JOC Article

Tandem Michael Addition/Amino-Nitrile Cyclization from 2-Formyl-1,4-DHP in the Synthesis of Novel Dihydroindolizine-Based Compounds

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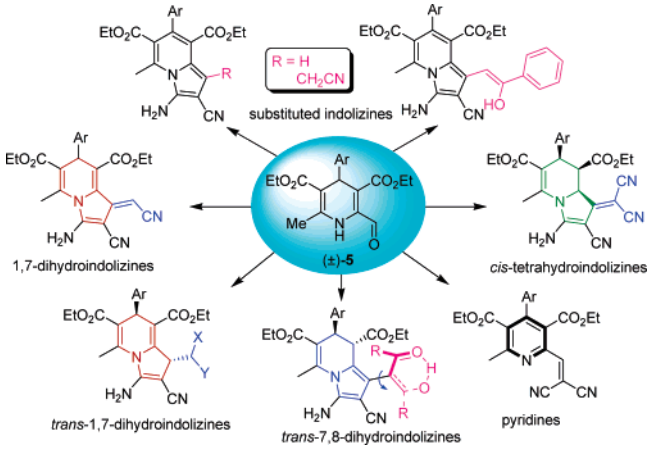

A simple and efficient methodology for the synthesis of a small library of substituted indolizines with different degrees of saturation starting from the racemic 2-formyl-1,4-DHP reagent **5** was described. The large synthetic possibilities of this reagent as well as of its Knoevenagel corresponding 2-dicyanovinyl-1,4-DHP reagent **14** were investigated using four kinds of activated methylenes as nucleophiles. The key step of the sequential reaction was based on the highly diastereoselective tandem Michael addition/intramolecular amino-nitrile cyclization catalyzed by an organic base, which resulted in the formation of 1,7-dihydroindolizines in a diastereoselective manner. The process seems to be a straightforward one and can be extended to numerous active methylenes such as malononitrile, 1,3-diketones, and alkyl acetoacetates. The 1,3-hydrogen shift of partially hydrogenated indolizines was accomplished easily with a base at room temperature, giving rise to the corresponding 7,8-dihydroindolizines in very good yields. Interestingly, when the active methylene bears a leaving group, the latter process could not be accomplished because a rare cis-elimination of phenylsulfinic acid and nitrous acid preceded the hydrogen shift. The resulting 1,7-dihydroindolizines bearing an *exo*-methylene group at C_1 were not isolated in all cases, as they turned rapidly to indolizines as the thermodynamically more stable products. During these investigations, oxidization of 1,7-dihydroindolizines with $CuCl_2$ resulted in the formation of polysubstituted pyridines. Also, the epimerization of certain 1,7-dihydroindolizines was evidenced in the solution studied by NMR spectroscopy, whereas in the solid state, they existed only in a unique form as shown by X-ray diffraction analysis of a representative structure. Finally, all products reported herein bear a primary amine and a nitrile function crucial for further transformations. These include the introduction of various pharmacophore groups at either NH_2 or CN groups as well as at both groups at the same time to access the more elaborated indolizines fused to *N*- or *N*,*N*-heterocycles.

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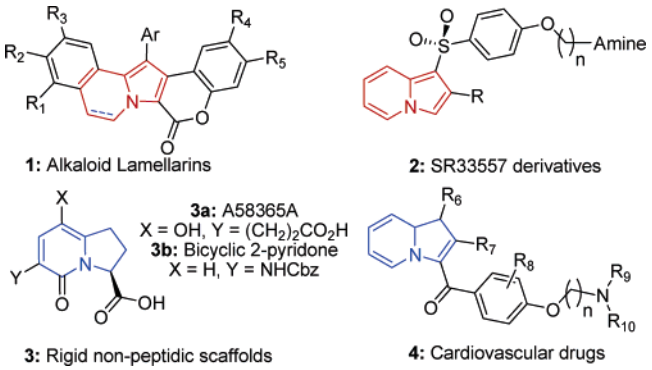
CHART 1. Representative Molecules Containing Indolizine and Dihydroindolizine Units



Introduction

Indolizines belonging to the azabicyclic compounds family are interesting compounds playing an important role in synthetic, therapeutic, and bioorganic chemistry. Octahydroindolizine alkaloids commonly known as indolizidines constitute a family of nitrogen-fused bicyclo[4.3.0]nonanes and have recently received considerable attention by virtue of their varied and pharmaceutically useful biological actions as potential antiviral, antitumor, and immunomodulating agents and as glycosidase inhibitors.[1]

Although aromatic indolizines have yet to be discovered in nature,[2] they constitute important subunits of numerous alkaloids as exemplified in the topoisomerase (Top1) inhibitor Lamellarin derivative **1** (Chart 1);[3] they were used successfully as intermediates in the total synthesis of the (±)-monomorine alkaloid.[4] Synthetic indolizines have found also other widespread applications. In medicine, they are useful for treating and preventing cancer, inflammatory disorders, autoimmune diseases, and other conditions involving PDE4 or elevated levels of cytokines.[5] The use of indolizines against other pathologies was associated with their phosphatase inhibitions, antioxidant activities, and CNS properties (see, for example, the channel calcium antagonist SR33557 (**2**)).[6] In addition, various studies have shown that substituted indolizines, including notably β-cyclodextrins, offer highly fluorescent materials[7] and chromophores[8] and constitute key intermediates for the synthesis of cyclazines,[9] redox-active cyclophanes, and substituted 3,3′-bisindolizines.[10]

Although the importance of aromatic indolizines has been widely demonstrated and extensively documented, the subgroup of dihydroindolizines on the other hand has hardly been explored. For example, the latter skeleton is incorporated in Lamellarins,[3] in the angiotensin-converting enzyme inhibitor A58365A (**3a**),[11] and in the constrained peptide mimics (**3b**)[12] and constitutes valuable intermediates in the synthesis of indolizidines,[13] the antitumor camptothecin,[14] and polysubstituted indoloindolizines.[15] Another aspect of this family was demonstrated by their highly interesting thermochromism and photochromism driven by a 6π-electron pericyclic reaction, which were discovered for the first time in 1979,[16] and by their uses for treating pathological syndromes of the heart, e.g., angina pectoris and cardiac arrhythmias (see general structure **4**).[17]

Most of the hitherto reported syntheses of these types of compounds rely on a small number of strategies, all based on the construction of the five-membered ring moiety of the indolizine framework:[18] (1) the Scholtz[19] and Tschitschibabin[20] reactions constitute important recurrent processes, in which the ring closure was accomplished by the reaction of 2-alkylpyridines with carboxylic acid anhydrides and 2-halo ketones, respectively; (2) the second approach takes advantage of the 1,3-dipolar cycloaddition reaction of pyridinium *N*-ylides with

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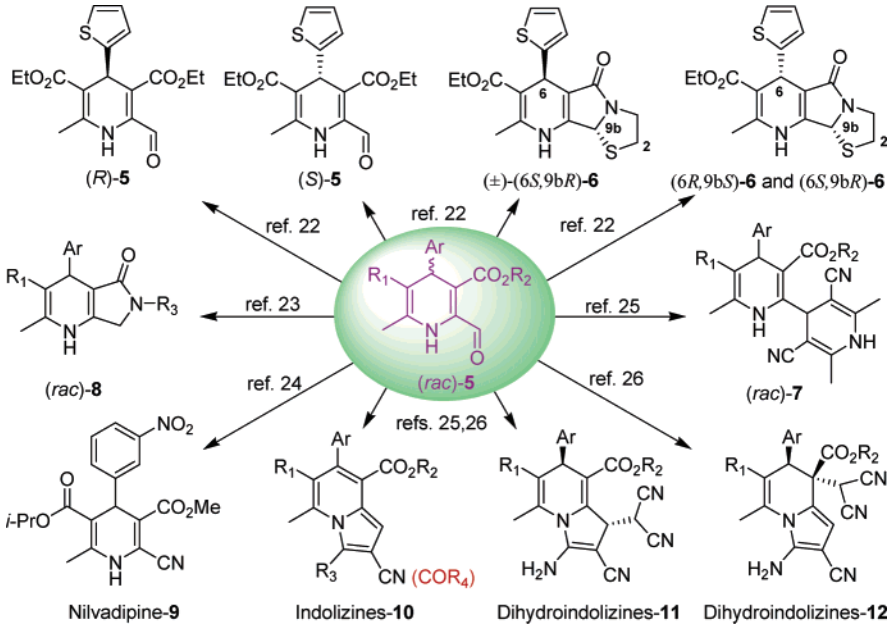
CHART 2. Structural Variety of Molecules Obtained from the 1,4-DHP Scaffold (*rac*-5)



various C=C- and C≡C-type bond Michael systems; and finally (3) reactions of pyridines unsubstituted in their α-position with substituted allylic or acetylenic halides or ester reagents. More recently, elegant approaches to access polysubstituted, fused and heterofused indolizines were explored. They are based on a background using Cu-assisted cycloisomerization of alkynyl imines,[4] Pd/Cu-catalyzed cross-coupling of acyl chlorides and alkynes,[7a] and a Wittig olefination−Sonogashira coupling sequence of 2-formyl aromatic azacycle followed by the cyclization of the silicon-capped (*Z*)-2-pyridone vinylacetylene with basic alcoholic solutions.[21]

For all these reasons, the development of simple and efficient methods for generating small molecules containing the indolizidine skeleton is vitally important to both the pharmaceutical and agrochemical sectors in the search for biologically active compounds. In particular, the development of an efficient route toward the regiocontrolled preparation of highly substituted indolizines with different degrees of saturation is still regarded as an important synthetic challenge in heterocyclic chemistry.

Our previous studies in the 1,4-DHPs chemistry demonstrated 2-formyl-1,4-DHP derivative (*rac*)-**5** to be a versatile synthon by which to access numerous azacycles and azathiacycles in racemic or chiral nonracemic form (Chart 2). Indeed, it has been resolved successfully by using CIDR methodology (crystallization-induced asymmetric resolution), and the enantiopure (*R*)-**5** and (*S*)-**5** obtained were used to access new racemic and chiral tricyclic thiolactams (±)-(6*S*,9b*R*)-**6**, (6*R*,9b*S*)-**6**, and (6*S*,9b*R*)-**6**, respectively.[22] We have also explored the utility of this substrate as a synthon that is remarkably suitable for the synthesis of various pyrrolo[3,4-*b*]-1,4-DHPs **8**,[23] the calcium antagonist Nilvadipine (**9**),[24] conformationally constrained bis-1,4-DHPs **7**,[25] substituted indolizines **10**,[25,26] and more interestingly polysubstituted amino-nitrile dihydroindolizines **11** and **12**.[26]

The first experiments toward indolizines **10**−**12** involved treatment of 2-formyl-1,4-DHPs (*rac*)-**5** with benzoylacetonitrile. The reaction proceeded smoothly under the catalytic influence of piperidine to furnish the Knoevenagel derivatives in a unique geometrical form (*E*-isomer), which underwent base-assisted transformation to 3-aminoindolizines **10** (R_4 = Ph). Interestingly, the ring closure took place only in the presence of a catalytic amount of nitrogen-type bases, such as piperidine, morpholine, and triethylamine.[25a−c] More recently, variations of this reaction with 2 equiv of malononitrile without catalyst resulted in the isolation of the *trans*-1,7-dihydroindolizines **11** in a one-pot procedure. The reaction proceeded via the tandem Knoevenagel condensation/intramolecular amino-nitrile-type cyclization of the Michael adduct. The reaction product is unstable in the solvent and rearranges to the corresponding *cis*-7,8-dihydroindolizines **12** by a suprafacial 1,3-sigmatropic alkyl shift at C_1 of the indolizine ring. This transformation seems to be driven favorably by the aromatization of the pyrrole ring (Chart 2).

Our own interest in the development of new transformations of 2-formyl-1,4-DHP derivatives (*rac*)-**5** and in extending this type of tandem reaction prompted us to examine potential applications and generalizations to the synthesis of substituted indolizines and dihydroindolizines. Optimization of this protocol was announced previously by us in a brief letter.[26] We now wish to present our findings from the related study dealing with the influence of several activated methylene reagents. The reactivity of 2-formyl-1,4-DHP (*rac*)-**5** would be regarded particularly closely during the cyclization step to shed further

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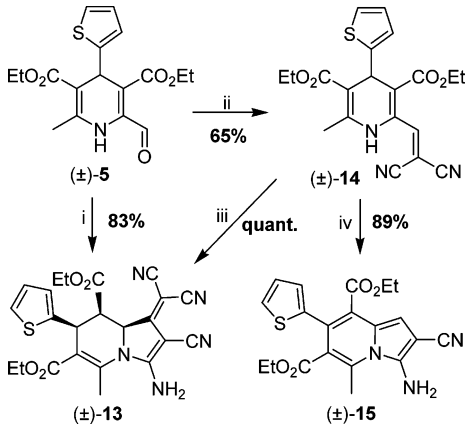
SCHEME 1. Reaction of 2-Formyl-1,4-DHP 5 with Malononitrile as a Highly Active Methylene[a]



[a] Key: (i) 2 equiv of $CH_2(CN)_2$, EtOH, piperidine$_{cat}$, rt; (ii) 1 equiv of $CH_2(CN)_2$, EtOH, EtONa$_{cat}$, rt; (iii) 1 equiv of $CH_2(CN)_2$, EtOH, piperidine$_{cat}$, rt; (iv) piperidine$_{cat}$, EtOH, reflux.

light on the course of this short transformation and, also, to gain further insight into the mechanistic aspects of this tandem reaction. In this sense, four classes of activated methylenes were examined in detail.

Results and Discussion

Use of the Highly Reactive Active Methylene Compound Malononitrile (Type A). Focusing our initial attention on reconsidering the 2-formyl-1,4-DHP (*rac*)-**5** with highly activated methylene, we investigated the influence of bases as a catalyst. Thus, in the presence of piperidine as the best among the nitrogen bases used, the reaction of (*rac*)-**5** with 2 equiv of malononitrile in dry ethanol at room temperature resulted in the formation of 3-amino-2-cyano-1-dicyanomethylenetetrahydroindolizine (**13**) in good yield (83%) after purification by recrystallization from ethanol. The same product was obtained, in a quantitative yield from 2-dicyanovinyl-1,4-DHP derivative **14** and 1 equiv of malononitrile under piperidine catalysis at the same temperature (Scheme 1). In all cases, the reaction led to the formation of crystalline materials as a single stereomer in which the three angular protons at positions 7, 8, and 8a are in a cis relationship, as established by NMR measurements.

The one-pot procedure starting from the formyl derivative (*rac*)-**5** seems to be simple and reproducible; it furnished the tetrahydroindolizine **13** in a yield better than that for the two-step reaction process. In this case, product **13** was isolated in the overall yield of 65%. It is noteworthy that the change of the nature of the nitrogen base used as the catalyst did not affect either the stereochemical outcomes or the yields of the reaction in both direct and indirect pathways. Also, because no other stereoisomers could be detected in either crude reaction mixtures or recrystallized products, we assume that the tandem process is highly diastereoselective. Interestingly, the reaction takes another course when diethyl 2-(2,2-dicyanovinyl)-1,4-DHP **14**, obtained in 65% yield from (*rac*)-**5** and 1 equiv of malononitrile in ethanol with EtONa as catalyst, was heated in refluxing ethanol in the presence of piperidine. Under these conditions, the most conjugated and thermodynamically stable indolizine **15** isolated in quantitative yield constituted the sole reaction product as expected.

Use of Enolizable Active Methylenes Such as 1,3-Diketones (Type B). To learn more about the reactivity of 2-formyl derivative (*rac*)-**5**, especially the one of the corresponding Knoevenagel product **14**, three different active methylenes of Type B capable of an oxo-enol tautomerism were investigated. Thus, according to the well-established protocol outlined above (i.e., active methylene, EtOH, piperidine$_{cat}$, rt), treatment of 2-dicyanovinyl-1,4-DHP **14** with acetylacetone led to a crystalline compound in very good yield (88%).

The structure of this product was identified as that of 7,8-dihydroindolizine **16a**, presumably obtained via intermediacy of the Michael adduct **Aa** followed by an intramolecular aminonitrile cyclization and an imino-enamine tautomerism in the ultimate stage (path a, in Scheme 2). The dihydroindolizine **16a** isolated from this tandem has the relative 1,7-trans configuration, confirmed by an X-ray crystallographic structure determination.[27] This principal fact that appears possible could illustrate the mechanistic paradigm in this cascade process. Thus, taking into account that the DHP double bond and the one of the dicyanovinyl group could take *s*-trans and *s*-cis conformations, the trans configuration of product **16** could be easily explained as indicated in the plausible model depicted in Scheme 2. There, only the diastereoselective addition of the enolate form of the acetylacetone reagent from the sterically less-encumbered face of the polarized double bond of the substrate **14** in an *s*-trans geometry as the more stable conformer could be considered.[28] Moreover, this fact was corroborated with a preliminary molecular modeling study and energy-minimized structures of both conformations of **14** optimized under the ChemDraw3D MM2 program. As a result, the incoming enolate nucleophile more easily approached the opposite less-hindered face of the olefin of the *s*-trans conformer than the *s*-cis one. In the latter case, the face of the olefin is encumbered by thienyl and/or ethoxycarbonyl groups. In addition, no 4*H*-pyran systems **19a**−**c**, which could have resulted from an intramolecular heterocyclization of the keto enol intermediates **18a**−**c** (addition of an OH to a CN group as in path b; Scheme 2), were isolated.[29] This is probably due to the highly conjugated bicyclic indolizine ring in **16a**−**c**, which becomes more stable than the pyran ring in **19a**−**c**.

Consistent with our previous reports outlining the formation of 7,8-dihydroindolizines **12** from 1,7-dihydroindolizines **11** via the 1,3-sigmatropic alkyl shift process, we envisioned to examine the behavior of 1,7-dihydroindolizines **16** (R = Me) under experimental conditions similar to those for **12**,[26] as outlined above in Scheme 2. Thus, treatment of **16a** with piperidine resulted in the formation of 7,8-dihydroindolizines **17a** in 66% yield. The formation of this product could be due to the 1,3-hydrogen shift instead of to an alkyl shift. The process commences probably with the formation of **Ba** by enolization of **16a** rendering the proton H_1 of dihydroindolizine more labile. Later, its extraction with a base takes place, and conjugation of

(27) For X-ray single-crystal structure determination of (±)-**16a**, see Supporting Information.

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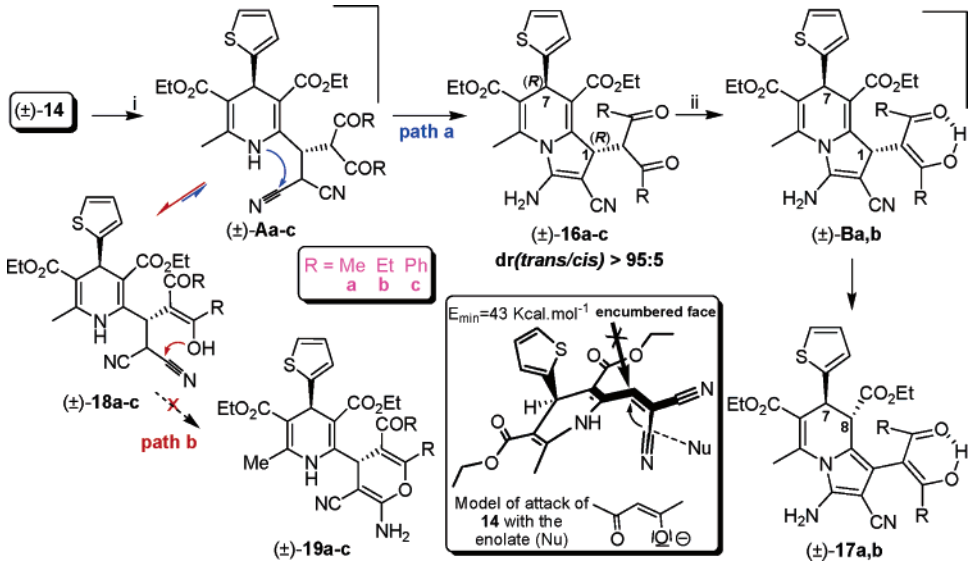
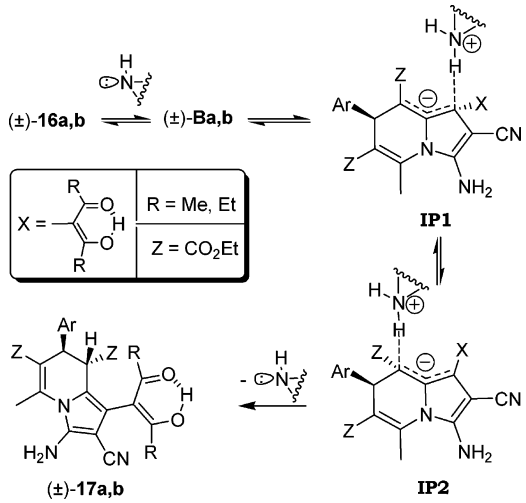
SCHEME 2. Reaction of 2-Formyl-1,4-DHP 5 with Enolizable Activated Methylene 1,3-Diketones[a]



[a] Key: (i) Ac_2CH_2, EtOH, $piperidine_{cat}$, rt; (ii) 1.2 equiv of piperidine, EtOH, rt.

SCHEME 3. Mechanistic Aspect of the Rearrangement of *trans*-1,7-Dihydroindolizine 16 to the Corresponding *trans*-7,8-Dihydroindolizine 17



the resulted anion followed by its protonation leads to **17a** in which the shifted hydrogen is attached at the same face of the bulky thienyl group (Scheme 3). Interestingly, the same sequence was effective with heptan-3,5-dione leading to **16b** and then **17b** in 90% and 69% yields, respectively. In contrast, the dicyanovinyl substrate **14** with dibenzoylmethane furnished **16c** via the tandem Michael condensation/amino-nitrile cyclization in 84% yield. All attempts at its transformation into the corresponding **17c** failed, probably due to the transformation of the intermediate **Bc** into **17c** that is problematic. In fact, at that stage, the conjugation between the stable diphenyl keto enol and the dihydroindolizine systems becomes possible, thus implying that these systems tend to be coplanar. For geometrical reasons found in **17c**, these facts could not be considered and non-dihydroindolizine **17c** could be formed.

The difference in reactivity observed between 1,7-dihydroindolizines **11**[26] and **16** during their reaction with piperidine could be attributed to the oxo-enol tautomerism of 3-substituted acetylacetone derivative **16** into its intermediate **B**. This phenomenon induces the absence of a proton at an adjacent position. Finally, the subsequent base-catalyzed 1,3-hydrogen shift with the supraselectivity[30] affords the *trans*-7,8-dihydroindolizine **17**.[30] In this case, piperidine does not split off the weakly acidic proton H on the "methylene" carbon in structure **B**, a process that would lead to tetrahydroindolizine, as in the case of malononitrile. Instead, we assume that the action of piperidine in a stoichiometric quantity only weakens the C_1-H bond, and the H_1 of dihydroindolizine shifts along the same face of the 1,7-dihydroindolizine ring to C_8. This running with the intermediacy of ion pairs **IP1** and **IP2** is depicted in Scheme 3 and is driven by the conjugation energy gained by the formation of the stable and favorable pyrrole ring.

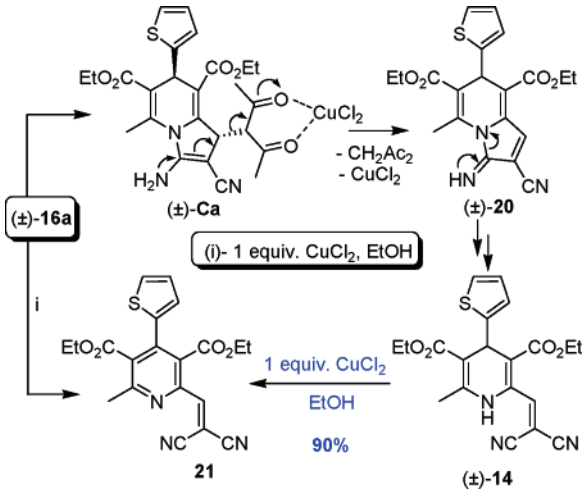
In the final effort to obtain the stabilized enolic form as in the presumed intermediate **Ba** in Scheme 2, we tried to prepare an acetonyl acetate cuprate **Ca** by the reaction of 1,7-dihydroindolizine **16a** with $CuCl_2$ in aqueous ethanol solution (70%) at room temperature.[31] Interestingly, the sole isolated reaction product seems to be the pentasubstituted pyridine **21**, obtained in 89% yield. The product was formed by the retro tandem process amino-nitrile cyclization/Michael addition as highlighted in Scheme 4. The intermediacy of the product (±)-**14** in this sequence was evidenced in a parallel experiment by treating (±)-**14** under the same conditions as those above (1 equiv of $CuCl_2$, EtOH 70%, rt). Under these conditions, we isolated also the expected pyridine product **21** in 90% yield.

Use of Enolizable Active Methylenes Such as Alkyl Acetoacetates (Type C). To learn more about the above-described process, additional reactions were performed. So, 2-(2,2-dicyanovinyl)-1,4-DHP **14**, when allowed to react with alkyl acetoacetates under the same conditions as those above with piperidine as the catalyst, the reaction proceeded with a mechanism similar to that of acetylacetone and yielded only

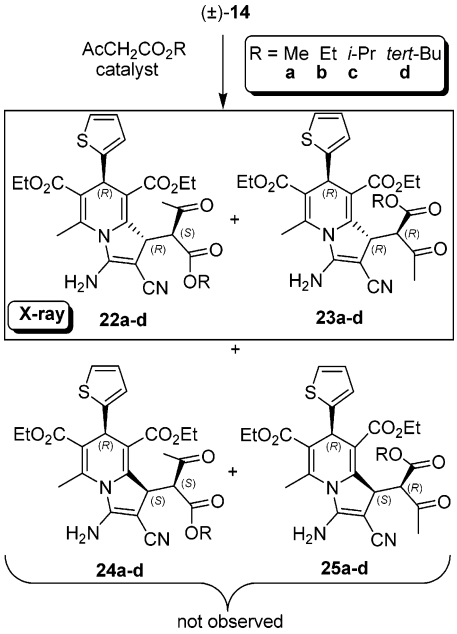
(30) (a) Hess, B. A., Jr.; Schaad, L. J.; Pancir, J. *J. Am. Chem. Soc.* **1985**, *107*, 149. (b) Jensen, F. *J. Am. Chem. Soc.* **1995**, *117*, 7487. (c) Hussénius, A.; Matsson, O.; Bergson, G. *J. Chem. Soc., Chem. Commun.* **1998**, *107*, 2693. (d) Okajima, T.; Imafuku, K. *J. Org. Chem.* **2002**, *67*, 625. (e) Hudson, C. E.; McAdoo, D. J. *J. Org. Chem.* **2003**, *68*, 2735.

(31) For a review for oxidations of DHP with metals, see: Han, B.; Liu, Z.; Liu, Q.; Zang, L.; Liu, Z.-L.; Yu, W. *Tetrahedron* **2006**, *62*, 2492 and citations therein.

SCHEME 4. Oxidization of *trans*-1,7-Dihydroindolizine 16a with $CuCl_2$ in Ethanol



SCHEME 5. Reaction of Alkyl Acetoacetates with 2-Dicyanovinyl-1,4-DHP 14 in a One-Pot Procedure



two diastereomers **22** and **23** from the possible four products **22**−**25** according to the NMR spectrum of the reaction mixture (Scheme 5). The relative configuration for these products was tentatively established as (1*R**,7*R**) in both cases for the dihydroindolizine carbons with an additional exocyclic carbon of the activated methylene which is *S** and *R** in products **22** and **23**, respectively.

Similarly, as in 1,3-diketones, the high diastereoselectivity of the addition reaction of alkyl acetoacetates into the vinyl fragment of substrate **14** was obtained. In fact, as in our proposed model in Scheme 2, the intermolecular attack of the enolate takes place through the governance of the 1,4-DHP ring conformation. The ratio of the diastereomers **22a**−**d** and **23a**−**d** is dependent on the structure of alkyl acetoacetates, on the reaction conditions used including reaction time, temperature, and solvent, and finally on the base used as the catalyst. This indicated clearly that the epimerization at the more acidic proton bearing the methylene carbon was effective. Furthermore, taking into account that the ratios of the products **22** and **23** were in favor of **22** in several cases, recrystallization of the crude mixture from dry ethanol resulted in the isolation of pure diastereomers **22a**, **22b**, **22c**, and **23d** in yields of 88%, 85%, 80%, and 58%, respectively. Although isomers **22a**−**c** have 1*R**, 7*R**, and 1′*S** relative configurations at the C_1, C_7, and C_1' stereocenters, respectively, as confirmed by X-ray crystallographic analysis of the representative dihydroindolizine **22b** (see Ortep drawing of compound **22b** in Supporting Information),[32] isomer **23b** had 1*R**, 7*R**, and 1′*R** relative configurations at stereocenters C_1, C_7, and C_1'. Although minor diastereomers **23a**−**c** could not be isolated in pure form, their NMR characterization had been done on the basis of the spectra of the pure major products and ^1H and ^{13}C NMR spectra of the crude materials obtained from the mother liquors partially enriched by **23a**−**c**.

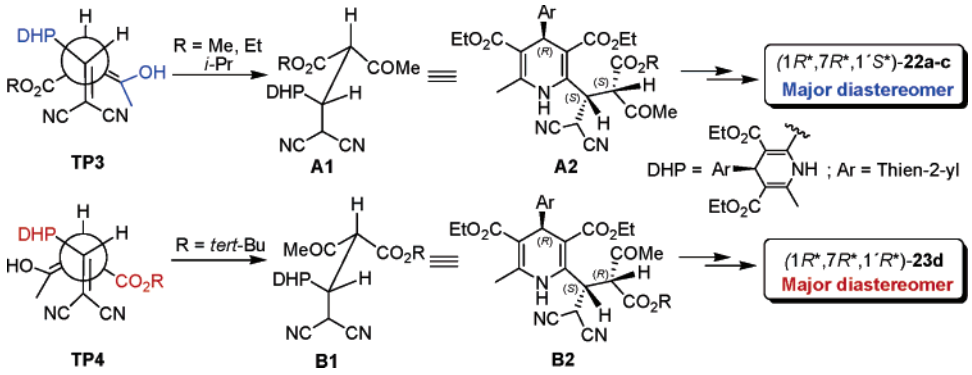
The difference in the reactivity of *tert*-butylacetoacetate compared to other alkyl butylacetoacetate-activated methylenes being allied to the fact that diastereomer **23d** was isolated in nearly 58% yield, lower than the yields of **22a**−**c**, prompted us to examine the behavior of this substrate in more detail. So, other tentative conventional recrystallizations or trituration with ethanol resulted in the slow and insignificant epimerization into its diastereomer **22d** (R = *tert*-Bu) without any precipitation. In this sense, the addition of piperidine in ethanol to the mother liquor containing **22d** and **23d** in a 5:1 ratio resulted, after 12 h of stirring, in the precipitation of the solution of the diastereomer **22d** initially formed as the minor one in a good yield (78%). Because of the fact that this process is not reversible as a consequence of the bulky *tert*-butyl group, we assume that the diastereomer **22d** is energetically more stable than its epimer **23d**. To gain more detailed information about this epimerization process, some investigations consisting of an NMR study of the reaction in an NMR tube were planned. The first test was done by taking purified, but unseparated, **22a** and **23a** and having their spectra recorded in DMSO-d_6 without a catalyst (see Tables 1 and 2 for NMR signals in Supporting Information). This showed no epimerization of the product **22a** into **23a** and vice versa. In parallel experiments, the spectrum was recorded immediately after the addition of a DMSO-d_6 solution of methyl acetoacetate to the starting 1,4-DHP derivative **14** solution in DMSO-d_6 present in the tube. The results indicated the effectiveness of the tandem addition/cyclization process, and **22a**/**23a** was formed with a dr of 72:28 indicating the catalytic effect of DMSO-d_6 on the reaction. Under these conditions, other active methylenes such as ethyl-, *i*-propyl-, and *tert*-butyl acetoacetates tested with 1,4-DHP **14** performed significantly better, with a dr of 70:30 for **22b**/**23b** (R = Et) and of 68:32 for **22c**/**23c** (R = *i*-Pr); in one case (R = *tert*-Bu), the dr value is reversed in comparison to the precedents because it was found to be 25:75 for **22d**/**23d**.

To identify and characterize all diastereomers **22a**−**d** and **23a**−**d**, an array of mono- and bidimensional NMR analyses including the NOE difference measurements were used. After that, the structure of all these epimers, **22a**−**d** and **23a**−**d**, was tentatively assigned (see the Experimental Section for complete NMR attribution, and significant signals are summarized in Tables 1 and 2 of the Supporting Information).

Scheme 6 demonstrates plausible transition states of the formation of major diastereomers **22a**−**c** and **23d**. In fact, on the basis of our above-proposed model for the Michael addition

(32) For X-ray single-crystal structure determination of (1*R**,7*R**,1′*S**)-**22b**, see crystallographic characteristics in Supporting Information.

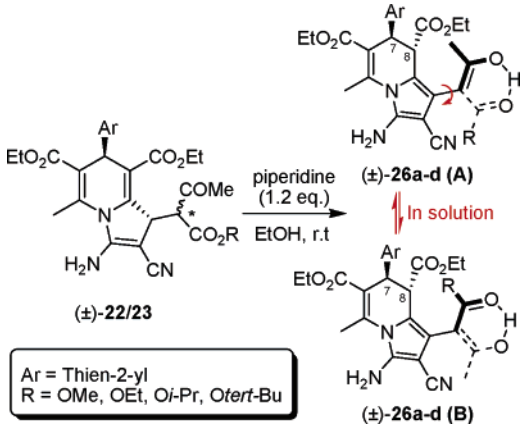
SCHEME 6. Plausible Transition States for the Formation of 1,7-Dihydroindolizines 22a−c and 23d



(Scheme 2), the approach of the enol form of the alkyl acetoacetates with R = Me, Et, or *i*-Pr from the opposite side of the dicyanomethylene residue could be represented by the transition state **TP3**. In this Newman projection, the more bulky ester group $-CO_2R$ is oriented preferentially down as are the nitrile groups, with the enol form being in the opposite region of the DHP nucleus. Consequently, after complete addition, the same conformation is formed in the Cram projection **A1**, which furnished after a cascade process the more stable 1,7-dihydroindolizines (1*R**,7*R**,1′*S**)-**22a**−**c** as major diastereomers. However, in the case of *tert*-butyl acetoacetate as an activated methylene, (1*R**,7*R**,1′*R**)-**23d** being obtained as the major diastereomer, in which the relative configuration at carbon C_1' is *R**, could be explained by considering the transition state **TP4**. In the latter, the approach of the *tert*-butyl group seems to be the more energetically favorable form when attached at the opposite side of the DHP ring.

We next studied the applicability of the 1,3-hydrogen or 1,3-alkyl shift process to produce component(s) **22** and/or **23** isolated above. Thus, when the 1,7-dihydroindolizine derivative **22a** having a methyl group was treated with piperidine under the same conditions as those used for **16a**,**b**, the proton at C_1 of the dihydroindolizine ring is similarly transferred to carbon C_8 of the same ring, despite a relatively slow reaction rate (95% conversion after 12 h). To our advantage, during the reaction process, the expected 7,8-dihydroindolizine product separates from the solution and its isolation becomes very easy. Again, the 7,8-dihydroindolizine **26a** isolated in 72% yield was formed by the enolization and a base-catalyzed hydrogen shift sequence demonstrating that the 1,3-alkyl shift process did not take place as reported for malononitrile and 1,4-DHP **14** described earlier.[26] The generalization of the process was extended successfully to other 1,7-dihydroindolizine derivatives **22b**,**c** and **23d** (Scheme 7). From that, the 7,8-dihydroindolizines **26b**,**c** and **26d** were isolated in pure form after recrystallization from anhydrous ethanol in yields of 66%, 70%, and 66%, respectively. Moreover, examination of the mother liquor indicated the presence of two products in variable proportions, and one of them, **26A**, was identical to that isolated in the crystalline form. Their separation could not be achieved by chromatography, but taking into account that **26A** had been fully characterized notably by NMR spectroscopic data, it was easily possible to distinguish the NMR signals of the minor 7,8-dihydroindolizine diastereomers **26B** from those of the major 7,8-dihydroindolizine ones (**26A**) directly in the mother liquor. In addition, we have also found that in solution the latter isomers **26A** existed as an equimolar mixture of conformers, arising from rotation around the C_1-C_1' bond of the enol form of alkyl acetoacetate. In the

SCHEME 7. 1,3-Hydrogen Shift Process for Obtaining 7,8-Dihydroindolizines 26 from 1,7-Dihydroindolizines 22/23 and Their Epimerization in Solution



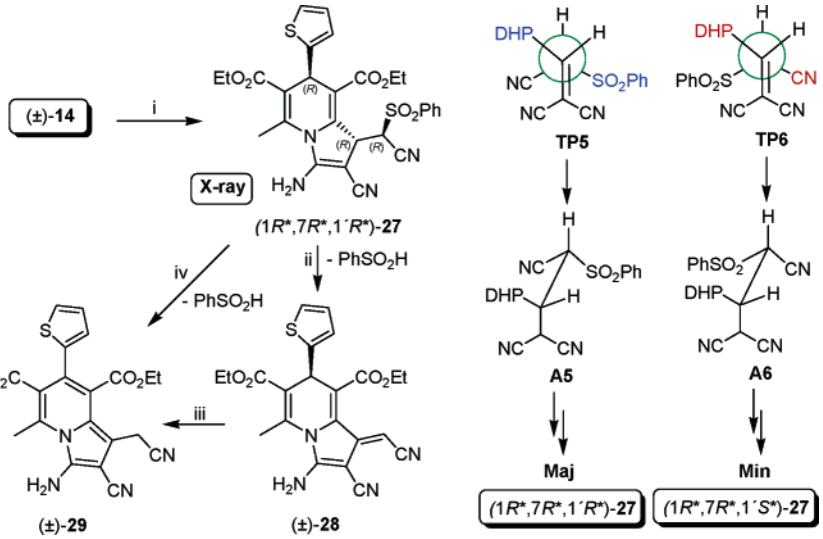
solid state, the atropoisomer **26A** is preferential to **26B**, as proved by X-ray analysis of the 7,8-dihydroindolizine diastereomer **26b** (Scheme 8).[33]

Reactivity of Active Methylene Compounds with a Leaving Group (Type D). To aid in a better understanding of the reactivity of 2-(2,2-dicyanovinyl)-1,4-DHP **14** toward active methylene nucleophiles and to measure the impact of the nature of these reagents on both the Michael addition and the aminonitrile cyclization steps during the formation of dihydroindolizines, elaboration of other kinds of activated methylene groups such as that bearing one leaving group, e.g., phenylsulfonyl, or nitro groups was explored under the same reaction protocol demonstrated above (Scheme 2). Thus, reaction of 1,4-DHP **14** with phenylsulfonylacetonitrile, similar to the case of reactants of **Types A** and **B**, gives after 3 h of reaction a unique product (Scheme 8). The latter isomer **27** which crystallized out of the solution was obtained in 86% yield and had 1*R**, 7*R**, and 1′*R** relative configurations (racemate) at the C_1, C_7, and C_1' stereocenters, respectively, as demonstrated by X-ray crystallographic analysis.[34] Interestingly, it has a configuration at the exocyclic carbon C_1' on the dihydroindolizine opposite to that of (1*R**,7*R**,1′*S**)-**22a**−**c** but similar to that of (1*R**,7*R**,1′*R**)-**23d** obtained above from racemic 1,4-DHP **14** and alkyl acetoacetates as starting materials (Schemes 2 and 5). These results showed analogy with the *tert*-butyl acetoacetate, and

(33) For X-ray single-crystal structure determination of **26bA**, see Supporting Information.

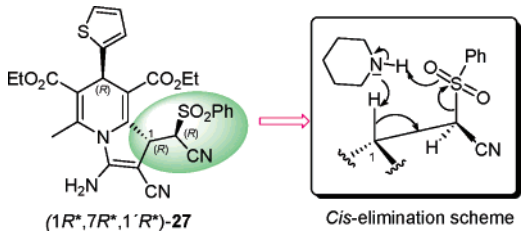
(34) For X-ray single-crystal structure determination of (1*R**,7*R**,1′*S**)-**27**, see crystallographic characteristics in Supporting Information.

SCHEME 8. Reaction of Alkyl Acetoacetates with 2-(2,2-Dicyanovinyl)-1,4-DHP 14[a]



[a] Key: (i) $PhSO_2CH_2CN$, $piperidine_{cat}$, EtOH, rt; (ii) 1.2 equiv of piperidine, EtOH, rt; (iii) *p*-TsOH, CH_2Cl_2, rt; (iv) 1.2 equiv of piperidine, EtOH, reflux.

CHART 3. Our Postulated Model of the Cis-Elimination Process



consequently, the bulky phenylsulfonyl group is found on the opposite side of the DHP nucleus as shown in Scheme 8. Herein, the reaction seems to possess more diastereoselectivity than the precedents because the diastereomer (1*R**,7*R**,1′*R**)-**27** has a dr of more than 95:5 indicating that the transition state **TP5** is more operated than the **TP6** one which could lead to the intermediate **A6** precursor of the minor diastereomer (1*R**,7*R**,1′*S**)-**27** after subsequent transformations as above.

As depicted in Scheme 8, when (1*R**,7*R**,1′*R**)-**27** was treated with piperidine, a β-elimination of benzenesulfinic acid gave rise to a novel type of dihydroindolizine identified as (±)-**28** which formed in 78% yield. The structure of the latter, which possess an exocyclic double bond with *E*-configuration at the C_1 of the indolizine skeleton, was secured by the spectroscopic NMR study. Taking into account that the phenylsulfonyl group at C_1' and the proton at C_1 of the dihydroindolizine moieties are in a cis relationship as confirmed by the X-ray and NMR study of the starting substrate (1*R**,7*R**,1′*R**)-**27**, the syn elimination in this case may be favored. This involves a synchronous attack of piperidine at the C_1 proton, which resulted in its abstraction followed by the departure of the adjacent antiperiplanar phenylsulfonyl leaving group via the transition state depicted in Chart 3.

This mechanism is suggested by analogy with the pyrolytic cis eliminations[35] as exemplified notably by thermolysis of menthyldiphenyl phosphate[36] and the simple esterification of primary alcohol with the Hendrickson reagent via the Mitsunobu reaction.[37] In our case, the process seems to be general and needs the assistance of a base. In addition, because no trace of the geometrical isomer *Z* was detected in the crude reaction mixture, we assume that despite the presence of piperidine possible epimerization of product **27** at the acidic proton bearing C_1' did not occur. Consequently, the *E*-alkene as the favored isomer was formed presumably with a kinetically rapid rate relative to the isomer *Z*. We cannot ignore also the fact that the product **28** has a more aromatic skeleton than its congener **27**, and this is probably one of the driving forces of the cis elimination process discussed.

In an ultimate stage, we found that in acidic media dihydroindolizine **28** was transformed in 85% yield to a thermodynamically more stable hexasubstituted indolizine **29**, the latter bearing a particularly interesting acetonitrile functionality in the side chain. Its aromatization into the indolizine system takes place via an operative 1,5-hydrogen shift with the assistance of PTSA in dichloromethane at room temperature. In addition, the process seems to be operating under the influence of a nitrogen base such as piperidine acting as the catalyst. The latter product **29** was also obtained in a one-pot procedure starting from **27** in refluxing ethanol under the influence of piperidine, demonstrating the effectiveness of the elimination−aromatization sequence partially invoked above.

Intrigued by these interesting results, another activated methylene reagent bearing a leaving group such as benzoylnitromethane was tested under similar conditions in the reaction with racemic 1,4-DHP **14** as outlined above; the result is highlighted in Scheme 9.

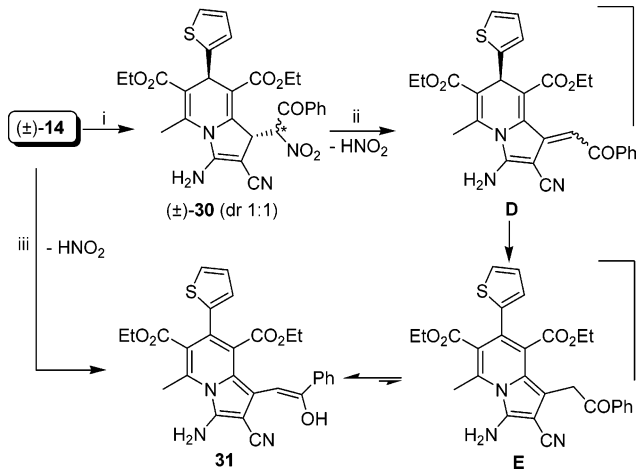
In contrast to all tandem reactions outlined above, with benzoylnitromethane and 1,4-DHP **14**, no complete stereoselectivity was observed and consequently the ratio of isolated

(35) (a) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431. (b) Kotani, R.; Satoh, S. *J. Org. Chem.* **1965**, *30*, 3245. (c) Adam, W.; Arce, J. *J. Org. Chem.* **1972**, *37*, 507.

(36) Quast, H.; Dietz, T. *Synthesis* **1995**, 1300.

(37) (a) Elson, K. E.; Jenkins, I. D.; Loughlin, W. A. *Org. Biomol. Chem.* **2003**, *1*, 2958. (b) Hendrickson, J. B. In *Encyclopaedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: 1995; Vol. 8, pp 5405−5407. (c) Hendrickson, J. B.; Schwartzman, S. M. *Tetrahedron Lett.* **1975**, 277.

SCHEME 9. Reaction of Benzoylnitromethane with 2-Dicyanovinyl-1,4-DHP 14[a]



[a] Key: (i) $PhCOCH_2NO_2$, $piperidine_{cat}$, EtOH, rt; (ii) 1.2 equiv of piperidine, EtOH, rt; (iii) $PhCOCH_2NO_2$, 1.5 equiv of piperidine, EtOH, reflux.

1,7-dihydroindolizidine **30** was approximately 1:1. Because the Michael addition is diastereoselective, the latter product **30** resulted probably from the epimerization of a proton at C_1' more acidic than the proton on the same carbon of 1,7-dihydroindolizidine (1*R**,7*R**,1′*R**)-**27**. Furthermore, we assume that the subsequent treatment of the crude product **30** with piperidine thus affords after syn and anti elimination of a nitrous acid[38] a mixture of isomeric 1,7-dihydroindolizines **D**, which then undergo rapid isomerization into **E**, followed in the ultimate stage by a keto enol tautomerism leading to the thermodynamically favorable enol **31**. Taking advantage of the large conjugation in the product **31**, when heated in ethanol 1,4-DHP **14** in the presence of piperidine (Scheme 9), the 1,7-dihydroindolizidine **30** as a valuable intermediate in this case turned rapidly to give the same polysubstituted highly conjugated indolizine in its enolic form **31** in a one-pot procedure in 88% yield.

Conclusions

In this report, we present the results concerning the reaction of 2-formyl-1,4-DHP substrate (±)-**5** and the corresponding Knoevenagel 2-(2,2-dicyanovinyl) derivative (±)-**14** with four kinds of active methylene reagents. Despite the variety of the formed reaction products, general regularities of the reactions could be distinguished. For instance, the primary stage of the reactions studied involves formation of the Michael adducts in a high diastereoselective manner followed by their spontaneous amino-nitrile cyclization into tetrahydroindolizine **13** and 1,7-dihydroindolizines **16**, **22**, **23**, **27**, and **30** bearing different substituents at the hybridized sp^3 C_1. The Michael reaction proceeded under the governance of the geometry of the DHP nucleus, which prefers a favorable boatlike conformation, allowing the formation of adducts with only the trans addition. The integrity of this stereochemistry was kept up in the 1,7-dihydroindolizines being formed via the intramolecular aza-Michael cyclization. The latter species, with additional piperidine treatment, furnished efficaciously the corresponding 7,8-dihydroindolizines **17** and **26** by an interesting stereoselective suprafacial 1,3-hydrogen shift. In the case of 1,7-dihydroindolizine **27**, only a 1,7-dihydroindolizine **28** hybridized sp^2 at C_1 was obtained as the consequence of the phenylsulfinic acid elimination.

Elsewhere, in thermal conditions, 1,4-DHP precursor (±)-**14** and 1,7-dihydroindolizines **27**, **28**, and **30** are further aromatized easily with very good yields into indolizines **15**, **29**, and **31**, respectively, and are more stable than their congeners due to conjugation. Finally, we observed a facile and specific transformation in a one-pot procedure of hydrogenated indolizine derivatives to the corresponding indolizines. This constitutes a distinctive feature of the reactions of active methylenes which bear a leaving group with 2-formyl- or 2-(2,2-dicyanovinyl)-1,4-DHP, (±)-**5** and (±)-**14**, unlike the widely studied reactions of malononitrile, 1,3-diketones, and alkyl acetoacetates. With those two reagents, an interesting and rare syn elimination of benzenesulfinic and nitrous acids via a concerted base-catalyzed process was invoked. Owing to the efficiency and simplicity of this method coupled with its remarkable modular character, this tandem associated or not with other transformations was used to access, in a one-pot protocol involving two steps, scaffolds with interesting biological profiles. These species might also find application as building blocks for structural diversification from amine and nitrile functionalities. Studies along this line are currently underway in our laboratory, and the results will be published soon.

Experimental Section

(±)-Diethyl 2-(2,2-Dicyanovinyl)-6-methyl-4-(2-thienyl)-1,4-dihydropyridine-3,5-dicarboxylate (14). A suspension of 2-formyl-1,4-dihydropyridine (*rac*)-**5** (1.00 g, 2.9 mmol) in ethanol (10 mL) was treated with a catalytic amount of sodium ethoxide, and then malononitrile (0.19 g, 2.9 mmol) in ethanol (5 mL) was added over 15 min. After the mixture was stirred at room temperature for 3 h, the resulting precipitated crystals of the crude product were filtered off. Recrystallization from ethanol gave 0.74 g (yield 65%) of 2-(2,2-dicyanovinyl)-1,4-DHP **14**: mp 136−138 °C; ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.31 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.87 (s, 3H, CH_3 at C-6), 4.10−4.35 (m, 4H, 2 × OCH_2), 5.49 (s, 1H, H-4), 6.79 (dd, 1H, H-4′, J = 1.5 and 4.7 Hz), 6.85 (dd, 1H, H-3′, J = 1.5 and 3.1 Hz), 7.11 (dd, 1H, H-5′, J = 1.6 and 4.7 Hz), 8.35 (s, 1H, CH=), 8.35 (s broad, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 × CH_3), 17.3 (CH_3 at C-5), 36.6 (C-4), 60.8 (OCH_2), 61.7 (OCH_2), 111.4 (2 × CN), 112.4, 114.6 (C-3 and C-5), 124.8, 125.1, 126.8 (C-3′, C-4′, and C-5′), 139.1 (CH=), 142.8 (C-2′), 143.2, 145.7 (C-2 and C-6), 159.1 (CH=*C*), 164.1 (CO_2), 166.7 (CO_2); IR (KBr) ν 3277 (s, NH), 3113 (w, =C−H), 2235 (s, CN), 1698 (s, C=O), 1681 (s, C=O), 1636 (s, C=C), 1611 (m, C=C), 1576 (w), 1444 (w), 1427 (w), 1387 (m), 1366 (m), 1317(m), 1301 (m), 1215 (s), 1181 (m), 1158 (s), 1119 (m), 1093 (s), 1037 (s), 951 (w), 887 (w), 855 (m), 835 (w), 824 (w), 698 (s) cm^{-1}; UV λ_{max} nm (log ϵ) 227 (2.61), 289 (2.54), 401 (1.98); MS, *m*/*z* (%) 398 (6), 397 $M^{+\bullet}$ (25), 326 (8), 325 (20), 324 (100), 323 (6), 296 (10), 294 (6), 250 (6), 212 (8). Anal. Calcd for $C_{20}H_{19}N_3O_4S$ (397): C, 60.44; H, 4.82; N, 10.57. Found: C, 60.38; H, 4.70; N, 10.36.

(±)-Diethyl (7*S,8*R**,8a*S**)-3-Amino-2-cyano-1-(dicyanomethylene)-5-methyl-7-(2-thienyl)-1,7,8,8a-tetrahydroindolizine-6,8-dicarboxylate (13).** To a suspension of 2-formyl-1,4-dihydropyridine **5** (1.00 g, 2.9 mmol) and malononitrile (0.38 g, 5.8 mmol) in ethanol (15 mL) was added a catalytic amount of piperidine. After stirring at room temperature for 3 h, the resulting precipitates of the crude product were collected by filtration. Recrystallization from ethanol

(38) For examples of nitrous acid elimination, see: (a) Danishefsky, S.; Prisbylla, M. P.; Hiner, S. *J. Am. Chem. Soc.* **1978**, *100*, 2918. (b) Ono, N.; Miyake, H.; Tanikaga, R.; Kaji, A. *J. Org. Chem.* **1982**, *47*, 5017. (c) Bernasconi, C. F.; Montanez, R. L. *J. Org. Chem.* **1997**, *62*, 8162.

gave 1.10 g of tetrahydroindolizine **13** in 83% yield: mp 269−273 °C; ^{1}H NMR (DMSO-d_6) δ 0.82 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 0.88 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.41 (s, 3H, CH_3 at C-5), 3.78 (dd, 1H, H-8, J = 3.6 and 7.5 Hz), 3.82−4.00 (m, 4H, 2 × OCH_2), 4.91 (d, 1H, H-7, J = 7.5 Hz), 5.43 (d, 1H, H-8a, J = 3.6 Hz), 6.75 (dd, 1H, H-3′, J = 1.5 and 3.2 Hz), 6.90 (dd, 1H, H-4′, J = 3.2 and 5.1 Hz), 7.35 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz), 8.75 (s broad, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 13.5 (CH_3), 13.7 (CH_3), 17.7 (CH_3 at C-5), 38.3 (C-7), 47.0 (C-8), 60.3 (OCH_2), 60.5 (OCH_2), 65.3 (C-8a), 76.2 (NC−*C*−CN), 112.1 (C-2), 114.4 (CN), 116.5 (CN), 119.6 (C-6), 125.2, 126.2, 126.7 (C-3′, C-4′, and C-5′), 138.4 (C-2′), 141.1 (C-5), 162.1 (C-3), 163.5 (C-1), 165.9 (CO_2), 167.5 (CO_2); IR (KBr) ν 3427 (w, N−H), 3337 (w, N−H), 2981-(w), 2221 (s, CN), 1731 (m, C═O), 1698 (m, C═O), 1669 (s, C═C), 1579 (m), 1556 (s), 1478 (s), 1414 (m), 1368 (w), 1277 (m), 1232 (m), 1182 (s), 1140 (w), 1114 (w), 1092 (m), 1015 (w), 933 (w), 852 (w), 702 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 204 (3.17), 234 (3.16), 285 (3.23), 375 (3.48); MS, *m*/*z* (%) 464 (15), 463 $M^{+\bullet}$ (31), 418 (15), 417 (15), 398 (15), 397 (54), 390 (31), 368 (15), 345 (23), 344 (100), 324 (15), 322 (15), 294 (15), 278 (15). Anal. Calcd for $C_{23}H_{21}N_5O_4S$ (463): C, 59.60; H, 4.57; N, 15.11. Found: C, 59.41; H, 4.39; N, 14.90.

Diethyl 3-Amino-2-cyano-5-methyl-7-(2-thienyl)indolizine-6,8-dicarboxylate (15). The 2-(2,2-dicyanovinyl)-1,4-dihydropyridine **14** (0.93 g, 2.3 mmol) in ethanol (10 mL) was treated with a catalytic amount of piperidine, and the mixture was heated at reflux for 3 h. After cooling, the resulting precipitates were collected by filtration and recrystallization from ethanol gave 0.83 g of indolizine **15** in 89% yield: mp 149−151 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.00 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.83 (s, 3H, CH_3 at C-5), 3.98 (q, 2H, OCH_2, J = 7.2 Hz), 4.10 (q, 2H, OCH_2, J = 7.2 Hz), 5.84 (s broad, 2H, NH_2), 6.60 (s, 1H, C-4), 6.88 (dd, 1H, H-3′, J = 1.5 and 3.7 Hz), 7.06 (dd, 1H, H-4′, J = 3.7 and 5.1 Hz), 7.59 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.4 (CH_3), 13.5 (CH_3), 17.3 (CH_3 at C-9), 61.3 (2 × OCH_2), 84.4 (C-2), 101.0 (C-1), 116.1 (CN), 119.1 (C-8a), 120.3 (C-6), 123.5 (C-8), 123.6 (C-7), 127.1, 127.3, 127.8 (C-3′, C-4′, and C-5′), 134.7 (C-2′), 136.6 (C-5), 142.6 (C-3), 164.9 (CO_2), 166.5 (CO_2); IR (KBr) ν 3374 (m), 3321 (m), 3230 (w), 2981 (m), 2902 (w), 2222 (s), 1733 (s), 1707 (s), 1637 (m), 1540 (m), 1456 (w), 1433 (w), 1402 (m), 1393 (m), 1372 (s), 1332 (s), 1292 (w), 1268 (m), 1237 (s), 1187 (m), 1146 (s), 1108 (m), 1045 (m), 1013 (w), 862 (w), 762 (w), 739 (w), 705 (s), 644 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 216 (2.82), 272 (2.81), 415 (1.91); MS, *m*/*z* (%) 399 (8), 397 $M^{+\bullet}$ (100), 371 (10), 353 (6), 322 (10), 295 (6), 294 (13), 278 (6), 250 (6). Anal. Calcd for $C_{20}H_{19}N_3O_4S$ (397): C, 60.44; H, 4.82; N, 10.57. Found: C, 60.32; H, 4.70; N, 10.41.

(±)-Diethyl (1,7-*trans*)-3-Amino-2-cyano-5-methyl-7-(2-thienyl)-1,7-dihydroindolizine-6,8-dicarboxylates (16). To a suspension of 2-(2,2-dicyanovinyl)-1,4-dihydropyridine **14** (0.80 g, 2.0 mmol) and 1,3-diketone (2.0 mmol) in ethanol (5 mL) was added a catalytic amount of piperidine. After stirring at room temperature for 3 h, the resulting precipitates of dihydroindolizine **16** were collected by filtration and recrystallized from ethanol.

(1*R,7*R**)-1-(1-Acetyl-2-oxopropyl)indolizine (16a).** This compound was prepared from **14** and pentane-2,4-dione in 88% yield (m = 0.88 g): mp 148−151 °C; ^{1}H NMR (DMSO-d_6) δ 1.25 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.30 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 2.06 (s, 3H, $COCH_3$), 2.36 (s, 3H, $COCH_3$), 2.59 (s, 3H, CH_3 at C-5), 4.06−4.35 (m, 4H, 2 × OCH_2), 4.57 (d, 1H, CH, J = 3.1 Hz), 4.61 (d, 1H, H-1, J = 3.1 Hz), 5.03 (s broad, 2H, NH_2), 5.45 (s, 1H, H-7), 6.71 (dd, 1H, H-3′, J = 1.6 and 3.3 Hz), 6.82 (dd, 1H, H-4′, J = 3.6 and 5.1 Hz), 7.04 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 14.5 (CH_3), 14.7 (CH_3), 17.5 (CH_3 at C-5), 30.0 (CH_3CO), 31.5 (CH_3CO), 36.1 (C-7), 41.8 (CH), 58.3 (C-2), 61.5 (OCH_2), 61.6 (OCH_2), 68.2 (CH), 108.4, 113.5 (C-8 and C-6), 118.8 (CN), 124.3, 125.1, 127.6 (C-3′, C-5′, and C-4′), 145.5, 146.5 (C-5 and C-2′), 154.7, 157.1 (C-8a and C-3), 165.3 (CO_2), 166.8 (CO_2), 203.9 (CO), 204.9 (CO); IR (KBr) ν 3426 (m), 3347(m), 3214 (w), 2976 (w), 2193 (s), 1696 (s), 1654 (s), 1613 (w), 1583 (s), 1437 (m), 1309 (m), 1286 (m), 1256 (m), 1221 (s), 1183 (m), 1151 (s), 1045 (m), 1022 (m), 960 (w), 854 (w), 791 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 228 (3.33), 282 (3.37), 333 (sh, 2.73); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_5H_8O_2$ (100). Anal. Calcd for $C_{25}H_{27}N_3O_6S$ (497): C, 60.35; H, 5.47; N, 8.45. Found: C, 60.21; H, 5.37; N, 8.29.

(1*R,7*R**)-1-(2-Oxo-1-propionylbutyl)indolizine (16b).** This compound was prepared from **14** and heptane-3,5-dione in 90% yield (m = 0.95 g): mp 140−143 °C; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.06 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.24 (t, 3H, CH_3), 1.29 (t, 3H, CH_3), 2.15 (dq, 1H, *H*−CH, J = 7.2 and 18.2 Hz), 2.45 (dq, 1H, *H*−CH, J = 7.2 and 18.2 Hz), 2.57 (q, 2H, CH_2, J = 7.2 Hz), 2.60 (s, 3H, CH_3 at C-5), 4.10−4.30 (m, 4H, 2 × OCH_2), 4.48 (d, 1H, CH, J = 3.03 Hz), 4.58 (d, 1H, H-1, J = 3.3 Hz), 5.11 (s broad, 2H, NH_2), 5.45 (s, 1H, H-7), 6.71 (dd, 1H, H-3′, J = 1.6 and 3.3 Hz), 6.81 (dd, 1H, H-4′, J = 3.6 and 5.1 Hz), 7.02 (dd, 1H, H-5′, J = 1.6 and 5.1 Hz); ^{13}C NMR ($CDCl_3$) δ 7.6 (CH_3), 7.7 (CH_3), 14.1 (CH_3), 14.2 (CH_3), 17.3 (CH_3 at C-5), 35.9 (C-7), 36.0 (CH_2CO), 37.5 (CH_2CO), 42.6 (C-1), 60.9 (OCH_2), 61.0 (OCH_2), 62.1 (C-2), 65.6 (CH), 109.0, 114.6 (C-8 and C-6), 117.7 (CN), 123.9, 126.8 (C-3′, C-5′, and C-4′), 143.1, 146.3 (C-5 and C-2′), 154.2, 156.1 (C-8a and C-3), 165.0 (CO_2), 166.4 (CO_2), 205.5 (CO), 204.9 (CO); IR (KBr) ν 3426 (m), 3347-(m), 3214 (w), 2976 (w), 2193 (s), 1696 (s), 1654 (s), 1613 (w), 1583 (s), 1437 (m), 1309 (m), 1286 (m), 1256 (m), 1221 (s), 1183 (m), 1151 (s), 1045 (m), 1022 (m), 960 (w), 854 (w), 791 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 229 (3.39), 285 (3.35), 391sh (2.67); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_7H_{12}O_2$ (100). Anal. Calcd for $C_{27}H_{31}N_3O_6S$ (525): C, 61.70; H, 5.94; N, 7.99. Found: C, 61.49; H, 5.77; N, 7.75.

(1*R,7*R**)-1-(1-Benzoyl-2-oxo-2-phenylethyl)indolizine (16c).** This compound was prepared from **14** and 1,3-diphenylpropane-1,3-dione in 84% yield (m = 1.05 g): mp 117−120 °C; ^{1}H NMR (DMSO-d_6) δ 1.04 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.27 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.70 (s, 3H, CH_3 at C-5), 4.10 (q, 2H, OCH_2), 4.21 (q, 2H, OCH_2), 4.94 (d, 1H, CH, J = 1.2 Hz), 5.36 (s, 1H, H-7), 6.13 (d, 1H, H-1, J = 1.5 Hz), 6.68 (d, 1H, H-3′, J = 1.5 and 3.3 Hz), 6.84 (dd, 1H, H-4′, J = 3.6 and 4.8 Hz), 6.93 (s broad, 2H, NH_2), 7.24 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz), 7.43 (t, 2H, H-3″, J = 7.8 Hz), 7.46 (t, 2H, H-3″, J = 7.8 Hz), 7.58 (t, 1H, H-4″, J = 7.5 Hz), 7.64 (t, 1H, H-4″, J = 7.5 Hz), 7.88 (d, 2H, H-2″, J = 7.5 Hz), 7.89 (d, 2H, H-2″, J = 7.5 Hz), 7.89 (d, 2H, H-2″, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 14.3 (CH_3), 16.4 (CH_3 at C-5), 35.2 (C-7), 41.7 (C-1), 58.8 (C-2), 59.0 (CH), 60.3 (OCH_2), 60.7 (OCH_2), 108.2, 111.5 (C-8 and C-6), 118.0 (CN), 123.5, 124.4, 126.8 (C-3′, C-5′, and C-4′), 128.2, 128.6, 128.9, 133.4, 134.1 (CH-arom), 135.4, 135.8 (C-benzene), 144.2, 146.3 (C-5 and C-2′), 153.8, 155.8 (C-8a and C-3), 164.6 (CO_2), 165.7 (CO_2), 194.6 (CO), 195.5 (CO); IR (KBr) ν 3350 (m), 3207 (m), 2977 (w), 2199 (s), 1697 (s), 1674 (s), 1581 (s), 1448 (s), 1385 (w), 1370 (m), 1311 (m), 1233 (s), 1209 (s), 1149 (s), 1129 (m), 1036 (m), 1001 (m), 795 (w), 765 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 223 (3.30), 348 (2.98); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_{15}H_{12}O_2$ (100). Anal. Calcd for $C_{35}H_{31}N_3O_6S$ (621): C, 67.62; H, 5.03; N, 6.76. Found: C, 67.51; H, 4.88; N, 6.59.

(±)-Diethyl (7,8-*trans*)-3-Amino-2-cyano-5-methyl-7-(2-thienyl)-7,8-dihydroindolizine-6,8-dicarboxylates (17). To a suspension of *trans*-dihydroindolizine **16** (1.0 mmol) in ethanol (5 mL) was added piperidine (0.125 mL, 1.2 mmol). After stirring at room temperature for 10 h, the resulting precipitates of dihydroindolizine **17** were collected by filtration and recrystallized from ethanol.

(7*S,8*S**)-1-[(1*Z*)-1-Acetyl-2-hydroxyprop-1-en-1-yl]dihydroindolizine (17a).** This compound was obtained from indolizine **16a** in 66% yield (m = 0.33 g): mp 211−214 °C; ^{1}H NMR ($CDCl_3$) δ 0.95−1.40 (m, 6H, 2 × OCH_2CH_3), 1.24 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 2.80 (s, 3H, CH_3 at C-5), 3.67 (d, 1H, H-8, J = 1.5 Hz), 4.02−4.30 (m, 4H, 2 × OCH_2), 4.34 (s broad, 2H, NH_2), 5.02 (d,

1H, H-7, J = 1.5 Hz), 6.66 (dd, 1H, H-3′, J = 1.6 and 3.3 Hz), 6.81 (dd, 1H, H-4′, J = 3.6 and 5.1 Hz), 7.03 (dd, 1H, H-5′, J = 1.6 and 5.1 Hz), 9.81 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 18.2 (CH_3 at C-5), 22.1 (*C*H_3C═), 23.9 (*C*H_3CO), 38.2 (C-7), 46.1 (C-8), 61.3 (OCH_2), 61.7 (OCH_2), 79.9 (C-2), 102.6 (*C*═C−CH_3), 115.6, 117.9, 118.1, 118.9 (CN, C-6, C-1, and C-8a), 124.4, 125.0, 127.1 (C-3′, C-5′, and C-4′), 142.4, 143.6, 145.2 (C-2′, C-5, and C-3), 165.9 (CO_2), 169.4 (CO_2), 191.8 (COH), 193.6 (CO); IR (KBr) ν 3435 (w), 3316 (m), 3227 (m), 3101 (w), 2993 (w), 2215 (s), 1726 (s), 1703 (s), 1642 (m), 1557 (s), 1460 (s), 1387 (m), 1367 (s), 1330 (m), 1281 (s), 1244 (m), 1213 (m), 1177 (m), 1132 (w), 1109 (m), 1024 (m), 912 (w), 858 (w), 791 (w), 712 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 211 (3.34), 249 (3.40), 263 (3.44), 285 (3.73), 350-sh; MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_5H_8O_2$ (100). Anal. Calcd for $C_{25}H_{27}N_3O_6S$ (497): C, 60.35; H, 5.47; N, 8.45. Found: C, 60.19; H, 5.35; N, 8.26.

(7*S,8*S**)-1-[(1*Z*)-2-Hydroxy-2-hydroxy-1-propionylbut-1-en-1-yl]dihydroindolizine (17b).** This compound was obtained from indolizine **16b** in 69% yield (m = 0.36 g): mp 209−212 °C; ^{1}H NMR ($CDCl_3$) δ 0.72 (t, 3H, CH_3, J = 7.2 Hz), 1.03 (t, 3H, CH_3, J = 7.2 Hz), 1.12−1.25 (m, 1H, *H*−CH), 1.21 (t, 3H, CH_3, J = 7.2 Hz), 1.24 (t, 3H, CH_3, J = 7.2 Hz), 1.58−1.72 (m, 1H, *H*−CH), 2.12−2.32 (m, 2H, CH_2), 2.82 (s, 3H, CH_3 at C-5), 3.66 (d, 1H, H-8, J = 1.6 Hz), 4.02−4.22 (m, 4H, 2 × OCH_2), 4.43 (s broad, 2H, NH_2), 5.01 (d, 1H, H-7, J = 1.6 Hz), 6.66 (dd, 1H, H-3′, J = 1.6 and 3.3 Hz), 6.82 (dd, 1H, H-4′, J = 3.6 and 5.1 Hz), 7.06 (dd, 1H, H-5′, J = 1.6 and 5.1 Hz), 16.87 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 9.1 (CH_3), 9.4 (CH_3), 14.1 (2 × OCH_2*C*H_3), 18.2 (CH_3 at C-5), 28.6 (*C*H_2C═), 29.2 (*C*H_2CO), 38.4 (C-7), 46.1 (C-8), 61.3 (OCH_2), 61.7 (OCH_2), 79.9 (C-2), 101.2 (*C*═C−CH_3), 115.7, 117.5, 118.1, 118.9 (CN, C-1, C-8a, and C-6), 124.3, 125.1, 127.1 (C-3′, C-5′, and C-4′), 142.5, 143.7, 145.3 (C-2′, C-5, and C-3), 165.9 (CO_2), 169.5 (CO_2), 195.6 (COH), 195.9 (CO); IR (KBr) ν 3392 (m), 3334 (m), 3316 (m), 3245 (m), 2984 (m), 2941 (w), 2208 (s), 1738 (s), 1392 (s), 1650 (m), 1613 (m), 1561 (s), 1462 (s), 1387 (m), 1367 (m), 13270 (w), 1276 (s), 1247 (s), 1178 (s), 1135 (m), 1063 (m), 1024 (m), 912 (w), 856 (w), 791 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 210 (3.38), 249 (3.45), 263 (3.49), 286 (3.49), 350-sh; MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_7H_{12}O_2$ (100). Anal. Calcd for $C_{27}H_{31}N_3O_6S$ (525): C, 61.70; H, 5.94; N, 7.99. Found: C, 61.52; H, 5.70; N, 7.65.

Diethyl 2-(2,2-Dicyanovinyl)-6-methyl-4-(2-thienyl)pyridine-3,5-dicarboxylate (21). Method A: The mixture of dihydroindolizine **16a** (0.50 g, 1.0 mmol) and copper(II) chloride (0.14 g, 1.0 mmol) in ethanol (70%) (10 mL) was stirred at room temperature for 3 h. The resulting precipitates of **21** were collected by filtration and recrystallized from ethanol. Pyridine **21** was obtained in 89% yield (m = 0.35 g): mp 184−185 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, OCH_2 CH_3, J = 7.1 Hz), 1.08 (t, 3H, OCH_2 CH_3, J = 7.1 Hz), 2.66 (s, 3H, CH_3 at C-6), 4.11 (q, 2H, OCH_2, J = 7.1 Hz), 4.16 (q, 2H, OCH_2, J = 7.1 Hz), 7.01−7.10 (m, 2H, H-3′, and H-4′), 7.45 (dd, 1H, H-5′, J = 1.0 and 5.1 Hz), 7.90 (s, 1H, ═CH); ^{13}C NMR ($CDCl_3$) δ 13.6 (CH_3), 13.7 (CH_3), 22.2 (CH_3 at C-6), 62.3 (OCH_2), 62.9 (OCH_2), 90.3 (CH═*C*), 111.8 (CN), 113.6 (CN), 127.4, 128.4, 129.3 (C-3′, C-5′, and C-4′), 129.9, 133.3 (C-3 and C-5), 134.5 (C-2′), 140.6 (C-4), 145.0 (CH═), 152.1 (C-2), 157.2 (C-6), 165.6 (CO_2), 166.1 (CO_2); IR (KBr) ν 3067 (w), 2981 (m), 2934 (w), 2231 (m), 1733 (s), 1608 (w), 1551 (s), 1521 (w), 1463 (w), 1401 (w), 1384 (s), 1370 (w), 1311 (m), 1299 (s), 1288 (s), 1252 (s), 1234 (s), 1217 (s), 1170 (m), 1133 (s), 1096 (s), 1057 (s), 1018 (m), 928 (m), 840 (w), 752 (w), 703 (s) cm^{-1}; UV λ_{max} nm (log ϵ) 202 (3.27), 228 (3.28), 285 (3.33), 316 (3.22); MS, *m*/z (%) 395 ($M^{+\bullet}$). Anal. Calcd for $C_{20}H_{17}N_3O_4S$ (395): C, 60.75; H, 4.33; N, 10.63. Found: C, 60.52; H, 4.19; N, 10.48. **Method B:** The mixture of 2-dicyanovinyl-1,4-dihydropyridine **14** (0.40 g, 1.0 mmol) and copper(II) chloride (0.37 g, 1.0 mmol) in ethanol (70%) (10 mL) was stirred at room temperature for 3 h. The resulting precipitates of pyridine **21** were collected by filtration and recrystallized from ethanol. Yield of **21**: 0.36 g (90%).

(±)-Diethyl (1,7-*trans*)-3-Amino-2-cyano-1-[1-alkoxycarbonyl-2-oxopropyl]-5-methyl-7-(2-thien-yl)-1,7-dihydroindolizine-6,8-dicarboxylates 22 and 23. To a suspension of 2-dicyanovinyl-1,4-dihydropyridine **14** (0.80 g, 2.0 mmol) and alkyl 3-oxobutanoate (2.0 mmol) in ethanol (5 mL) was added a catalytic amount of piperidine. After stirring at room temperature for 3 h, the resulting precipitate mixture of dihydroindolizines **22** and **23** was collected by filtration and recrystallized from ethanol.

(1*R,7*R**)-1-[(1′*S**)-1-Methoxycarbonyl]indolizine (22a).** This compound was prepared from 2-(2,2-dicyanovinyl)-1,4-dihydropyridine **14** and methyl 3-oxobutanoate in 88% yield (m = 0.90 g): mp 146−149 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.22 (s, 3H, COCH_3), 2.49 (s, 3H, CH_3 at C-5), 3.54 (s, 3H, OCH_3), 4.04−4.24 (m, 4H, 2 × OCH_2), 4.29 (d, 1H, C*H*, J = 1.8 Hz), 4.58 (d, 1H, H-1, J = 1.8 Hz), 5.36 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.86 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.21 (s broad, 2H, NH_2), 7.26 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 14.2 (CH_3), 17.1 (CH_3 at C-5), 29.1 (CH_3CO), 35.4 (C-7), 41.0 (C-1), 52.3 (OCH_3), 57.6 (C-2), 60.5 (OCH_2), 60.7 (OCH_2), 61.8 (CH), 107.0 (C-8), 112.3 (C-6), 117.9 (CN), 123.5, 124.5, 126.8 (C-3′, C-5′, and C-4′), 145.0, 146.1 (C-5 and C-2′), 154.7, 156.7 (C-8a and C-3), 164.6 (CO_2), 166.0 (CO_2), 168.3 (CO_2), 200.8 (CO); IR (KBr) ν 3399 (m), 3206 (m), 2973 (w), 2199 (s), 1737 (s), 1694 (s), 1674 (s), 1583 (s), 1455 (s), 1387 (m), 1368 (m), 1311 (m), 1230 (s), 1160 (s), 1130 (m), 1095 (m), 1035 (m), 993 (w), 856 (w), 707 (w); UV λ_{max} nm (log ϵ) 229 (3.47), 317 (3.39); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_5H_8O_3$ (100). Anal. Calcd for $C_{25}H_{27}N_3O_7S$ (513): C, 58.47; H, 5.30; N, 8.18. Found: C, 58.31; H, 5.19; N, 8.01.

(1*R,7*R**)-1-[(1′*R**)-1-Methoxycarbonyl]indolizine (23a):** ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.25 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.03 (s, 3H, $COCH_3$), 2.49 (s, 3H, CH_3 at C-5), 3.70 (s, 3H, OCH_3), 4.04−4.24 (m, 4H, 2 × OCH_2), 4.34 (d, 1H, CH, J = 3.3 Hz), 4.47 (d, 1H, H-1, J = 3.3 Hz), 5.34 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.86 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.21 (s broad, 2H, NH_2), 7.26 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 14.2 (CH_3), 17.1 (CH_3 at C-5), 30.5 (*C*H_3CO), 35.5 (C-7), 42.5 (C-1), 52.3 (OCH_3), 57.0 (C-2), 59.3 (CH), 60.5 (OCH_2), 60.7 (OCH_2), 107.8 (C-8), 112.5 (C-6), 118.1 (CN), 123.5, 124.5, 126.8 (C-3′, C-5′, and C-4′), 145.5 (C-5), 145.9 (C-2′), 153.7 (C-8a), 156.7 (C-3), 164.4 (CO_2), 166.0 (CO_2), 168.7 (CO_2CH_3), 202.0 (CO).

(1*R,7*R**)-1-[(1′*S**)-1-Ethoxycarbonyl]indolizine (22b).** This compound was prepared from 2-(2,2-dicyanovinyl)-1,4-dihydropyridine **14** and ethyl 3-oxobutanoate in 85% yield (m = 0.90 g): mp 143−146 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.15 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.22 (s, 3H, $COCH_3$), 2.50 (s, 3H, CH_3 at C-5), 3.95 (q, 1H, OCH-*H*, J = 7.1 Hz), 4.04−4.23 (m, 5H, OCH_2), 4.24 (d, 1H, CH, J = 1.8 Hz), 4.60 (d, 1H, H-1, J = 1.8 Hz), 5.37 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.85 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.21 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.8 (CH_3), 13.9 (CH_3), 14.2 (CH_3), 17.1 (CH_3 at C-5), 29.0 (*C*H_3CO), 35.4 (C-7), 41.0 (C-1), 57.8 (C-2), 60.5 (OCH_2), 60.7 (OCH_2), 61.1 (OCH_2), 62.2 (CH), 107.0 (C-8), 112.2 (C-6), 118.0 (CN), 123.5, 124.4, 126.8 (C-3′, C-5′, and C-4′), 145.1, 146.1 (C-5 and C-2′), 154.7 (C-8a), 156.7 (C-3), 164.6 (CO_2), 166.0 (CO_2), 167.6 (CO_2), 200.7 (CO); IR (KBr) ν 3392 (m), 3351 (m), 3282 (w), 3210 (m), 2982 (w), 2194 (m), 1735 (m), 1698 (s), 1676 (m), 1664 (m), 1583 (s), 1446 (m), 1370 (m), 1311 (m), 1258 (m), 1228 (s), 1194 (m), 1170 (s), 1097 (w), 1038 (m), 706 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 228 (3.48), 316 (3.40); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_6H_{10}O_3$ (100). Anal. Calcd for $C_{26}H_{29}N_3O_7S$ (527): C, 59.19; H, 5.54; N, 7.96. Found: C, 58.95; H, 5.37; N, 7.72.

(1*R,7*R**)-1-[(1′*R**)-1-Ethoxycarbonyl]indolizine (23b):** ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.15 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.0 Hz),

2.05 (s, 3H, $COCH_3$), 2.53 (s, 3H, CH_3 at C-5), 3.95 (q, 1H, OCH−*H*, J = 7.1 Hz), 4.04−4.23 (m, 4H, 2 × OCH_2), 4.30 (d, 1H, CH, J = 3.3 Hz), 4.49 (d, 1H, H-1, J = 3.3 Hz), 5.36 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.85 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.21 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.8 (CH_3), 13.9 (CH_3), 14.2 (CH_3), 17.1 (CH_3 at C-5), 29.0 (*C*H_3CO), 35.4 (C-7), 42.5 (C-1), 57.1 (C-2), 59.6 (CH), 60.5 (OCH_2), 60.7 (OCH_2), 61.3 (OCH_2), 107.8 (C-8), 112.5 (C-6), 118.1 (CN), 123.5, 124.4, 126.8 (C-3′, C-5′, and C-4′), 145.5 (C-5), 145.9 (C-2′), 153.7 (C-8a), 156.7 (C-3), 164.6 (CO_2), 166.0 (CO_2), 168.2 (CO_2), 202.0 (CO).

(1*R,7*R**)-1-[(1′*S**)-1-Isopropoxycarbonyl]indolizine (22c).** This compound was prepared from 2-(2,2-dicyanovinyl)-1,4-dihydropyridine **14** and isopropyl 3-oxobutanoate in 80% yield (m = 0.86 g): mp 145−148 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.15 (d, 3H, OCHC*H*$_3$, J = 6.3 Hz), 1.19 (d, 3H, OCHC*H*$_3$, J = 6.3 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.21 (s, 3H, $COCH_3$), 2.49 (s, 3H, CH_3 at C-5), 4.08−4.27 (m, 4H, 2 × OCH_2), 4.15 (d, 1H, CH, J = 1.8 Hz), 4.59 (d, 1H, H-1, J = 1.8 Hz), 4.84 (septet, 1H, OCH, J = 6.3 Hz), 5.38 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.5 and 3.4 Hz), 6.85 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.16 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.8 (CH_3), 14.2 (CH_3), 17.1 (CH_3 at C-5), 21.0 (CH*C*H_3), 21.1 (CH*C*H_3), 28.6 (CH_3CO), 35.3 (C-7), 41.0 (C-1), 58.0 (C-2), 60.3 (OCH_2), 60.6 (OCH_2), 62.6 (CH), 68.7 (OCH), 106.9 (C-8), 112.3 (C-6), 117.9 (CN), 123.4, 124.4, 126.8 (C-3′, C-5′, and C-4′), 145.0, 146.0 (C-5 and C-2′), 154.68 (C-8a), 156.7 (C-3), 164.4 (CO_2), 166.0 (CO_2), 166.8 (CO_2), 200.4 (CO); IR (KBr) ν 3392 (m), 3325 (w), 3196 (m), 2981 (m), 2205 (m), 2185 (s), 1740 (m), 1696 (s), 1658 (s), 1618 (m), 1587 (s), 1555 (w), 1453 (m), 1372 (m), 1317 (m), 1291 (w), 1259 (s), 1235 (s), 1172 (m), 1105 (m), 1031 (m), 965 (w), 709 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 229 (3.49), 318 (3.43); MS, m/z (%) 397 $M^{+\bullet}$ − $C_7H_{12}O_3$ (100). Anal. Calcd for $C_{27}H_{31}N_3O_7S$ (541): C, 59.87; H, 5.77; N, 7.76. Found: C, 59.62; H, 5.56; N, 7.51.

(1*R,7*R**)-1-[(1′*R**)-1-Isopropoxycarbonyl]indolizine (23c):** ^{1}H NMR (DMSO-d_6): δ 1.15 (d, 3H, OCHC*H*$_3$, J = 6.3 Hz), 1.19 (d, 3H, OCHC*H*$_3$, J = 6.3 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.26 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.04 (s, 3H, $COCH_3$), 2.50 (s, 3H, CH_3 at C-5), 4.07−4.27 (m, 4H, 2 × OCH_2), 4.20 (d, 1H, CH, J = 3.2 Hz), 4.48 (d, 1H, H-1, J = 3.2 Hz), 5.00 (septet, 1H, OCH, J = 6.3 Hz), 5.36 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.5 and 3.4 Hz), 6.85 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.24 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 14.2 (CH_3),16.9 (CH_3 at C-5), 21.2 (CH*C*H_3), 21.3 (CH*C*H_3), 30.2 (CH_3CO), 35.4 (C-7), 42.3 (C-1), 57.0 (C-2), 60.1 (CH), 60.4 (OCH_2), 60.7 (OCH_2), 69.1 (OCH), 107.8 (C-8), 112.5 (C-6), 118.0 (CN), 123.4, 124.3, 126.7 (C-3′, C-5′, and C-4′), 145.3 (C-5), 145.8 (C-2′), 153.5 (C-8a), 156.6 (C-3), 164.4 (CO_2), 165.9 (CO_2), 167.5 (CO_2), 201.9 (CO).

(1*R,7*R**)-1′-[(1′*S**)-*tert*-Butoxycarbonyl]dihydroindolizine (22d).** This compound was prepared from **14** and *tert*-butyl 3-oxobutanoate in 58% yield (m = 0.65 g): mp 182−185 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.39 (s, 9H, *tert*-CH_3), 2.20 (s, 3H, $COCH_3$), 2.48 (s, 3H, CH_3 at C-5), 4.05 (d, 1H, CH, J = 1.5 Hz), 4.07−4.16 (m, 4H, OCH_2), 4.15−4.24 (m, 4H, OCH_2), 4.56 (d, 1H, H-1, J = 1.5 Hz), 5.38 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.5 and 3.4 Hz), 6.86 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.16 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.8 (CH_3), 14.2 (CH_3), 17.0 (CH_3 at C-5), 27.3 (3 × CH_3), 28.6 (CH_3CO), 35.3 (C-7), 40.7 (C-1), 58.1 (C-2), 60.3 (OCH_2), 60.5 (OCH_2), 64.1 (CH), 81.8 (C-*tert*-Bu), 106.5 (C-8), 112.1 (C-6), 117.9 (CN), 123.4, 124.3, 126.7 (C-3′, C-5′, and C-4′), 145.0 (C-5), 146.1 (C-2′), 154.9 (C-8a), 156.5 (C-3), 164.5 (CO_2), 166.0 (CO_2), 166.4 (CO_2), 200.1 (CO); IR (KBr) ν 3399 (m), 3325 (m), 3210 (m), 2984 (w), 2937 (w), 2182 (s), 1737 (m), 1711 (s), 1696 (s), 1658 (s), 1620 (w), 1588 (s), 1448 (m), 1394 (w), 1370 (m), 1317 (m), 1296 (w), 1259 (s), 1233 (m), 1154 (s), 1128 (m), 1097 (w), 1031 (m), 964 (w), 843 (w), 706 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 228 (3.40), 316 (3.36); MS, m/z (%) 397 $M^{+\bullet}$ − $C_8H_{14}O_3$ (100). Anal. Calcd for $C_{28}H_{33}N_3O_7S$ (555): C, 60.52; H, 5.99; N, 7.56. Found: C, 60.40; H, 5.74; N, 7.41.

(1*R,7*R**)-1-[(1′*R**)-1-*tert*-Butoxycarbonyl]dihydroindolizine (23d).** The crude product of the reaction of **14** with *tert*-butyl 3-oxobutanoate as a mixture of diastereomers **22d/23d** (dr = 5:1) (0.56 g, 1.0 mmol) in ethanol was treated with a catalytic amount of a base. After stirring at room temperature for 12 h, the resulting precipitates of dihydroindolizine **23d** were collected by filtration and recrystallized from ethanol. Diastereomer **23d** was obtained in 78% yield (m = 0.44 g): mp 158−161 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.26 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.49 (s, 9H, *tert*-CH_3), 2.06 (s, 3H, $COCH_3$), 2.50 (s, 3H, CH_3 at C-5), 4.06 (d, 1H, CH, J = 3.0 Hz), 4.12−4.26 (m, 4H, 2 × OCH_2), 4.50 (d, 1H, H-1, J = 2.7 Hz), 5.38 (s, 1H, H-7), 6.72 (dd, 1H, H-3′, J = 1.5 and 3.4 Hz), 6.86 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.25 (s broad, 2H, NH_2), 7.27 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz); ^{13}C NMR (DMSO-d_6) δ 13.9 (CH_3), 14.1 (CH_3), 16.9 (CH_3 at C-5), 27.4 (3 × CH_3), 30.3 (CH_3CO), 35.4 (C-7), 42.3 (C-1), 57.1 (C-2), 60.4 (OCH_2), 60.7 (OCH_2), 61.3 (CH), 82.3 (C-*tert*-Bu), 107.7 (C-8), 112.4 (C-6), 118.2 (CN), 123.5, 124.3, 126.7 (C-3′, C-5′, and C-4′), 145.2 (C-5), 145.8 (C-2′), 153.6 (C-8a), 156.7 (C-3), 164.4 (CO_2), 165.8 (CO_2), 167.1 (CO_2), 202.2 (CO); IR (KBr) ν 3391 (m), 3334 (w), 3210 (m), 2978 (m), 2932 (w), 2194 (s), 1736 (s), 1705 (s), 1685 (s), 1656 (s), 1614 (w), 1581 (s), 1455 (m), 1388 (w), 1368 (ms), 1314 (s), 1257 (s), 1230 (s), 1152 (s), 1116 (m), 1044 (m), 1015 (w), 981 (w), 849 (w), 809 (w), 709 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 228 (3.45), 318 (3.36); MS, m/z (%) 397 $M^{+\bullet}$ − $C_8H_{14}O_3$ (100). Anal. Calcd for $C_{28}H_{33}N_3O_7S$ (555): C, 60.52; H, 5.99; N, 7.56. Found: C, 60.31; H, 5.70; N, 7.38.

(±)-Diethyl 3-Amino-2-cyano-1-[(1*Z*)-2-hydroxy-1-(alkoxycarbonyl)prop-1-en-1-yl]-5-methyl-7-(2-thienyl)-7,8-dihydroindolizine-6,8-dicarboxylates (26a−d). To a suspension of the mixture of corresponding *trans*-dihydroindolizines **22/23** (1.0 mmol) in ethanol (5 mL) was added piperidine (0.12 mL, 1.2 mmol). After stirring at room temperature for 12 h, the resulting precipitates of dihydroindolizine **26a−d** were collected by filtration and recrystallized from ethanol.

(7*S,8*S**,a*R*)-1-[1-Methoxycarbonyl]dihydroindolizine (26aA).** This compound was obtained from **22a/23a** in 72% yield (m = 0.37 g): mp 168−171 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, 2 × OCH_2CH_3, J = 7.1 Hz), 1.23 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.26 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.44 (s, 3H, CH_3), 2.78 (s, 3H, CH_3 at C-5), 3.65 (s, 3H, OCH_3), 3.66 (d, 1H, H-8, J = 1.8 Hz), 4.04−4.24 (m, 4H, 2 × OCH_2), 4.30 (s broad, 2H, NH_2), 4.91 (d, 1H, H-7, J = 1.8 Hz), 6.67 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.81 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.02 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.07 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 × CH_3), 18.2 (CH_3 at C-5), 18.8 (*C*H_3COH), 38.2 (C-7), 45.3 (C-8), 51.7 (OCH_3), 61.1 (OCH_2), 61.2 (OCH_2), 80.9 (C-2), 92.2 (*C*=C−CH_3), 115.8 (CN), 116.1 (C-6), 117.7 (C-8a), 118.6 (C-1), 124.2, 124.9, 126.8 (C-3′, C-5′, and C-4′), 142.7 (C-2′), 143.4 (C-5), 144.7 (C-3), 166.1 (CO_2), 169.5 (CO_2), 172.4 (CO_2), 176.9 (COH); IR (KBr) ν 3437 (w), 3367 (m), 3328(m), 3239 (m), 2983 (w), 2205 (s), 1740 (s), 1693 (s), 1652 (s), 1612 (s), 1561 (s), 1463 (s), 1443 (s), 1364 (m), 1345 (s), 1251 (brs), 1212 (s), 1175 (s), 1137 (s), 1064 (m), 1017 (m), 912 (w), 862 (w), 701 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 212 (3.38), 249 (3.53), 289 (3.33); MS, m/z (%) 397 $M^{+\bullet}$ − $C_5H_8O_3$ (100). Anal. Calcd for $C_{25}H_{27}N_3O_7S$ (513): C, 58.47; H, 5.30; N, 8.18. Found: C, 58.29; H, 5.11; N, 7.96.

(7*S,8*S**,a*S*)-1-[1-Methoxycarbonyl]dihydroindolizine (26aB):** ^{1}H NMR ($CDCl_3$) δ 1.19 (t, 3H, 2 × OCH_2CH_3, J = 7.1 Hz), 1.30 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.88 (s, 3H, CH_3), 2.78 (s, 3H, CH_3 at C-5), 3.33 (s, 3H, OCH_3), 3.74 (d, 1H, H-8, J = 1.8 Hz), 4.04−4.24 (m, 4H, 2 × OCH_2), 4.30 (s broad, 2H, NH_2), 4.96 (d, 1H, H-7, J = 1.8 Hz), 6.63 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz),

6.82 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.05 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.11 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 (2 × CH_3), 18.0 (CH_3 at C-5), 19.7 (CH_3−C−OH), 38.1 (C-7), 45.2 (C-8), 51.7 (OCH_3), 61.3 (OCH_2), 61.6 (OCH_2), 80.9 (C-2), 92.1 (C═C− CH_3), 115.8 (CN), 116.0 (C-6), 117.6 (C-8a), 118.9 (C-1), 124.0, 124.6, 126.4 (C-3′, C-5′, and C-4′), 142.7 (C-2′), 143.1 (C-5), 144.7 (C-3), 165.9 (CO_2), 169.8 (CO_2), 172.0 (CO_2), 177.6 (COH).

(7*S,8*S**,a*R*)-1-[1-Ethoxycarbonyl]dihydroindolizine (26bA).** This compound was obtained from **22b/23b** in 66% yield (m = 0.35 g): mp 150−153 °C; ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, OCH_2CH_3, J = 7.2 Hz), 1.19−1.35 (m, 6H, 2 × OCH_2CH_3), 1.37 (s, 3H, CH_3), 2.82 (s, 3H, CH_3 at C-5), 3.69 (d, 1H, H-8, J = 1.8 Hz), 3.83 (qd, 1H, OC*H*), 4.00−4.26 (m, 6H, 3 × OCH_2), 4.27 (s broad, 2H, NH_2), 4.94 (d, 1H, H-7, J = 1.8 Hz), 6.67 (d, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.80 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.05 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.20 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2 (3 × CH_3), 18.2 (CH_3 at C-5), 18.6 (═C−CH_3), 38.2 (C-7), 45.4 (C-8), 60.9 (OCH_2), 61.2 (2 × OCH_2), 81.0 (C-2), 92.4 (C═C−CH_3), 115.9 (CN), 116.3 (C-6), 117.5 (C-8a), 118.5 (C-1), 124.2, 124.9, 126.9 (C-3′, C-5′, and C-4′), 142.7 (C-2′), 143.6 (C-5), 144.7 (C-3), 166.1 (CO_2 at C-6), 169.5 (CO_2 at C-8), 172.2 (CO_2), 176.6 (COH); IR (KBr) ν 3380 (m), 3328 (m), 3242 (m), 2982 (m), 2207 (s), 1744 (m), 1729 (s), 1693 (s), 1685 (s), 1651 (s), 1628 (s), 1560 (s), 1461 (s), 1388 (m), 1369 (m), 1333 (s), 1271 (s), 1249 (s), 1221 (s), 1193 (s), 1156 (s), 1069 (m), 1024 (m), 960 (w), 853 (w), 713 (w), 688 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 214 (3.77), 245 (3.95), 288 (3.78). MS, m/z (%) 397 $M^{+\bullet}$ − $C_6H_{10}O_3$ (100). Anal. Calcd for $C_{26}H_{29}N_3O_7S$ (527): C, 59.19; H, 5.54; N, 7.96. Found: C, 59.01; H, 5.31; N, 7.69.

(7*S,8*S**,a*S*)-1-[1-Ethoxycarbonyl]dihydroindolizine (26bB):** ^{1}H NMR ($CDCl_3$) δ 1.19−1.35 (m, 9H, 3 × OCH_2CH_3), 1.88 (s, 3H, CH_3), 2.77 (s, 3H, CH_3 at C-5), 3.77 (d, 1H, H-8, J = 1.8 Hz), 4.02−4.26 (m, 6H, 3 × OCH_2), 4.26 (s broad, 2H, NH_2), 4.95 (d, 1H, H-7, J = 1.8 Hz), 6.64 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.82 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.05 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.28 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.2 (3 × CH_3), 18.1 (CH_3 at C-5), 19.8 (═C−CH_3), 38.2 (C-7), 44.3 (C-8), 60.7 (OCH_2), 61.2 (OCH_2), 61.5 (OCH_2), 81.0 (C-2), 92.5 (C═C−CH_3), 115.9 (CN), 116.7 (C-6), 118.1 (C-8a), 118.7 (C-1), 124.1, 124.7, 126.4 (C-3′, C-5′, and C-4′), 142.6 (C-2′), 143.2 (C-5), 144.6 (C-3), 166.0 (CO_2), 169.9 (CO_2), 171.7 (CO_2), 177.4 (COH).

(7*S,8*S**,a*R*)-1-[1-Isopropoxycarbonyl]dihydroindolizine (26cA).** This compound was obtained from **22c/23c** in 70% yield (m = 0.38 g): mp 182−185 °C; ^{1}H NMR (acetone-d_6) δ 0.97 (d, 3H, $OCHCH_3$, J = 6.1 Hz), 1.14 (d, 3H, $OCHCH_3$, J = 6.1 Hz), 1.18 (t, 3H, OCH_2CH_3, J = 7.3 Hz), 1.23 (t, 3H, OCH_2CH_3, J = 7.3 Hz), 1.26 (s, 3H, CH_3), 2.81 (s, 3H, CH_3 at C-5), 2.97 (s broad, 2H, NH_2), 3.76 (d, 1H, H-8, J = 2.4 Hz), 4.06−4.25 (m, 4H, 2 × OCH_2), 4.90−5.05 (m, 2H, OC*H*CH_3 and H-7), 6.75 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.87 (dd, 1H, H-4′, J = 3.4 and 4.9 Hz), 7.24 (dd, 1H, H-5′, J = 1.2 and 4.9 Hz), 13.39 (s, 1H, OH); ^{13}C NMR (acetone-d_6) δ 15.4 (CH_3), 15.5 (CH_3), 19.1 (CH_3 at C-5), 19.5 (═C−CH_3), 22.7 (2 × CH_3), 40.2 (C-7), 46.4 (C-8), 62.4 (OCH_2), 62.6 (OCH_2), 70.1 (OCH), 81.0 (C-2), 93.0 (C═C−CH_3), 117.4 (CN), 118.3 (C-6), 119.1 (C-8a), 119.8 (C-1), 126.3, 126.5, 128.3 (C-3′, C-5′, and C-4′), 145.1 (C-2′), 146.1 (C-5), 146.9 (C-3), 167.7 (CO_2), 167.8 (CO_2), 171.0 (CO_2), 171.6 (COH); IR (KBr) ν 3396 (m), 3342 (m), 3246 (m), 3108 (w), 2986 (m), 2941 (w), 2206 (s), 1744 (s), 1692 (s), 1649 (s), 1618 (s), 1563 (s), 1465 (m), 1430 (w), 1385 (m), 1367 (m), 1332 (m), 1270 (s), 1252 (s), 1227 (s), 1172 (s), 1106 (s), 1065 (m), 1023 (m), 883 (w), 703 (m), 690 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 212 (3.38), 249 (3.53), 289 (3.33); MS, m/z (%) 397 $M^{+\bullet}$ − $C_7H_{12}O_3$ (100). Anal. Calcd for $C_{27}H_{31}N_3O_7S$ (541): C, 59.87; H, 5.77; N, 7.76. Found: C, 59.61; H, 5.49; N, 7.52.

(7*S,8*S**,a*S*)-1-[1-Isopropoxycarbonyl]dihydroindolizine (26cB):** ^{1}H NMR (acetone-d_6) δ 1.14 (d, 3H, $OCHCH_3$, J = 6.1 Hz), 1.18 (d, 3H, $OCHCH_3$, J = 6.1 Hz), 1.20 (t, 3H, OCH_2CH_3, J = 7.3 Hz), 1.28 (t, 3H, OCH_2CH_3, J = 7.3 Hz), 1.83 (s, 3H, CH_3), 2.89 (s, 3H, CH_3 at C-5), 3.83 (d, 1H, CH-8, J = 1.8 Hz), 4.06−4.25 (m, 4H, 2 × OCH_2), 4.90−5.05 (m, 2H, OC*H*CH_3 and H-7), 5.57 (s broad, 2H, NH_2), 6.81 (dd, 1H, H-3′, J = 1.2 and 3.7 Hz), 6.87 (dd, 1H, H-4′, J = 3.7 and 4.9 Hz), 7.24 (dd, 1H, H-5′, J = 1.2 and 6.7 Hz), 13.39 (s, 1H, OH); ^{13}C NMR (acetone-d_6) δ 15.4 (CH_3), 15.5 (CH_3), 19.2 (CH_3 at C-5), 20.8 (═C−CH_3), 22.8 (2 × CH_3), 40.3 (C-7), 47.8 (C-8), 62.5 (OCH_2), 62.9 (OCH_2), 70.3 (OCH), 81.0 (C-2), 93.0 (C═C−CH_3), 117.5 (CN), 117.7 (C-6), 118.6 (C-8a), 119.8 (C-1), 126.3, 127.0, 128.8 (C-3′, C-5′, and C-4′), 145.1 (C-2′), 146.1 (C-5), 146.9 (C-3), 167.7 (CO_2), 167.8 (CO_2), 171.0 (CO_2), 171.6 (COH).

(7*S,8*S**,a*R*)-1-[1-*tert*-Butoxycarbonyl]dihydroindolizine (26dA).** This compound was obtained from **22d/23d** in 66% yield (m = 0.37 g): mp 207−210 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (s, 3H, CH_3), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.25 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.41 (s, 9H, 3 × CH_3), 2.82 (s, 3H, CH_3 at C-5), 3.70 (d, 1H, H-8, J = 1.8 Hz), 4.07−4.27 (m, 4H, 2 × OCH_2), 4.24 (s broad, 2H, NH_2), 4.93 (d, 1H, H-7, J = 1.8 Hz), 6.67 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.81 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.04 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.31 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 14.2 (CH_3), 18.2 (═CH−CH_3), 18.3 (CH_3 at C-5), 28.1 (3 × CH_3), 38.3 (C-7), 45.7 (C-8), 61.1 (OCH_2), 61.2 (OCH_2), 81.3 (C-2), 81.8 (*C*-CH_3), 93.6 (*C*═C−CH_3), 115.9 (CN), 117.1 (C-6), 117.6 (C-8a), 118.2 (C-1), 124.3, 125.0, 127.0 (C-3′, C-5′, and C-4′), 142.8 (C-2′), 143.7 (C-5), 144.4 (C-3), 166.2 (CO_2), 169.5 (CO_2), 172.0 (CO_2), 175.5 (CO); IR (KBr) ν 3389 (m), 3323 (w), 3240 (w), 2983 (w), 2203 (s), 1738 (m), 1702 (s), 1650 (s), 1616 (s), 1561 (s), 1459 (m), 1387 (m), 1368 (m), 1352 (m), 1328 (w), 1274 (s), 1253 (s), 1240 (s), 1180 (s), 1160 (s), 1136 (s), 1061 (w), 1024 (w), 865 (w), 708 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 211 (3.88), 250 (4.07), 289 (3.90); MS, m/z (%) 397 $M^{+\bullet}$ − $C_8H_{14}O_3$ (100). Anal. Calcd for $C_{28}H_{33}N_3O_7S$ (555): C, 60.52; H, 5.99; N, 7.56. Found: C, 60.39; H, 5.71; N, 7.37.

(7*S,8*S**,a*S*)-1-[1-*tert*-Butoxycarbonyl]dihydroindolizine (26dB):** ^{1}H NMR ($CDCl_3$) δ 1.22 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.30 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.39 (s, 9H, 3 × CH_3), 1.79 (d, 3H, CH_3), 2.77 (s, 3H, CH_3 at C-5), 3.82 (d, 1H, CH-8, J = 1.8 Hz), 4.07−4.27 (m, 4H, 2 × OCH_2), 4.24 (brs, 2H, NH_2), 4.90 (d, 1H, H-7, J = 1.8 Hz), 6.65 (dd, 1H, H-3′, J = 1.2 and 3.4 Hz), 6.82 (dd, 1H, H-4′, J = 3.4 and 5.1 Hz), 7.06 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 13.47 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.2 (2 × CH_3), 18.3 (CH_3 at C-5), 19.7 (═CH−CH_3), 27.9 (3 × CH_3), 38.8 (C-7), 44.1 (C-8), 61.2 (OCH_2), 61.4 (OCH_2), 81.5 (C-2), 82.1 (*C*−CH_3), 93.9 (*C*═C−CH_3), 116.2 (CN), 117.3 (C-6), 117.5 (C-8a), 118.0 (C-1), 124.1, 124.4, 126.6 (C-3′, C-5′, and C-4′), 142.9 (C-2′), 143.6 (C-5), 144.6 (C-3), 166.1 (CO_2), 169.8 (CO_2), 171.6 (CO_2), 176.1 (CO).

Diethyl (1*R,7*R**,1′*R**)-3-Amino-2-cyano-1-cyano(phenylsulfonyl)methyl-5-methyl-7-(2-thien-yl)-1,7-dihydroindolizine-6,8-dicarboxylate (27).** To a suspension of 2-dicyanovinyl-1,4-dihydropyridine **14** (0.80 g, 2.0 mmol) and phenylsulfonylacetonitrile (0.36 g, 2.0 mmol) in ethanol (5 mL) was added a catalytic amount of piperidine. After stirring at room temperature for 3 h, the resulting precipitates of **27** were collected by filtration and recrystallized from ethanol. Compound **27** was obtained in 86% yield (m = 1.00 g): mp 171−175 °C; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.49 (s, 3H, CH_3 at C-5), 4.01−4.28 (m, 4H, 2 × OCH_2), 4.81 (d, 1H, H-1, J = 2.6 Hz), 5.36 (s, 1H, H-7), 5.44 (d, 1H, CH), 6.75 (dd, 1H, H-3′, J = 1.5 and 3.4 Hz), 6.87 (dd, 1H, H-4′, J = 3.4 and 5.2 Hz), 7.29 (dd, 1H, H-5′, J = 1.5 and 5.1 Hz), 7.70 (s broad, 2H, NH_2), 7.80 (t, 2H, H-3″, J = 7.8 Hz), 7.88 (t, 1H, H-4″, J = 7.8 Hz), 7.94 (t, 2H, H-2″, J = 7.8 Hz); ^{13}C NMR (DMSO-d_6) δ 14.0 (CH_3), 14.1 (CH_3), 16.8 (CH_3 at C-5), 35.7 (C-7), 41.2 (CH), 55.4 (C-2), 59.6 (CH), 60.5 (OCH_2), 61.0 (OCH_2), 110.2 (C-8), 112.9 (C-6), 113.0 (CN), 117.5 (CN), 123.8, 124.6, 126.8 (C-3′, C-5′, and C-4′), 128.9,

129.8, 135.4 (CH-arom), 136.6 (C-arom), 144.8 (C-5), 145.1 (C-2′), 149.8 (C-8a), 157.8 (C-3), 163.9 (CO_2), 165.7 (CO_2); IR (KBr) ν 3415 (m), 3334 (m), 2981 (w), 2929 (w), 2196 (s), 1709 (s), 1697 (s), 1652 (s), 1585 (s), 1446 (s), 1372 (w), 1351 (m), 1312 (m), 1261 (m), 1229 (s), 1207 (w), 1158 (s), 1211 (m), 1092 (m), 1030 (m), 960 (w), 851 (w), 741 (w), 714 (w), 690 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 198 (3.56), 223 (3.54), 303 (3.29); MS, *m*/*z* (%) 397 $M^{+\bullet}$ − $C_8H_7NO_2S$ (100). Anal. Calcd for $C_{28}H_{26}N_4O_6S_2$ (578): C, 58.12; H, 4.53; N, 9.68. Found: C, 57.89; H, 4.34; N, 9.41.

Diethyl (1*E*)-3-Amino-2-cyano-1-cyanomethylene-5-methyl-7-(2-thienyl)-1,7-dihydroindolizine-6,8-dicarboxylate (28). To a suspension of *trans*-dihydroindolizine **27** (0.58 g, 1.0 mmol) in ethanol (5 mL) was added piperidine (0.12 mL, 1.2 mmol). After stirring at room temperature for 10 h, the resulting precipitates of **28** were collected by filtration and recrystallized from ethanol. Compound **28** was obtained in 78% yield (m = 0.34 g): mp 217−220 °C; ^{1}H NMR (DMSO-d_6) δ 1.23 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.24 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.55 (s, 3H, CH_3 at C-5), 4.14−4.23 (m, 4H, 2 × OCH_2), 5.43 (s, 1H), 6.43 (s, 1H), 6.78 (dd, 1H, H-3′, J = 1.2 and 3.6 Hz), 6.89 (dd, 1H, H-4′, J = 3.6 and 5.1 Hz), 7.32 (dd, 1H, H-5′, J = 1.2 and 5.1 Hz), 8.63 (s broad, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ 13.8 (CH_3), 14.1 (CH_3), 17.0 (CH_3 at C-5), 37.7 (C-7), 60.8 (OCH_2), 61.7 (OCH_2), 66.9 (C-2), 78.8 (C═H), 114.2, 114.3, 114.5, 117.3 (2 × CN, C-3 and C-5), 124.5, 125.1, 126.9 (C-3′, C-5′, and C-4′), 143.3, 143.4, 143.6, 143.9 (C-8a, C-5, C-7, and C-2′), 159.1 (C-1), 164.6 (CO_2), 165.3 (CO_2); IR (KBr) ν 3417 (w), 3323 (m), 3201 (m), 3101 (w), 2987 (w), 2204 (s), 1691 (s), 1657 (s), 1647 (s), 1650 (s), 1480 (s), 1383 (m), 1370 (m), 1303 (m), 1278 (s), 1244 (s), 1187 (m), 1172 (m), 1158 (m), 1108 (w), 1092 (w), 1044 (m), 1018 (w), 901 (w), 849 (w), 714 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 230 (3.39), 261 (3.24), 325 (3.20), 438 (2.82); MS, *m*/*z* (%) 436 ($M^{+\bullet}$). Anal. Calcd for $C_{22}H_{20}N_4O_4S$ (436): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.45; H, 4.49; N, 12.63.

Diethyl 3-amino-2-cyano-1-cyanomethyl-5-methyl-7-(2-thienyl)indolizine-6,8-dicarboxylate (29). To a solution of *trans*-dihydroindolizine **28** (0.44 g, 2.0 mmol) in dichloromethane (10 mL) was added a catalytic amount of *p*-toluenesulfonic acid. After stirring at room temperature for 5 h, the solvent was evaporated and the resulting precipitates of **29** were recrystallized from ethanol. Compound **29** was obtained in 85% yield (m = 0.37 g): mp 170−172 °C; ^{1}H NMR (DMSO-d_6) δ 0.92 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 0.98 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.80 (s, 3H, CH_3 at C-5), 3.73 (s, 2H, CH_2), 3.96 (q, 2H, OCH_2, J = 7.1 Hz), 4.09 (q, 2H, OCH_2, J = 7.1 Hz), 6.11 (s broad, 2H, NH_2), 6.89 (dd, 1H, H-3′, J = 1.7 and 3.5 Hz), 7.06 (dd, 1H, H-4′, J = 3.5 and 5.3 Hz), 7.63 (dd, 1H, H-5′, J = 1.7 and 5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 13.3 (CH_3), 13.4 (CH_3), 13.7 (CH_2), 17.5 (CH_3 at C-5), 61.5 (OCH_2), 62.1 (OCH_2), 85.3 (C-2), 102.2, 114.7, 117.3, 119.3, 119.9, 120.2, 123.2 (C-6, C-3, C-2, 2 × CN, C-7, C-8), 127.1, 127.7, 128.5 (C-3′, C-5′, and C-4′), 135.1, 135.7, 143.1 (C-8a, C-5, and C-2′), 165.7 (CO_2), 166.3 (CO_2); IR (KBr) ν 3347 (m), 3234 (m), 3108 (w), 2981 (m), 2937 (w), 2222 (s), 1724 (s), 1700 (s), 1646 (m), 1554 (m), 1469 (m), 1407 (m), 1374 (m), 1343 (m), 1274 (m), 1241 (s), 1175 (m), 1149 (m), 1094 (w), 1075 (m), 1038 (m), 1010 (m), 856 (m), 759 (w), 707 (m) cm^{-1}; UV λ_{max} nm (log ϵ) 217 (3.58), 225 (3.58), 269 (3.60), 410 (2.79); MS, *m*/*z* (%) 436 ($M^{+\bullet}$). Anal. Calcd for $C_{22}H_{20}N_4O_4S$ (436): C, 60.54; H, 4.62; N, 12.84. Found: C, 60.54; H, 4.62; N, 12.84.

Diethyl 3-Amino-2-cyano-1-[(*Z*)-2-hydroxy-2-phenylvinyl]-5-methyl-7-(2-thienyl)indolizine-6,8-dicarboxylate (31). The mixture of 2-dicyanovinyl-1,4-dihydropyridine **14** (0.80 g, 2.0 mmol), 2-nitro-1-phenylethanone (0.33 g, 2.0 mmol), and piperidine (0.24 mL, 2.4 mmol) in ethanol (10 mL) was refluxed for 1 h. After cooling the resulting precipitates of polysubstituted indolizine **31** were collected by filtration and recrystallized from ethanol. Compound **31** was obtained in 88% yield (m = 0.91 g): mp 182−186 °C; ^{1}H NMR (DMSO-d_6) δ 0.96 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 1.05 (t, 3H, OCH_2CH_3, J = 7.1 Hz), 2.87 (s, 3H, CH_3 at C-5), 3.99 (q, 2H, OCH_2, J = 7.1 Hz), 4.23 (q, 2H, OCH_2, J = 7.1 Hz), 6.39 (s broad, 2H, NH_2), 6.52 (s, 1H, H−C═), 6.91 (dd, 1H, H-3′, J = 3.4 and 1.6 Hz), 7.07 (dd, 1H, H-4′, J = 5.1 and 3.4 Hz), 7.37 (t, 1H, H-4″, J = 7.0 Hz), 7.46 (t, 2H, H-3″, J = 7.0 Hz), 7.59 (dd, 1H, H-5′, J = 5.1 and 1.6 Hz), 7.69 (d, 2H, H-2″, J = 7.0 Hz), 8.24 (s broad, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 13.5 (CH_3), 13.6 (CH_3), 17.0 (CH_3 at C-5), 61.4 (OCH_2), 61.9 (OCH_2), 94.1 (CH═), 97.2 (C-2), 108.1, 115.1, 115.8, 120.2 (C-8, CN, C-8a, C-6), 123.8 (2 × C-3″), 124.8 (C-7), 127.1, 127.2, 127.9 (C-3′, C-5′, and C-4′), 128.7 (C-4″), 128.9 (C-2″), 132.7 (C-benzene), 134.2 (C-2′), 136.7, 138.1, 148.4 (C-5, C-1, and C-3), 155.1 (C−OH), 166.0 (CO_2), 166.7 (CO_2); IR (KBr) ν 3396 (w), 3296 (w), 2982 (w), 2208 (w), 1716 (s), 1660 (s), 1630 (s), 1594 (w), 1435 (w), 1370 (m), 1352 (w), 1332 (w), 1301 (m), 1286 (m), 1243 (s), 1181 (m), 1154 (m), 1056 (m), 1045 (s), 1016 (w), 988 (w), 800 (m), 761 (m), 710 (w), 689 (w) cm^{-1}; UV λ_{max} nm (log ϵ) 227 (3.37), 289 (3.39), 397 (3.19); MS, *m*/*z* (%) 515 ($M^{+\bullet}$). Anal. Calcd for $C_{28}H_{25}N_3O_5S$ (515): C, 65.23; H, 4.89; N, 8.15. Found: C, 65.01; H, 4.80; N, 8.03.

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Supporting Information Available: Spectroscopic data of all products reported herein including ^{1}H NMR, ^{13}C NMR, IR, and UV spectra; ORTEP plot of 1,7-dihydroindolizines **16a**, **22b**, and **27** and 7,8-dihydroindolizines **26bA**; and X-ray data (CIF files). This material is available free of charge via the Internet at http://pubs.acs.org.

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