.6, 50.2, 63.9, 64.1, 64.5, 69.7, 112.8, 157.6, 162.1. HRMS (ES Q-TOF) calcd for $C_{11}H_{17}N_2O_6$ $(M+H)^+$: 273.1087; found: 273.1095.

4.5. Synthesis of diethyl (2*R*,3*R*)-3-[(1*R*)-1-amino-2-hydroxyethyl]-2-cyanoaziridine-1,2-dicarboxylate (20)

Starting from **13**, the above procedure was followed, heating the mixture at 65 °C for 1.5 h. After working, the crude mixture was purified by flash chromatography (ethyl acetate/methanol 95:5) giving a viscous oil (0.029 g, 51%). $[\alpha]_D$ +9.2 (*c* 1.0, $CHCl_3$). IR: 3593, 3372, 2253, 1757, 1697 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.25–1.34 (m, 6H), 2.80 (br, 2H), 3.26 (d, *J* 8.1 Hz, 1H), 3.50–3.95 (m, 2H), 4.18–4.29 (m, 5H), 6.52 (br, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 14.3, 35.6, 50.0, 53.9, 59.8, 61.8, 62.9, 115.5, 157.8, 166.7. HRMS (ES Q-TOF) calcd for $C_{11}H_{18}N_3O_5$ $(M+H)^+$: 272.1246; found: 272.1252.

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