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Ring-opening reaction of unactivated 3-arylaziridine-2-carboxylates with nitrile reagents

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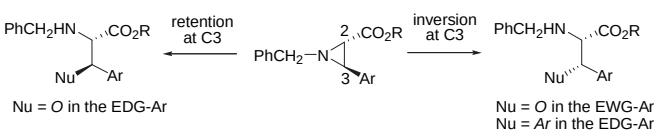
ABSTRACT

Ring-opening reactions of unactivated 3-arylaziridine-2-carboxylates with nitrile reagents, using *trans*-1-benzyl-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate as a typical aziridine substrate, were examined. Formation of azomethine ylide by C2–C3 bond cleavage was observed when the aziridine was treated with trimethylsilyl cyanide under thermal conditions. On the other hand the use of bromine cyanide (BrCN) and diethylaluminum cyanide (Et_2AlCN) led to N–C3 bond cleavage and the stereospecificity was found to be dependent on the reagent used. Additional aluminum-catalyzed ring-opening reactions disclosed that the potential cationic character of the C3 benzylic position and stereochemical requirements of substituents in the arylaziridine system control the reactivity. Furthermore, the synthetic utility of the ring-opening reaction was demonstrated not only by application to the cyclization of a ring-opened cyanopropanoate to an isoquinoline skeleton but also by the extension of other carbon nucleophile from nitrile (C1) to a ketene acetal (C2).

1. Introduction

Three-membered nitrogen heterocycles, aziridines, are very important molecules not only as key components of biologically active natural products such as mitomycins, but also as reactive synthetic precursors for a wide variety of nitrogen-containing compounds.[1] Among them aziridine-2-carboxylates are, in particular, versatile synthetic intermediates[1–3] for the preparation of biologically active nitrogen-containing compounds because they are convertible to α- or β-amino acid derivatives, including unnatural amino acids, by regioselective ring-opening reactions.[1,4–6] Aziridines are classified into two groups, activated and unactivated (or non-activated) aziridines, dependent upon substituent on the ring N-atom;[1,4] the former category includes electron-withdrawing substituents such as tosyl or acyl functions, whereas hydrogen and alkyl substituents are typical for the latter one. Although the reactivity of activated aziridines has been well investigated, only limited reports[7–12] discussed on unactivated aziridines.

Recently, we found a unique atom-economical aziridine synthesis from guanidinium salts and aryl aldehydes[13] (or unsaturated aldehydes[14]) applicable to asymmetric synthesis, in which 1-alkyl-3-arylaziridine-2-carboxylates (or the corresponding unsaturated derivatives) are produced. These findings prompted us to investigate the unexplored ring-opening reaction of unactivated aziridines effectively formed and, thus, the nucleophilic ring-opening reactions of 'unactivated' 3-arylaziridine-2-carboxylates using oxygen (O-) and aromatic carbon (Ar-) nucleophiles were examined[15] (Scheme 1). As a result, N–C3 bond cleavage preferentially occurred and the stereospecificity in the products was found to be dependent on substrates and conditions used. Stereochemical inversion at the C3 was observed as a major reaction path in the ring-opening reactions of 3-arylaziridines carrying an electron-withdrawing group (EWG) on the aromatic ring with O-nucleophiles, whereas *syn*-preferred diastereomeric mixtures were generally obtained when aziridines with electron-donating group (EDG)-substituted aryl function were used. In addition, in the ring-opening reactions of EDG-substituted arylaziridines with Ar-nucleophiles, only S_N2 reaction yielding *anti*-type products was observed as the preferred reaction.



Scheme 1. Nucleophilic ring-opening reactions of unactivated 3-arylaziridine-2-carboxylates using O- and Ar-nucleophiles.

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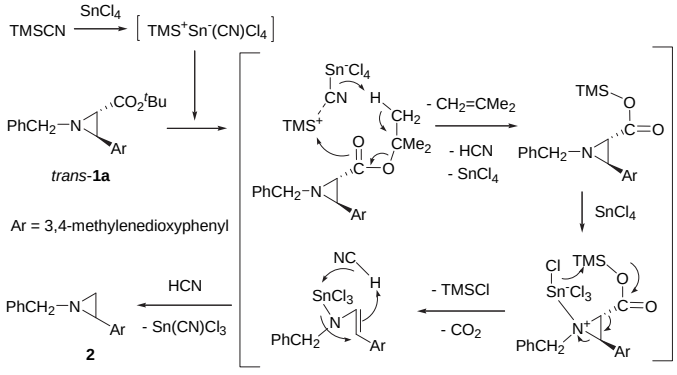
We further examined ring-opening reactions with aliphatic carbon (C-) nucleophiles for advanced synthetic utility of unactivated aziridines; however, several trials for the C–C bond formation using C-nucleophiles such as organocuprates,[7] allylsilane, and Grignard reagent failed. Thus, we decided to investigate cyanation reaction using nitrile reagents as a particularly interesting C-nucleophile because of its low cost and the synthetic versatility of the nitrile-inserted ring-opened products leading to α- or β-functionalized β- or α-amino acid derivatives after suitable chemical modifications. In this paper we will discuss on the reactions of unactivated aziridines with nitrile reagents, such as trimethylsilyl cyanide (TMSCN), bromine cyanide (BrCN), and diethylaluminum cyanide (Et_2AlCN), using *trans-tert*-butyl 1-benzyl-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate[13,15] (*trans*-**1a**) as a typical EDG-substituted arylaziridine substrate.

2. Results and discussion

Ring-opening reactions with nitrile reagents such as sodium cyanide (NaCN),[16] TMSCN,[16a,17] and Et_2AlCN[16a] have been reported on only activated aziridine substrates. In general, NaCN and Et_2AlCN act as nucleophiles even in the absence of catalyst, whereas activation of the reagent by either Lewis acid or Lewis base, including tetrabutylammonium fluoride (TBAF), is needed for the completion of ring-opening reaction in the case of TMSCN. We at first examined the ring-opening of *trans*-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate *trans*-**1a** with TMSCN either in the presence of Lewis acid or Lewis base. In the former reactions, although only epimerization of the starting aziridine was observed when treated in dichloromethane (CH_2Cl_2) in the presence of zinc chloride or indium chloride,[18] the reaction in the presence of stannic chloride ($SnCl_4$) unexpectedly and interestingly afforded a decarboxylated aziridine **2** in 48% yield. Chirality of *trans*-**1a** was not preserved in the product **2** when an optically active *trans*-**1a**[13] was used as a starting material. Thus, mechanism for the decarboxylation could be supposed as shown in Scheme 2, in which a complex of TMSCN and $SnCl_4$ triggered the reaction, albeit not clearly explained at this stage.



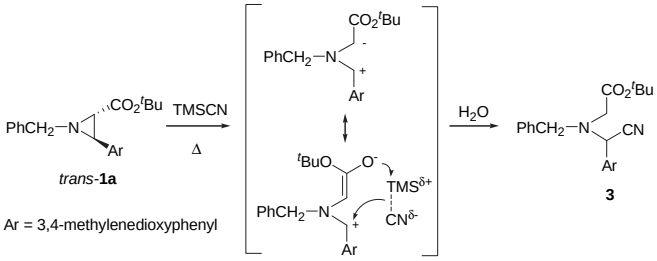
Scheme 2. Supposed mechanism for the decarboxylation of aziridine-2-carboxylate *trans*-**1a** with TMSCN and $SnCl_4$.

On the other hand, no reaction occurred when TMSCN was used together with Lewis bases such as tetramethylethylenediamine, TBAF, and tetramethylguanidine in acetonitrile (MeCN); however, a ring-opened product **3**[19] was yielded as colorless prisms even in 20% yield when refluxed for a longer time (5 days) in the presence of a catalytic amount of triethylamine (TEA) (run 1 in Table 1). Microwave (MW) greatly improved the product formation and, thus, treatment at 120 °C for 30 min under irradiation of MW afforded the same product quantitatively (run 2 in Table 1). The product was found to be formed even without Et_3N (runs 3 and 4 in Table 1).

Table 1
Reaction of aziridine-2-carboxylate *trans*-**1a** with TMSCN in MeCN

Run	Additive	Conditions	**3** (%)
1	TEA (0.3 equiv)	Reflux, 5 d	20
2	TEA (0.3 equiv)	MW, 120 °C, 30 min	100
3	None	MW, 120 °C, 30 min	96
4	None	Reflux, 5 d	56

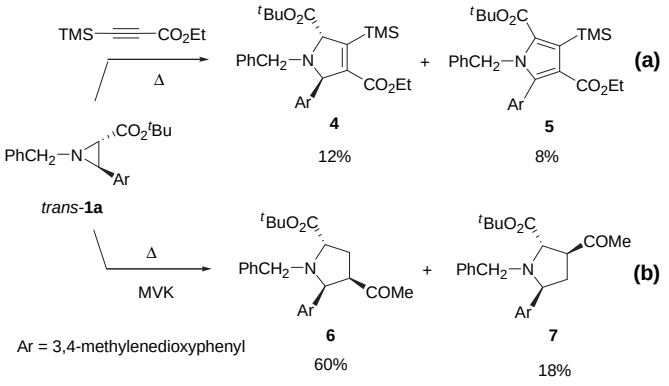
It is known that thermolysis of aziridine produces the corresponding azomethine ylide, resulted from cleavage between C2–C3 bond, which undergoes 1,3-dipolar cycloaddition to electron-deficient alkenes.[20] In particular, carbonyl-stabilized azomethine ylide is conveniently generated by thermolytic ring-opening when substitution of carbonyl group at C2 (or C3) position. Thus, aziridine-participated [3+2] cycloaddition reactions have been reported as typical reaction paths in both activated and unactivated aziridines when treated with an appropriate dipolarophile. It may be difficult to straightforwardly discuss the above thermal cyanation because of no role of TMSCN as a dipolarophile; however, it could be reasonable that azomethine ylide species formed from aziridine under thermal condition reacts with a potentially polarized TMSCN to afford *N*-benzyl-*N*-(*tert*-butoxycarbonylmethyl)-α-cyano-(3,4-methylenedioxyphenyl)methylamine (**3**), as shown in Scheme 3. In this reaction chirality in the product, as expected, disappeared.



Scheme 3. Thermal cyanation of aziridine-2-carboxylate *trans*-**1a** with TMSCN.

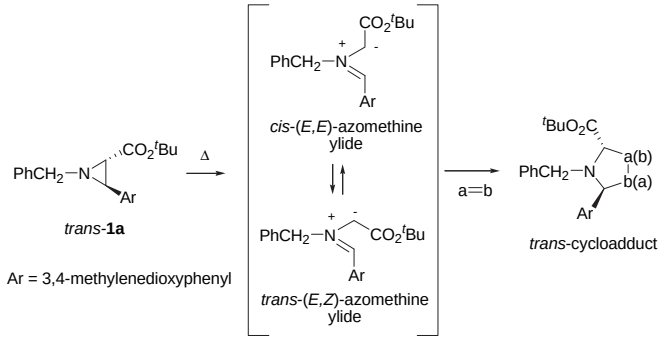
This speculation was experimentally supported by successful cycloaddition reactions using ethyl trimethylsilylpropiolate (TMS-propiolate) and methyl vinyl ketone (MVK) as dipolarophiles (Scheme 4). Heating *trans*-**1a** with TMS-propiolate at 120 °C for 30 min under MW-irradiation afforded 1-benzyl-2-(*tert*-butoxycarbonyl)-4-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)-3-trimethylsilyl-2,5-dihydropyrrole (**4**) as an isolable, but unstable, product together with the corresponding aromatized product **5**. Regiochemistry in the reaction and relative stereochemistry between 2- and 5-substituents in **4** could not be determined due to the easy aromatization of **4** to **5** during the NMR measurement. On the other hand, treatment with MVK afforded isomeric cycloadducts as colorless prisms and a colorless oil in 60% and 18% yields, respectively. The structure of the major crystalline isomer was deduced to be a 4-acetylprolinate **6**, which was formed by a regiochemically expected approach of MVK to an intermediate azomethine ylide, based on precise NMR analysis including HMBC experiments. Thus, newly born methylene signal [δ_H 1.80 (1H, dd, J=13.2, 8.1 Hz), 2.72 (1H, ddd, J=13.2, 10.0, 8.1 Hz); δ_C 29.5] was coupled with C2 [δ_H 3.64 (d, J=8.1 Hz); δ_C 61.6] and C4 methine protons [δ_H 3.75 (ddd, J=10.1, 10.0, 8.1 Hz); δ_C 55.4]. In addition, the lowest field-shifted methine signal assignable to C5 proton was observed

at δ_H 4.67 as doublet (J=10.1 Hz). The stereochemical alignments of substituents were reasonably deduced to be (2*S**,4*R**,5*S**)-configurations by coupling constants of ring protons, which were supported by NOE experiments. Similar analysis on a minor isomer based on the NMR spectral data allowed us to deduce to be (2*S**,3*S**,5*S**)-*tert*-butyl 3-acetyl-1-benzyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2-carboxylate (**7**).



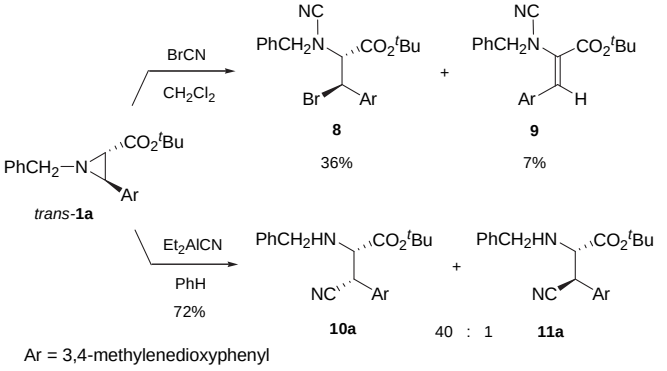
Scheme 4. MW-mediated [3+2]-cycloadditions of aziridine-2-carboxylate *trans*-**1a** with TMS-propiolate and MVK.

Huisgen and Maeder[20b] had demonstrated that *cis*-aziridine affords *trans*-cycloadduct through *trans*-(*E*,*Z*)-azomethine ylide, whereas *trans*-aziridine affords *cis*-cycloadduct through *cis*-(*E*,*E*)-azomethine ylide, by conrotatory thermal ring cleavage. However, in the reaction with less reactive dipolarophiles a *trans*-1,3-dipolar addition product is expected from either *cis*- or *trans*-aziridine after equilibrium to the more stable *trans*-(*E*,*Z*)-azomethine ylide.[20c] Furthermore, an *endo* approach had been observed in the [3+2]-cycloaddition reaction of azomethine ylide with dipolarophile.[20a,d] Thus, it could be reasonably supposed that the reaction of *trans*-3-arylaziridine-2-carboxylate *trans*-**1a** with MVK was stereochemically controlled as follows: (1) conrotatory ring-opening of the *trans*-aziridine to *cis*-(*E*,*E*)-azomethine ylide, (2) isomerization to a more stable *trans*-(*E*,*Z*)-azomethine ylide under the MW conditions, and (3) [3+2] cycloaddition via an *endo* approach of the dipolarophile, resulting in the formation of cycloadducts **6** and **7** with trans-alignment of substituents at 2 and 5 positions (Scheme 5).



Scheme 5. Formation of 2,5-*trans*-cycloadducts from *trans*-3-arylaziridine-2-carboxylate *trans*-**1a** through equilibrium between *cis*-(*E*,*E*)- and *trans*-(*E*,*Z*)-azomethine ylides.

Next, *trans*-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate *trans*-**1a** was subjected to the reactions with BrCN and Et_2AlCN (Scheme 6). Treatment with excess amount of BrCN in CH_2Cl_2 under reflux for 10 h afforded an N–C3 cleaved product **8** in 36% yield as a single diastereoisomer together with 3-aryl-2-cyanoaminoacrylate **9** (7%). The *syn* stereochemistry of **8** was deduced by coupling constant (J=10.8 Hz)[15] between C2–H and C3–H and the (*Z*)-configuration of the acrylate **9** was established by NOE experiment [(a) in Fig. 1], respectively, indicating that bromo anion attacks the C3 carbon of *trans*-**1a** with retention of the configuration. On the other hand, treatment of *trans*-**1a** with excess amount (5 equiv) of a commercially available 1 M solution of Et_2AlCN in toluene at room temperature (rt) for 1 day afforded 3-aryl-2-benzylamino-3-cyanopropanoate as an inseparable mixture of diastereoisomers **10a** and **11a** in 72% yield. The regioisomeric ratio of the products was estimated to be **10a**/**11a**=40:1 by the ^1H NMR spectrum. Coupling constant[15] between C2–H and C3–H strongly indicated that the major **10a** is *anti* (J=5.1 Hz) and the minor **11a** *syn* (J=7.0 Hz), respectively. Thus, it was found that the ring-opened process with a nitrile function as a C-nucleophile is controlled by S_N2 type reaction at C3 position of the aziridine system with inversion of the configuration, even the major formation of *syn*-product like **11a** in the ring-opening reaction of *trans*-**1a** with O-nucleophile.[15]



Scheme 6. Ring-opening reactions of aziridine-2-carboxylate *trans*-**1a** with BrCN and a commercially available Et_2AlCN.

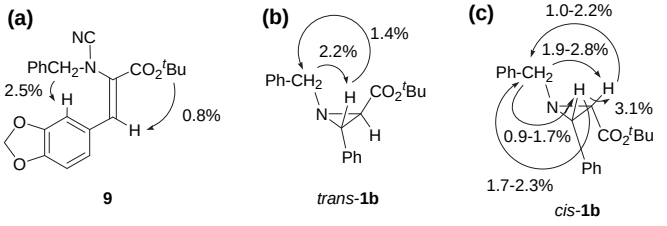
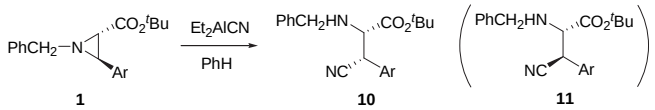


Figure 1. Selected NOE enhancements of (a) the acrylate **9**, (b) *trans*-3-phenylaziridine-2-carboxylate *trans*-**1b**, and (c) *cis*-3-phenylaziridine-2-carboxylate *cis*-**1b**.

Et_2AlCN can be prepared from triethylaluminum (Et_3Al) and TMSCN.[21] Ring-opening reactions of some kinds of aziridines using a freshly prepared Et_2AlCN were summarized in Table 2. Product formation from *trans*-**1a** was greatly improved, in which the *anti*-cyanopropanoate **10a** was given in 92% yield as a single diastereoisomer (run 1 in Table 2). Similar ring-opening products **10b** and **10c** with inversion at the C-3 benzylic position were produced, albeit less effectively, when *trans*-phenylaziridine-2-carboxylate *trans*-**1b** or *trans*-4-chlorophenylaziridine-2-carboxylate[13,15] *trans*-**1c** were subjected to the ring-opening reaction (runs 2 and 3 in Table 2). On the other hand, no reactions occurred when diastereomeric *cis*-aziridines[13,15] *cis*-**1a** and *cis*-**1b** were used as staring materials (runs 4 and 5 in Table 2). We[15] have observed that ring-opening reaction of 3-arylaziridine-2-carboxylates **1** with O-nucleophile is dependent upon the electronic character of the 3-aryl pendant rather than the relative configuration of the C2- and C3-substituents in aziridine system. The difference of stereoselectivity in the ring-opening reactions with C-nucleophile from that with O-nucleophile could be explained based on their stereochemical alignment of the substituents on the aziridine system.

Table 2
Reactions of aziridines **1** with a freshly prepared Et_2AlCN

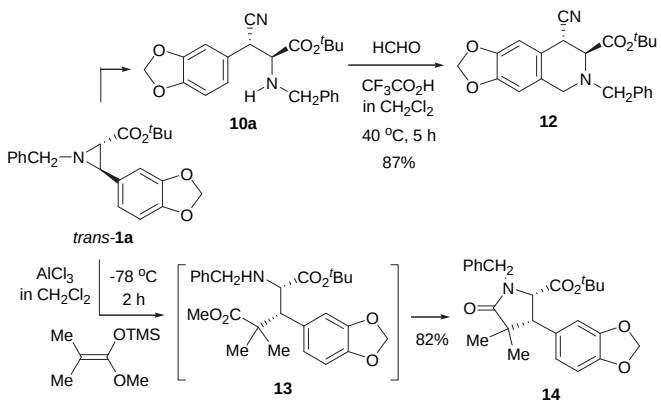


Run	1	Conditions	Results
1	*trans*-**1a**	0 °C, 2.5 h	**10a** (92%)
2	*trans*-**1b**	rt, 24 h	**10b** (40%)[a]
3	*trans*-**1c**	0 °C, 2 h then rt, 15 h	**10c** (27%)
4	*cis*-**1a**	0 °C, 2.5 h	NR[b]
5	*cis*-**1b**	rt, 24 h	NR[b]

[a] Starting *trans*-**1b** was recovered in 43% yield.
[b] No reaction occurred.

It is possible for some substituted aziridines to exist as invertomers due to the steric requirement of substituents.[13,22] NOE experiments of 3-phenylaziridine-2-carboxylates *trans*-**1b** and *cis*-**1b** showed *trans*-configuration between *N*-benzyl and 3-phenyl groups in both diastereomers [(b) and (c) in Fig. 1]. The nitrile-inserted reaction should be triggered by coordination of reagent itself (Et_2AlCN) to aziridine nitrogen, while protonation leads to ring-opening in the reaction with O-nucleophiles. Thus, loose coordination of more bulky Et_2AlCN than proton to aziridine nitrogen due to steric hindrance of the 3-aryl substituent causes S_N2 type reaction, not S_Ni type one, to give a product with stereochemical inversion at C3 position when *trans*-aziridines are used as starting materials. On the other hand, in the cases of *cis*-3-arylaziridine-2-carboxylates impossible coordination of Et_2AlCN with aziridine nitrogen due to profound steric hindrance generated from an additional C2-ester substituent resulted in leading to no reaction.

Pictet–Spengler reaction of the cyanopropanoate **10a** smoothly afforded an isoquinoline skeleton **12** (Scheme 7), showing the synthetic utility of a nitrile-inserted ring-opened product. Furthermore, ring-opening reaction using a ketene acetal as a C2 carbon nucleophile was also examined for the further potentiality of the Lewis acid-catalyzed ring-opening reaction on *trans*-*tert*-butyl 3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate (*trans*-**1a**) (Scheme 7). Treatment of *trans*-**1a** with 2,2-dimethyl-1-methoxy-1-trimethylsilyloxyethene in CH_2Cl_2 in the presence of aluminum chloride gave a pyrrolidone product **14** in 82% yield, which could be produced through spontaneous amidation of the expected ring-cleaved product **13** incorporating the carbon nucleophile at the C3 position of aziridine-2-carboxylate system during work-up. Although other Lewis acids such as indium chloride and triethylaluminum were ineffective as catalysts, the reaction in the presence of boron trifluoride-etherate afforded **14** albeit in lower yield (37%).



Scheme 7. Pictet–Spengler reaction of **10a** and the aluminum-catalyzed ring-opening reaction of *trans*-**1a** with a ketene acetal.

Examination of the ^1H NMR spectrum of a crude **13** based on the coupling constant ($J_{2,3}$=4.0 Hz), as expected, suggested an *anti*-type ring-opening in the latter Lewis acid-catalyzed reaction.[15] Furthermore, the fact that a larger coupling constant (J=9 Hz) between the C4–H and C5–H had been observed in *cis*-5-ethoxycarbonyl-1-methyl-4-phenylpyrrolidin-2-one (*cis*-**15**) compared to that (J=4 Hz) in the *trans*-derivative *trans*-**15** [(a) in Figure 2][23] also supported the *cis*-configuration of **14** due to the coupling constant of $J_{4,5}$=7.2 Hz. These speculations were confirmed by NOE experiment [(b) in Fig. 2]. Thus, the Lewis acid-catalyzed ring-opening reaction with a ketene acetal occurred with the same inversion mode as in the cyanation with Et_2AlCN.

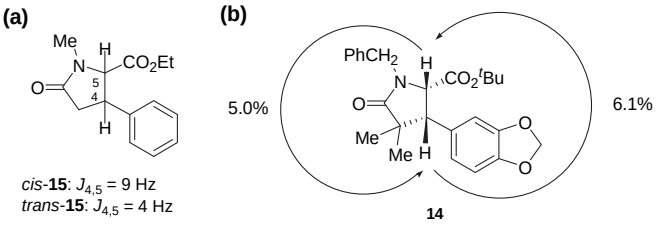


Figure 2. (a) Coupling constants of *cis*- and *trans*-5-ethoxycarbonyl-1-methyl-4-phenylpyrrolidin-2-one (*cis*- and *trans*-**15**) and (b) selected NOE enhancements of **14**.

In conclusion, in the ring-opening reactions of unactivated *trans*-3-(3,4-methylenedioxyphenyl)aziridine-2-carboxylate with nitrile reagents formation of azomethine ylide by C2–C3 bond cleavage was observed when TMSCN was treated under thermal conditions. On the other hand the uses of BrCN and Et_2AlCN led to N–C3 bond cleavage and stereochemical retention at the C3 was observed as a major reaction path in the case of the former BrCN, whereas inversion in the case of the latter Et_2AlCN. Et_2AlCN-participating ring-opening reactions using *trans*-3-arylaziridine-2-carboxylates carrying electron-deficient aromatic substituent and their cis-derivatives disclosed that the potential cationic character of the C-3 benzylic position and stereochemical requirements of substituents in the arylaziridine system controls the reactivity. Furthermore, synthetic utilities of the ring-opening reaction for unactivated, but electron-rich, 3-arylaziridine-2-carboxylate was demonstrated not only by application to the cyclization of a ring-opened cyanopropanoate product to an isoquinoline skeleton under Pictet–Spengler reaction condition but also by the extension of other C-nucleophiles from nitrile (C1) to a ketene acetal (C2).

3. Experimental

3.1. General

IR spectra were recorded on a JASCO IR-230E spectrophotometer. EIMS, FABMS, and ESIMS spectra were measured by JEOL GC-Mate, JEOL JMS-HX 110A and JMS-AX 500, and Thermo Scientific Exactive Bentitop Orbitrap spectrometers, respectively. ^1H NMR spectra were obtained on JEOL JNM ECP 600 (600 MHz) or 400 (400 MHz). ^{13}C NMR spectra were obtained on JEOL JNM ECP 600 (150 MHz), JEOL GSX-500α (125 MHz), or JEOL JNM ECP 400 (100 MHz). For TLC was used SiO_2 $60F_{254}$, 0.25 mm (Merck) and for column chromatography SiO_2 60 (63–210 μm) (Kanto-Cica) or FL100D SiO_2 (Fuji Silysia Chemical Ltd). Reactions under MW irradiation were carried out using CEM Discover with sealed tube. Dry tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. as 'Dehydrated'.

3.2. 1-Benzyl-2-(3,4-methylenedioxyphenyl)aziridine (2)

To a solution of *trans*-**1a** (93 mg, 0.26 mmol) in CH_2Cl_2 (1.5 mL), TMSCN (0.07 mL, 0.53 mmol) and $SnCl_4$ (0.03 mL, 0.27 mmol) were dropwise added at 0 °C. The mixture was stirred at 0 °C for 90 min, quenched by addition of satd aqueous $NaHCO_3$ solution (4 mL), and extracted with CH_2Cl_2 (4 mL×4). The organic solution was dried and evaporated under reduced pressure. Column chromatography of the residue (*n*-hexane/AcOEt=10:1) afforded **2** (32 mg, 48%) as a yellow oil. ^{1}H NMR (400 MHz): δ (ppm) 2.94 (dd, *J*=13.7, 7.1 Hz, 1H), 3.02 (dd, *J*=13.7, 5.7 Hz, 1H), 3.69 (dd, *J*=7.1, 5.7 Hz, 1H), 3.82 and 4.06 (each d, *J*=13.1 Hz, 1H), 5.95 (s, 2H), 6.73 (dd, *J*=8.1, 1.4 Hz, 1H), 6.76 (br s, 1H), 6.77 (d, *J*=8.1 Hz, 1H), 7.25–7.35 (m, 5H). ^{13}C NMR (100 MHz): δ (ppm) 39.0, 50.9, 51.5, 101.1, 108.5, 109.7, 119.4, 122.7, 127.6, 128.3, 128.6, 137.9, 147.1, 147.9. HREIMS *m*/*z*: 253.1097 (calcd for $C_{16}H_{15}NO_2$: 253.1103).

3.3. *N*-Benzyl-*N*-(*tert*-butoxycarbonylmethyl)-α-cyano-(3,4-methylenedioxyphenyl)methylamine (3)

A solution of *trans*-**1a** (49 mg, 0.14 mmol) and TMSCN (0.05 mL, 0.34 mmol) in MeCN (1.5 mL) was stirred at 120 °C for 30 min under MW irradiation. After evaporation of the solvent, the residue was purified by column chromatography (*n*-hexane/AcOEt=20:1) to afford **3** (50 mg, 96%) as colorless prisms, mp 105–106 °C. IR ν_{max} (cm^{-1}): 2235 (CN), 1734 (CO). ^{1}H NMR (400 MHz): δ (ppm) 1.45 (s, 9H), 3.18, 3.26 (each d, *J*=17.1 Hz, 1H), 3.51 and 3.97 (each d, *J*=13.4 Hz, 1H), 5.00 (s, 1H), 5.98 (d, *J*=1.8 Hz, 2H), 6.79 (d, *J*=8.1 Hz, 1H), 7.11 (br d, *J*=8.1 Hz, 1H), 7.13 (s, 1H), 7.28 (d, *J*=7.1 Hz, 1H), 7.34 (t, *J*=7.1 Hz, 2H), 7.41 (d, *J*=7.1 Hz, 2H). ^{13}C NMR (100 MHz): δ (ppm) 28.1, 52.4, 55.4, 57.5, 81.6, 101.4, 108.1, 108.2, 115.9, 121.3, 127.2, 127.8, 128.6, 128.8, 137.1, 148.2×2, 169.3. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.38; H, 6.22; N, 7.39.

3.4. Reaction of *trans*-1a with ethyl TMS-propiolate under MW irradiation

A solution of *trans*-**1a** (60 mg, 0.17 mmol) and ethyl TMS-propiolate (0.03 mL, 0.17 mmol) in MeCN (1.0 mL) was stirred at 120 °C for 30 min under MW irradiation. After evaporation of the solvent the residue was purified by PTLC (*n*-hexane/AcOEt=5:1) to give a labile **4** (11 mg, 12%) and **5** (7 mg, 8%), respectively. *(a) 1-Benzyl-2-(tert-butoxycarbonyl)-4-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)-3-trimethylsilyl-2,5-dihydropyrrole (**4**)*: a colorless oil. IR ν_{max} (cm^{-1}): 1716 (CO). ^{1}H NMR (400 MHz): δ (ppm) 0.23 (s, 9H), 1.05 (t, *J*=7.1 Hz, 3H), 1.47 (s, 9H), 3.73 and 3.88 (each br s, 1H), 3.99 (m, 2H), 4.55 (br s, 1H), 5.20 (br s, 1H), 5.94 and 5.95 (each d, *J*=1.5 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 6.77–6.83 (m, 2H), 7.24–7.26 (m, 5H). *(b) 1-Benzyl-2-(tert-butoxycarbonyl)-4-ethoxycarbonyl-5-(3,4-methylenedioxyphenyl)-3-trimethylsilylpyrrole (**5**)*: a colorless oil. IR ν_{max} (cm^{-1}): 1700 (CO). ^{1}H NMR (400 MHz): δ (ppm) 0.31 (s, 9H), 1.10 (t, *J*=7.1 Hz, 3H), 1.28 (s, 9H), 4.08 (*q*, *J*=7.1 Hz, 2H), 5.24 (s, 2H), 5.96 (s, 2H), 6.65–6.68 (m, 2H), 6.74 (dd, *J*=7.7, 0.7 Hz, 1H), 6.77–6.80 (m, 2H), 7.18–7.19 (m, 1H), 7.22–7.26 (m, 2H). ^{13}C NMR (150 MHz): δ (ppm) 0.78, 13.9, 27.8, 49.4, 60.2, 82.2, 101.2, 108.0, 110.9, 121.4, 124.2, 124.3, 124.7, 125.6, 127.0, 128.5, 132.1, 138.3, 140.4, 147.2, 147.9, 161.9, 166.5. HREIMS *m*/*z*: 521.2233 (calcd for $C_{29}H_{35}NO_6Si$: 521.2234).

3.5. Reaction of *trans*-1a with MVK under MW irradiation

A solution of *trans*-**1a** (60 mg, 0.17 mmol) and MVK (0.03 mL, 0.31 mmol) in THF (1.2 mL) was stirred at 120 °C for 15 min under MW irradiation. After evaporation of the solvent, the residue was purified by PTLC (*n*-hexane/Et_2O=4:1) to afford **6** (43 mg, 60%) and **7** (11 mg, 15%), respectively. *(a) (2R*,4R*,5R*)-tert-Butyl 4-acetyl-1-benzyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2-carboxylate (**6**)*: colorless prisms, mp 114–116 °C. IR ν_{max} (cm^{-1}): 1712 (CO). ^{1}H NMR (400 MHz): δ (ppm) 1.46 (s, 9H), 1.68 (s, 3H), 1.80 (dd, *J*=13.2, 8.1 Hz, 1H), 2.72 (ddd, *J*=13.2, 10.0, 8.1 Hz, 1H), 3.57 (d, *J*=13.4 Hz, 1H), 3.64 (d, *J*=8.1 Hz, 1H), 3.69 (d, *J*=13.4 Hz, 1H), 3.75 (ddd, *J*=10.1, 10.0, 8.1 Hz, 1H), 4.67 (d, *J*=10.1 Hz, 1H), 5.94 (m, 2H), 6.73 (d, *J*=8.0 Hz, 1H), 6.80 (br d, *J*=8.0 Hz, 1H), 6.83 (br s, 1H), 7.19–7.28 (m, 5H). ^{13}C NMR (100 MHz): δ (ppm) 28.1, 29.5, 31.0, 51.9, 55.4, 61.6, 67.5, 81.0, 101.0, 107.8, 108.9, 122.4, 126.9, 128.1, 128.6, 134.1, 138.8, 147.2, 147.4, 173.6, 207.4. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.73; H, 7.01; N, 3.32. *(b) (2S*,4S*,5S*)-tert-Butyl 3-acetyl-1-benzyl-5-(3,4-methylenedioxyphenyl)pyrrolidine-2-carboxylate (**7**)*: a colorless oil. IR ν_{max} (cm^{-1}): 1736 and 1714 (CO). ^{1}H NMR (400 MHz): δ (ppm) 1.46 (s, 9H), 2.09 (ddd, *J*=13.2, 7.9, 5.9 Hz, 1H), 2.18 (s, 3H), 2.52 (ddd, *J*=13.2, 9.6, 7.9 Hz, 1H), 3.03 (ddd, *J*=9.6, 5.9, 2.2 Hz, 1H), 3.60 and 3.69 (each d, *J*=13.7 Hz, 1H), 3.83 (d, *J*=2.2 Hz, 1H), 4.33 (dd, *J*=7.9, 7.9 Hz, 1H), 5.93 and 5.94 (each d, *J*=1.2 Hz, 1H), 6.75 (d, *J*=7.8 Hz, 1H), 6.86 (br d, *J*=7.8 Hz, 1H), 6.99 (s, 1H), 7.22–7.31 (m, 5H). ^{13}C NMR (100 MHz): δ (ppm) 27.8, 28.1, 36.2, 51.0, 53.4, 63.3, 66.1, 81.4, 100.9, 107.5, 108.0, 121.2, 126.9, 128.2×2, 136.7, 138.9, 146.9, 148.0, 172.3, 206.5. HREIMS *m*/*z*: 423.2032 (calcd for $C_{25}H_{29}NO_5$: 423.2045).

3.6. Reaction of *trans*-1a with BrCN

To a solution of BrCN (152 mg, 1.37 mmol) in CH_2Cl_2 (1.5 mL), *trans*-**1a** (84 mg, 0.24 mmol) in CH_2Cl_2 (1.5 mL) was dropwise added. The mixture was refluxed for 10 h, quenched by addition of satd aqueous $NaHCO_3$ solution (6 mL), and extracted with CH_2Cl_2 (5 mL×3). The organic solution was dried and evaporated under reduced pressure. Recrystallization of the residue from *n*-hexane/AcOEt (5:1) afforded **8** (21 mg, 19%). Column chromatography of the mother liquor with *n*-hexane/AcOEt (20:1) afforded an additional **8** (18 mg, 16%) and **9** (7 mg, 7%). *(a) (2S*,3R*)-tert-Butyl 2-(N-benzyl-N-cyanoamino)-3-bromo-3-(3,4-methylenedioxyphenyl)-propanoate (**8**)*: colorless prisms, mp 132–135 °C. IR ν_{max} (cm^{-1}): 2212 (CN), 1716 (CO). ^{1}H NMR (400 MHz): δ (ppm) 1.16 (s, 9H), 3.76 (d, *J*=10.8 Hz, 1H), 4.38, 4.44 (each d, *J*=14.1 Hz, 1H), 5.19 (d, *J*=10.8 Hz, 1H), 5.96 and 5.97 (each d, *J*=1.6 Hz, 1H), 6.72 (d, *J*=8.1 Hz, 1H), 6.82 (dd, *J*=8.1, 1.8 Hz, 1H), 6.86 (d, *J*=1.8 Hz, 1H), 7.39–7.41 (m, 5H). ^{13}C NMR (100 MHz): δ (ppm) 27.5, 51.5, 57.2, 68.8, 83.7, 101.5, 108.1, 108.7, 114.5, 122.4, 128.95, 129.05, 130.1, 133.7, 147.9, 148.5, 165.6. Anal. Calcd for $C_{22}H_{23}BrN_2O_4$: C, 57.53; H, 5.05; N, 6.10. Found: C, 57.46; H, 4.93; N, 6.07. *(b) (Z)-tert-Butyl 2-(benzylcyanoamino)-3-(3,4-methylenedioxyphenyl)propenoate (**9**)*: a colorless oil. IR ν_{max} (cm^{-1}): 2216 (CN), 1707 (CO). ^{1}H NMR (400 MHz): δ (ppm) 1.48 (s, 9H), 4.32 (s, 2H), 6.05 (s, 2H), 6.84 (d, *J*=8.1 Hz, 1H) 7.09 (dd, *J*=8.1, 1.6 Hz, 1H), 7.21 (d, *J*=1.6 Hz, 1H), 7.28–7.34 (m, 5H), 7.38 (s, 1H). ^{13}C NMR (100 MHz): δ (ppm) 28.0, 57.5, 82.8, 101.7, 108.6, 109.4, 115.0, 126.0 126.6, 126.8, 128.7, 128.9, 129.7, 133.6, 136.3, 148.3, 149.7, 162.8. HREIMS *m*/*z*: 378.1577 (calcd for $C_{22}H_{22}N_2O_4$: 378.1579).

3.7. Reaction of *trans*-1a with a commercially available Et_2AlCN: a 40:1 mixture of (2S*,3S*)- (10a) and (2S*,3R*)-*tert*-butyl 2-(*N*-benzylamino)-3-cyano-3-(3,4-methylenedioxyphenyl)propanoate (11a)

To a solution of *trans*-**1a** (102 mg, 0.29 mmol) in benzene (1.5 mL), a 1 M solution of Et_2AlCN in toluene (1.5 mL, 1.50 mmol) was added. The mixture was stirred at room temperature for 1 day, quenched by slow addition of 2 N NaOH solution (2 mL), and extracted with AcOEt (4 mL×5). The organic solution was dried and evaporated under reduced pressure. Column chromatography of the residue (*n*-hexane/AcOEt=10:1) afforded a 40:1 mixture of **10a** and **11a** (80 mg, 72%) as a colorless oil.

3.8. Reaction of 1 with a freshly prepared Et_2AlCN (Table 2)

According to the reported method,[21] distilled TMSCN (2.5 mL, 20.2 mmol) was added to a 1 M solution of Et_3Al in toluene (20 mL, 20.2 mmol) under ice-cooling and then the colorless solution was refluxed for 30 min. A pale yellow solution given was used in the ring-opening reaction as a freshly prepared Et_2AlCN without further purification.

*3.8.1. On trans-**1a** (run 1): (2S*,3S*)-tert-butyl 2-(N-benzylamino)-3-cyano-3-(3,4-methylenedioxyphenyl)propanoate (**10a**).* A mixture of *trans*-**1a** (60 mg, 0.17 mmol) in benzene (0.5 mL) and a 1 M solution of Et_2AlCN in toluene (0.9 mL, 0.9 mmol) was reacted for 2.5 h at 0 °C to give **10a** (59 mg, 92%) as a colorless oil. IR ν_{max} (cm^{-1}): 3340 (NH), 2247 (CN), 1728 (CO). ^1H NMR (400 MHz) for **10a**: δ (ppm) 1.43 (s, 9H), 2.08 (br s, 1H), 3.56 (d, J=5.1 Hz, 1H), 3.74, 3.90 (each d, J=13.2 Hz, 1H), 4.16 (d, J=5.1 Hz, 1H), 5.96 (s, 2H), 6.75 (d, J=8.0 Hz, 1H), 6.78 (dd, J=8.0, 1.6 Hz, 1H), 6.84 (d, J=1.6 Hz, 1H), 7.24–7.32 (m, 5H). ^{13}C NMR (100 MHz) for **10a**: δ (ppm) 28.0, 40.7, 52.3, 63.5, 83.0, 101.4, 108.3, 108.9, 118.8, 122.2, 125.0, 127.4, 128.3, 128.5, 138.8, 147.9, 148.0, 170.0. HREIMS m/z: 378.1577 (calcd for $C_{22}H_{22}N_2O_4$: 378.1579).

*3.8.2. On trans-**1b** (run 2): (2S*,3S*)-tert-butyl 2-(N-benzylamino)-3-cyano-3-phenylpropanoate (**10b**).* A mixture of *trans*-**1b** (60 mg, 0.19 mmol) in benzene (0.5 mL) and a 1 M solution of Et_2AlCN in toluene (0.9 mL, 0.9 mmol) was reacted for 24 h at rt to give **10b** (26 mg, 40%) as a colorless oil. IR ν_{max} (cm^{-1}): 3320 (NH), 2244 (CN), 1727 (CO). ^1H NMR (400 MHz): δ (ppm) 1.39 (s, 9H), 3.60 (d, J=5.4 Hz, 1H), 3.73,and 3.89 (each d, J=13.4 Hz, 1H), 4.23 (d, J=5.4 Hz, 1H), 7.25–7.34 (m, 10H). ^{13}C NMR (100 MHz): δ (ppm) 27.9, 41.2, 52.2, 63.5, 82.9, 118.7, 127.3, 128.2, 128.4, 128.5, 128.6, 128.7, 131.5, 139.0, 169.9. HRFABMS m/z: 375.1487 (calcd for $C_{21}H_{24}KN_2O_2$: 375.1475).

*3.8.3. On trans-**1c** (run 3) (2S*,3S*)-tert-butyl 2-(N-benzylamino)-3-cyano-3-(4-chlorophenyl)propanoate (**10c**).* A mixture of *trans*-**1c** (61 mg, 0.18 mmol) in benzene (0.5 mL) and a 1 M solution of Et_2AlCN in toluene (0.9 mL, 0.9 mmol) was reacted at 0 °C for 2 h and then at rt for 15 h to give **10c** (18 mg, 27%) as a colorless oil. IR ν_{max} (cm^{-1}): 3320 (NH), 2243 (CN), 1728 (CO). ^1H NMR (400 MHz): δ (ppm) 1.41 (s, 9H), 1.99 (br s, 1H), 3.58 (d, J=5.3 Hz, 1H), 3.73 and 3.89 (each d, J=13.2 Hz, 1H), 4.18 (d, J=5.3 Hz, 1H), 7.26–7.51 (m, 9H). ^{13}C NMR (100 MHz): δ (ppm) 27.9, 40.6, 52.3, 63.4, 83.2, 118.4, 127.4, 128.2, 128.5, 128.9, 129.9, 134.7, 138.8, 169.8. HRESIMS m/z: 371.1511 (calcd for $C_{21}H_{24}{}^{35}ClN_2O_2$: 371.1521).

3.9. (2S*,3R*)-tert-Butyl 2-benzyl-4-cyano-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (12)

To a solution of **10a** (25 mg, 0.07 mmol) in CH_2Cl_2 (0.2 mL), 37% HCHO aqueous solution (0.2 mL, 2.69 mmol) was dropwise added. After stirring at rt for 20 min, trifluoroacetic acid (0.2 mL, 2.69 mmol) was added and the mixture was stirred at 40 °C for 4 h, quenched by addition of satd $NaHCO_3$ solution (3 mL), and extracted with CH_2Cl_2 (5 mL×4). The organic solution was washed with H_2O and brine, dried, and evaporated under reduced pressure. Column chromatography of the residue (*n*-hexane/AcOEt=10:1) afforded **12** (22 mg, 87%) as a pale yellow oil. IR ν_{max} (cm^{-1}): 2242 (CN), 1719 (CO). ^1H NMR (400 MHz): δ (ppm) 1.39 (s, 9H), 3.86 (s, 2H), 3.90 (d, J=2.3 Hz, 1H), 4.06 and 4.12 (each d, J=13.4 Hz, 1H), 4.20 (d, J=2.3 Hz, 1H), 5.93 and 5.94 (each d, J=0.9 Hz, 1H), 6.48 and 6.71 (each s, 1H), 7.29 (d, J=7.3 Hz, 1H), 7.36 (t, J=7.3 Hz, 2H), 7.47 (d, J=7.3 Hz, 2H). ^{13}C NMR (100 MHz): δ (ppm) 28.1, 34.0, 50.0, 59.2, 60.8, 82.8, 101.2, 106.5, 108.3, 119.8, 120.0, 127.5, 127.8, 128.5, 128.9, 137.6, 146.7, 147.9, 168.4. HREIMS m/z: 392.1723 (calcd for $C_{23}H_{24}N_2O_4$: 392.1736).

3.10. Reaction of *trans*-1a with 2,2-dimethyl-1-methoxy-1-trimethylsilyloxyethene: (2S*,3R*)-1-benzyl-5-(*tert*-buthoxycarbonyl)-4-(3,4-methylenedioxyphenyl)pyrrolidin-2-one (14)

To a suspension of $AlCl_3$ (25 mg, 0.19 mmol) in CH_2Cl_2 (1.5 mL), *trans*-**1a** (60 mg, 0.17 mmol) in CH_2Cl_2 (1.5 mL) and a ketene silyl acetal (0.1 mL, 0.49 mmol) were dropwise added at −78 °C. After being stirred at the same temperature for 2 h, the mixture was quenched by addition of satd $NaHCO_3$ solution (1 mL) and extracted with AcOEt (10 mL×3). The organic solution was successively washed with satd $NaHCO_3$ solution, H_2O, and brine, dried, and evaporated under reduced pressure. Column chromatography of the residue (*n*-hexane/AcOEt=20:1) afforded **14** (59 mg, 82%) as colorless needles, mp 138–141 °C. IR ν_{max} (cm^{-1}): 1743 and 1683 (CO). ^1H NMR (400 MHz): δ (ppm) 0.92 (s, 3H), 1.12 (s, 9H), 1.14 (s, 3H), 3.14 and 4.03 (each d, J=7.2 Hz, 1H), 4.36 and 5.36 (each d, J=14.0 Hz, 1H), 5.91 (d, J=3.5 Hz, 2H), 6.58 (dd, J=8.0, 1.7 Hz, 1H), 6.65 (d, J=1.7 Hz, 1H), 6.68 (d, J=8.0 Hz, 1H), 7.18–7.20 (m, 2H), 7.29–7.34 (m, 3H). ^{13}C NMR (100 MHz): δ (ppm) 20.5, 25.6, 27.5, 45.0, 45.5, 53.1, 60.4, 81.7, 100.9, 107.7, 109.7, 122.8, 127.8, 128.7, 128.9, 131.2, 135.8, 146.8, 147.2, 168.2, 180.2. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.74; H, 6.93; N, 3.34.

Supplementary data

NMR charts of new compounds characterized and X-ray data of **3** (CIF). Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2010.03.063.

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19. Crystal data for **3**: $C_{22}H_{24}N_2O_4$; M=380.43 g mol^{-1}, monoclinic, $bP2_1/c$, colorless prism measuring 0.40×0.35×0.25 mm, T=90 K, a=10.8630(17) Å, b=11.3675(17) Å, c=16.727(3) Å, β=97.242(3)°, V=2049.1(5) $Å^3$, Z=4, D_{calcd}=1.233 Mg m^{-3}, μ=0.085 mm^{-1}, GOF on F^2=1.059, $R1$=0.0553, $wR2$=0.1439 [$I>2\sigma(I)$], $R1$=0.0782, and $wR2$=0.1574 (all data). CCDC 721783.
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