Toward a Stable α-Cycloalkyl Amino Acid with a Photoswitchable Cationic Side Chain

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S *Supporting Information*

ABSTRACT: The N-alkylated indanylidenepyrroline (NAIP) Schiff base **3** is an unnatural α-amino acid precursor potentially useful for the preparation of semisynthetic peptides and proteins incorporating charged side chains whose structure can be modulated via Z/E photoisomerization. Here we report that the heteroallylic protons of **3** led to partial loss of ethanol accompanied by formation of the novel heterocyclic system **4** during attempted deprotection. We also show that the same protons catalyze the thermal isomerization of **3**, making the light-driven conformational control concept ineffective for times longer than a few hours. These problems are not present in the previously unreported compound **5** where the acidic methyl group is replaced by an H atom. Therefore, **5**, rather than **3**, constitutes a promising prototype for the design of building blocks capable to modulate the electrostatic potential of a protein in specific locations via light irradiation.
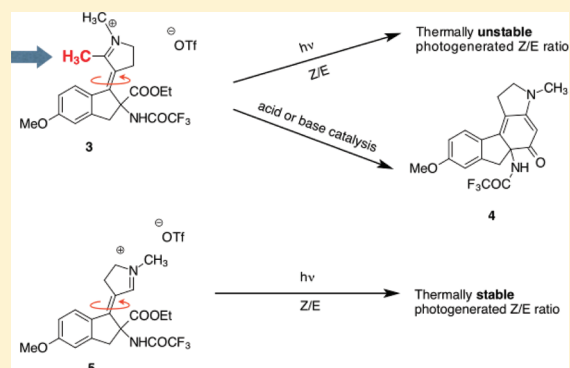
INTRODUCTION

Photochemical switches are bistable compounds that can be interconverted between two different isomers (states) via light irradiation. The most widely used photoswitch is azobenzene that has been employed to control different biomolecular functions[1−3] via a −N=N− double-bond photoisomerization interconverting its Z and E states. Owing to the significant change in molecular length (ca. 3.5 Å between the two p-carbons) but limited change in dipole moment (ca. 3 D) between its Z- and E-isomers,[4] azobenzene is considered a mechanical rather than electrostatic switch. Literature examples of electrostatic photoswitches are compounds of the spiropyran-type[5,6] that can be changed between a neutral state and a zwitterionic state via a photochemical ring-opening reaction. Such property has been employed to reversibly modulate α-helix→random coil conformational transitions[7] and the activity of enzymes[8] and channel proteins[9] and to achieve novel sensors.[10]

N-Alkylated indanylidenepyrroline Schiff bases (NAIPs) are novel biomimetic photochemical switches that replicate the efficient −C=C− double-bond photoisomerization occurring in visual pigments (e.g., the dim-light receptor rhodopsin).[11−13] These molecules, which feature a permanently charged[12] or zwitterionic[14] pyrroline unit (see **1** and **2** in Figure 1), have been proposed to function both as mechanical[11,15] and/or

electrostatic[14] switches. As illustrated in Figure 2A for **2**, upon photoisomerization of the exocyclic double bond, the pyrroline unit undergoes a ca. 180° twisting yielding a spatial relocation of the charges and, in turn, a change in the orientation of the electric dipole moment with respect to the indanylidene framework. We have reported[14] that the photolysis of **2** may induce a ca. 30 D dipole moment change which modulates the spectra of nearby fluorophores. Since NAIPs are photochromic compounds, irradiation at different wavelengths can be used to establish the isomer dominating the system photostationary state (see the histogram of Figure 2B) and implement the electrostatic switching concept.

It is apparent that the properties mentioned above provide the basis for achieving novel functional building blocks capable of modulating steric and electrostatic interactions in diverse macromolecular or supramolecular environments (see examples in ref 16). In spite of their interest for the preparation of novel photoresponsive materials, **1**, **2**, and their analogues (see for instance ref 17) cannot be used in a block synthesis due to the lack of suitable functional groups for the coupling to a macromolecular or solid-state framework. For this reason, we have recently reported the preparation of **3**, a NAIP switch
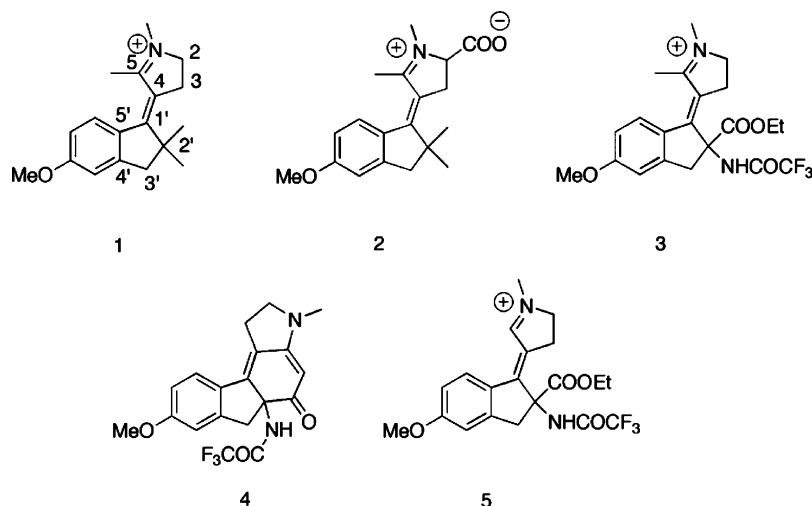
Figure 1. Structures discussed in the present work. Compound **3** is an α-cycloalkyl amino acid derivative of **1**, and **4** is an undesirable tetracyclic synthesis byproduct obtained during the synthesis of **3**. Compound **5** represents the main synthesis target.
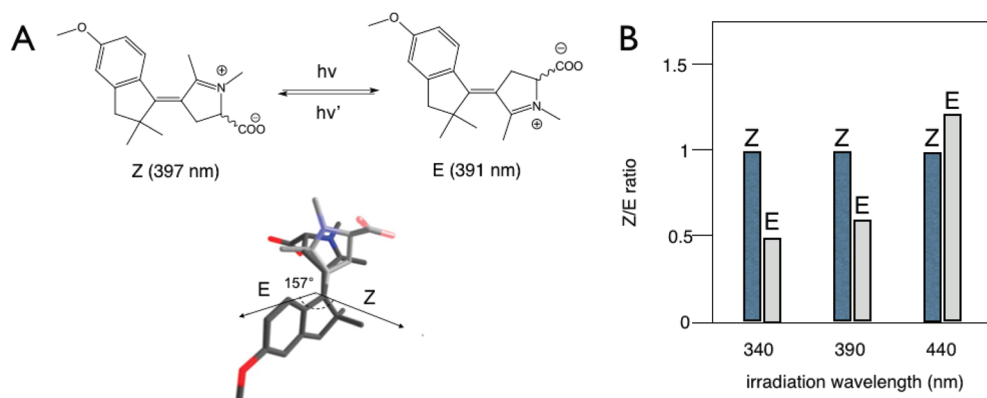
Figure 2. Zwitterionic NAIP switch. (A) Schematic representation of an electrostatic switch based on the Z/E isomerization of **2**. The absorption maxima of the E- and Z-isomers in methanol solution are given in parentheses. The 180° rotation of the pyrrolinium unit will invert the dipole moment vector with respect to the indanylidene unit. The angle between the simulated dipole moment vectors of the E- and Z-isomers is from ref 14. The computed dipole moment values are 15.7 and 14.8 D, respectively. (B) Observed E/Z photostationary state ratio of **2** as a function of the irradiation wavelength.

featuring an indanylidene unit bearing protected amino and carboxylic groups at position C2'.[14] The NAIP switch **3** constitutes an α-cycloalkyl amino acid building block that could potentially be employed for the preparation of photoresponsive peptides or proteins. Indeed, methods for the incorporation of bulky α-alkyl amino acid in synthetic peptides have been established.[18−23] On the other hand, such incorporation requires, invariably, the deprotection of the amino and carboxyl functions.

In the next section we show that compound **3** is not a suitable building block for the preparation of photoresponsive peptides due to its chemical and thermal instability. With the aim to overcome the above drawbacks, we embarked on a combination of kinetic, synthesis, and structural studies whose main goal is represented by the successful preparation of the unprecedented unnatural α-cycloalkyl amino acid precursor **5**. Besides being stable both to acidic and basic environments, the new aldimine-type NAIP has been found to display the wanted stable light-driven switching behavior in the presence of protecting groups mimicking, locally, the incorporation in a peptide side chain.

■ RESULTS AND DISCUSSION

Nitrilium Cyclization and Formation of a Tetracyclic Byproduct. In the past,[24] we have shown that an indanylidene nucleus can be successfully transformed into a polyconjugated iminium ion featuring a protonated or alkylated Schiff base function. Therefore, we envisioned that the same nitrilium cyclization chemistry could be employed to introduce the amino and carboxyl functional groups on the indanylidene portion of **1** giving access to a new class of unnatural α-cycloalkyl amino acids suitable for peptide synthesis. Accordingly, we successfully prepared[14] the NAIP switch **3**: a protected α-amino acid featuring a quaternary α-carbon locked into a rigid indanylidene ring.

As shown in Scheme 1, the ethoxycarbonylated 5-methoxyindan-1-one, subjected to the action of N-bromosuccinimide and Amberlyst-15,[25,26] gave almost quantitatively the brominated compound **6**. The C-2 nitrogen introduction, easily accomplished via bromide displacement with sodium azide, followed by Staudinger reduction and trifluoroacetylation of the resulting primary amine,[27] gave compound **7**. The structure of the protected α-amino acid featuring a quaternary stereocenter

**Scheme 1. Synthesis of Free Base Protected α-Cycloalkyl Amino Acid 10**
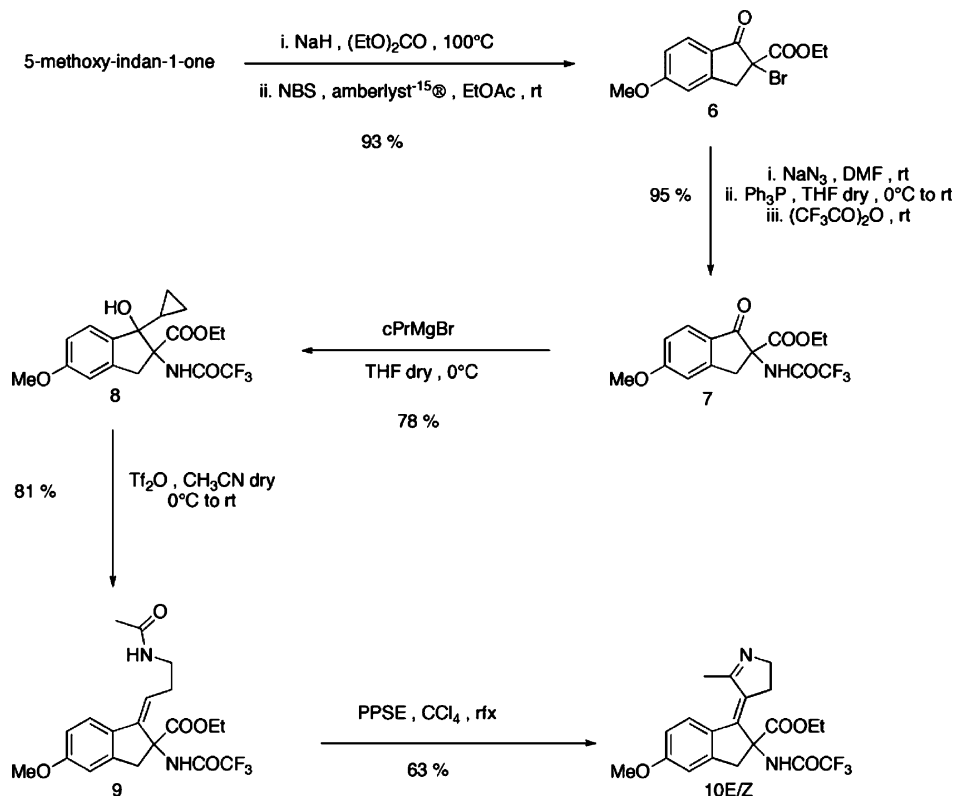
was confirmed by RX crystallography (see the Supporting Information).

The subsequent steps were devoted to the installation of the homoallyl acetamide group on the indan nucleus by exploiting the previously reported homoallyl rearrangement of cyclopropylindanol derivatives.[24,28] Thus, the Grignard adduct **8** exposed to the action of triflic anhydride in the presence of acetonitrile afforded compound **9**. Dehydration of the secondary amide by using trimethylsilyl polyphospate (PPSE) and the quenching of the resulting nitrilium ion on the internal olefin yielded the expected free base **10** (Scheme 1) as a mixture of geometric isomers (E/Z 1:2).

While we demonstrated that the above protocol leads to the wanted Schiff base precursor, evidence for undesirable instabilities of the IP framework and Z/E ratio started to emerge. First, it was found that protons of the methyl group at $\delta = 2.27$ ppm of **10** underwent a fast exchange in CD_3OD indicating a prototropic tautomeric equilibration of the Schiff base function with the corresponding enamine via the methyl group in vinyl position (see first line in Scheme 2). The acidity of the same methyl group was also held responsible for the transformation of the prepared **10E/10Z** mixture into the tetracyclic compound **11** by simple elution through a column of silica gel. The structure of compound **11** is confirmed by RX crystallography (see the Supporting Information). On the basis of these data, we assume that **11** results from an intramolecular enamine acylation reaction whose mechanism is shown in Scheme 2. Notice that the equilibration between the E/Z steroisomers, as well as the tautomerization to the reacting enamine, are prerequisites for the acylation step.

In spite of the undesirable transformation described above, it was possible to prepare the geometric isomers of **10** by flash chromatographic separation on silica gel conditioned with TEA.

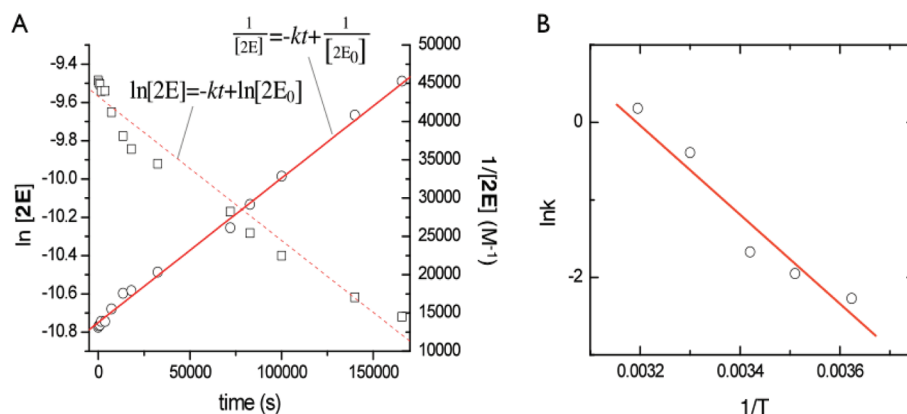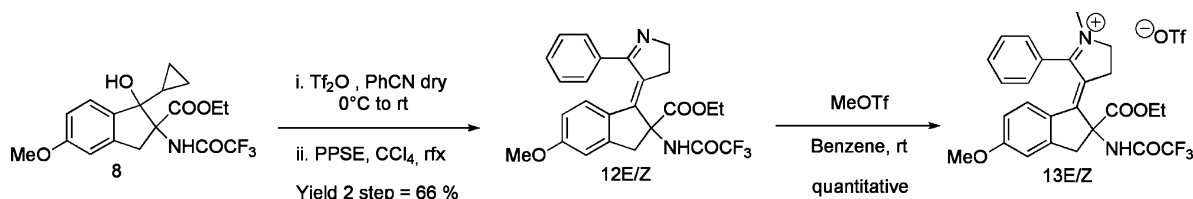**Scheme 2. Mechanism Assumed for the Formation of Tetracyclic Compound 11**
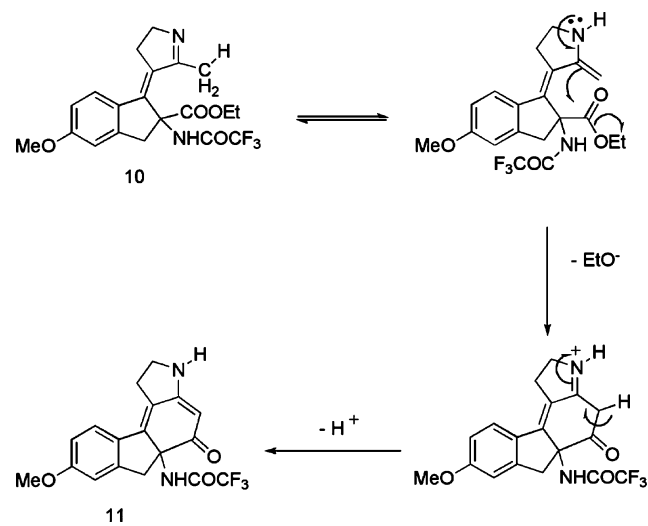
Their treatment with methyl triflate gave the target isomers **3E** and **3Z** (Scheme 3), whose geometrical identity was ascertained

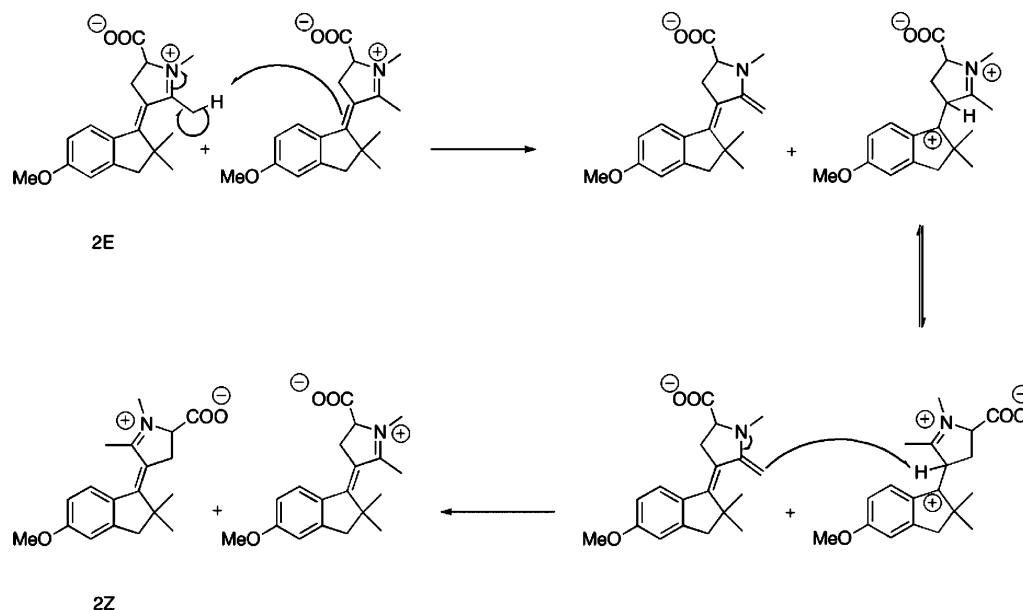**Scheme 3. Methylation of Free Base NAIP Precursor 10**
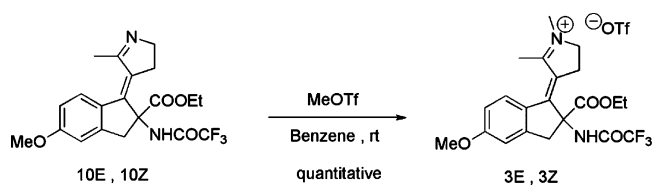
Scheme 4. Synthesis of the NAIP Schiff Base Phenyl Derivative 13E/Z

Figure 3. Kinetic studies on **2**. (A) Kinetic analysis of the spectrophotometric data obtained at 292 K. (B) Arrhenius plot giving an E_a = 12100 cal mol^{-1}.

Scheme 5. Proposed Bimolecular Mechanism for the Isomerization of the NAIP Schiff Base 2E

by NOESY experiment. These isomers were stable enough to be well-characterized; however, attempts to perform the hydrolysis of their ethoxycarbonyl groups, as a step toward the corresponding α-amino acid, were completely unsuccessful. The only detectable material in the reaction mixture was the tetracyclic compound **4** that similarly to **11** could result from an intramolecular enamine acylation. The structure of compound **4** was demonstrated via RX diffraction analysis (see the Supporting Information). This finding reinforced the idea that, in order to access a photoresponsive amino acid that could be employed in peptide synthesis, it is necessary to access NAIP frameworks not bearing a methyl group (or any other alkyl group) in position C5 on the pyrroline ring. In other words, the

behavior of both **3** and **10** indicated that the ethoxycarbonyl group at the C-2 indanylidene carbon suffered from the presence of hydrogens in heteroallylic position with respect to the C−C5═N bond and that the presence of the methyl substituent on the pyrroline ring has, therefore, to be avoided.

To demonstrate our mechanistic hypothesis for the formation of **4**, we prepared compound **12** where the methyl substituent on the pyrroline ring was replaced with a phenyl group. As expected, the absence of C−H bonds capable to conjugate with the C5═N double bond led to the stable Schiff base. The preparation of **12** and of the final NAIP **13** corresponding to a protected α-amino acid was accomplished by following the synthetic strategy used to prepare **10** but using
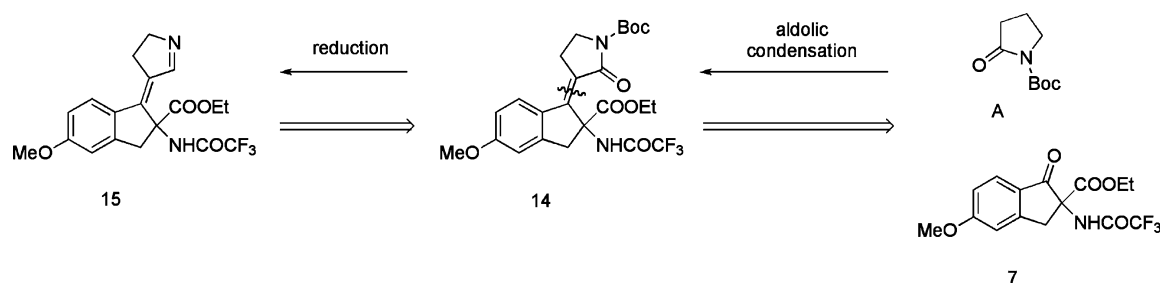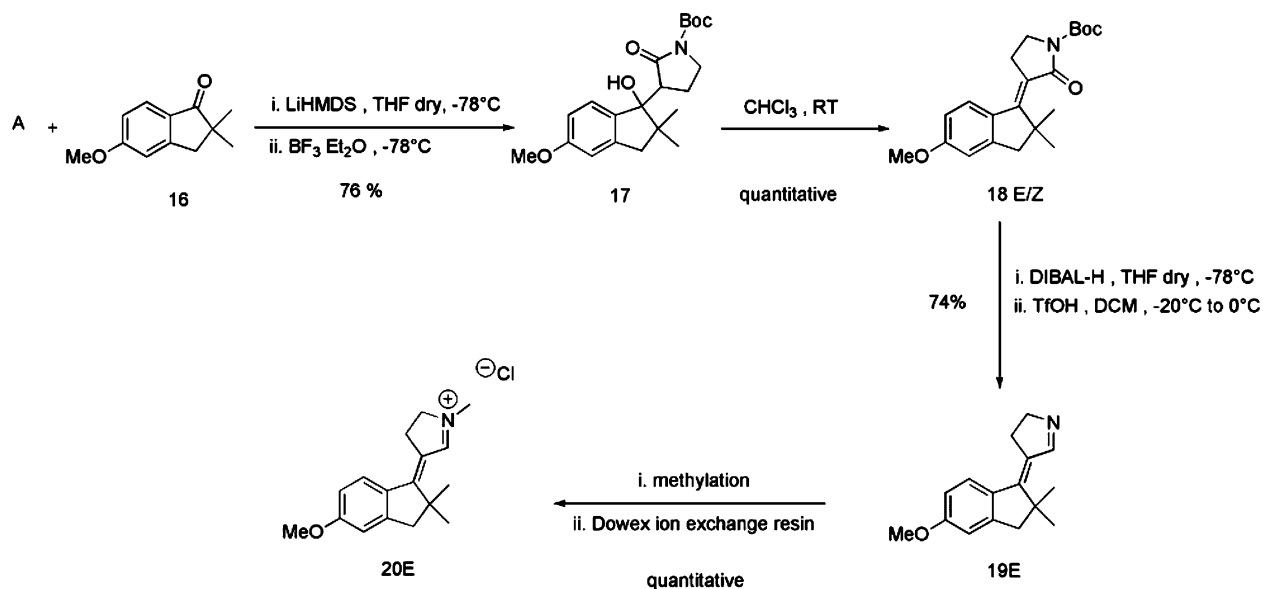
Figure 4. Retrosynthetic analysis of compound **15**.

Scheme 6. Synthesis of the NAIP 20

benzonitrile instead of acetonitrile in the homoallylic rearrangement step (see Scheme 4).

Thermal Isomerization. As anticipated above, an additional unfavorable feature of compounds **1**, **2** and **3** is the thermal isomerization of the exocyclic C1'=C4 double bond. For instance, for **1** we have reported that, in the dark, a 1:1.4 **1Z/1E** photostationary state, generated via a 440 nm irradiation, evolves to 1:0.6 ratio in 24 h at 0 °C.[11] At −40 °C, the same mixture only evolves to a 1.0:1.2 ratio indicating a barrier controlled change toward a thermal equilibrium dominated by **1Z**. In order to clarify the origin of this process, we carried out kinetic studies taking **2** as a model system. As previously reported,[14] the room-temperature **2Z/2E** ratio in the dark is 1:0.01, and it is therefore fully dominated by **2Z**. Irradiation with a 440 nm wavelength leads to a room temperature photostationary state with a 1.0:1.2 composition dominated by **2E**; however, such a mixture reverts in the dark eventually leading to a reconstitution of the original composition (in more than 24 h).

The kinetic of the thermal re-equilibration process has been investigated by monitoring the **2E** concentration as a function of time via spectrophotometric analysis after the composition of the starting photoequilibrated mixture was determined via HPLC analysis and found to be consistent with the data reported in ref 14. The thermal isomerization was spectrophotometrically monitored at regular times via absorption spectroscopy. The spectrophotometric data were then analyzed using the previously determined absorption coefficients[14] for

the *Z* and *E* isomers to determine the increase in the concentration of **2Z**. The results of the measurements are reported in Figure 3A, which shows that the inverse of the concentration of the reacting **2E** isomer fits the experimental data while the logarithm of the same concentration does not. This indicates a second order rather that the expected (for a net monomolecular isomerization) first-order kinetics. The same procedure was followed at different temperatures in the 276–313 K range to determine the rate constants. Figure 3B shows the corresponding Arrhenius plot whose linear correlation allows to determine a value of 12.1 kcal mol^{-1} for the activation energy.

The observed second order kinetics is hypothetically explained on the basis of the reaction mechanism given in Scheme 5. This suggests that two molecules of **2E** are required to achieve the observed rate. Taking into account the results of the previous subsection, which demonstrate the presence of acidic hydrogens in all Schiff bases prepared using the nitrilium cyclization route, we propose the initial formation of a transient dimer. One monomer in the dimer acts as a proton donor while the other as a proton acceptor. The proton is added to the exocyclic C1'=C4 double bond in such a way to produce a stable benzyl cation which is further stabilized by the electron-releasing methoxy substituent. In the cationic intermediate the twisting about the C1'−C4 single bond must be controlled by a small barrier leading to a fast *Z*/*E* equilibration. Back proton transfer then leads to reconstitution of the double bond with a **2Z** stereochemistry.

Scheme 7. Synthesis of NAIP 5Z
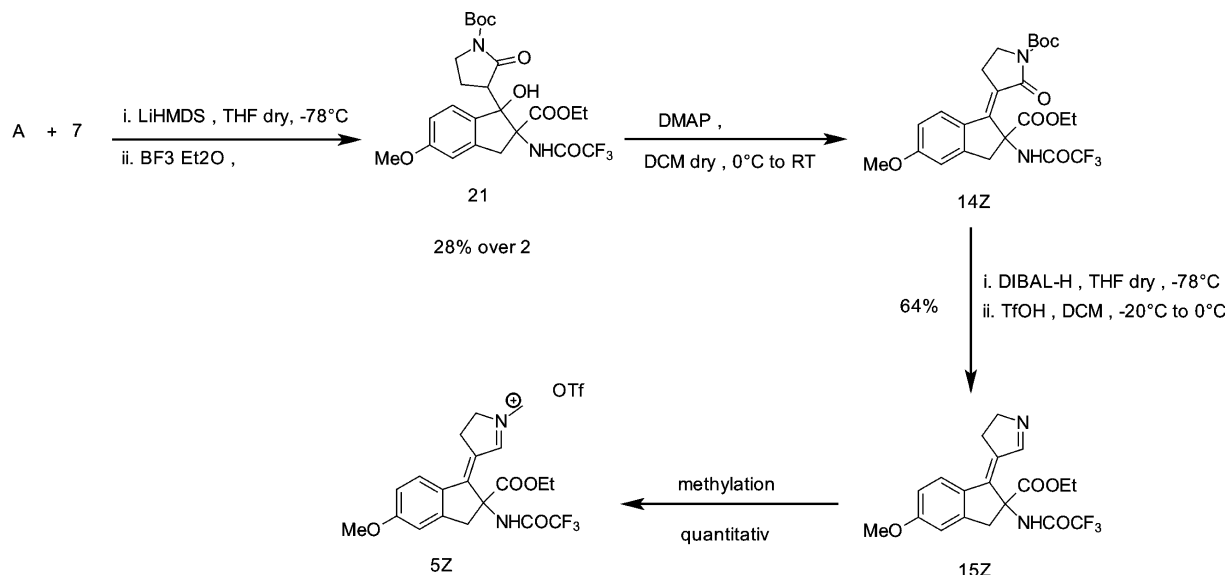
An evidence in favor of the above mechanism is based on the observation that the phenyl derivative **13** (see Scheme 4), lacking acidic hydrogens, not only does not undergo any cyclization but has a fully stable thermally *E/Z* ratio at room temperature.

The Aldolic Approach to NAIPs. Because of its chemical and conformational stability, compound **13** would constitute a first possible precursor of a *α*-cycloalkyl amino acid building block featuring a NAIP side chain. On the other hand, the bulky phenyl group located in an allylic position with respect to the light-responsive exocyclic double bond imposes serious steric impediment to the isomerization motion. For this reason, it is desirable to replace the original methyl group with a hydrogen atom that also results in the removal of hyperconjugating C—H bonds. In other words, we would like to prepare NAIPs featuring an unsubstituted pyrroline ring. The preparation of such compounds via the hitherto used nitrilium strategy appeared to be unachievable as the insertion of an alkyl or aryl (i.e., depending on the employed nitrile) substituent on the pyrroline ring is inevitable. Little consolation came from the potential accessibility to the hexahydroindeno[1,2-*e*]indole framework related to known polycyclic compounds endowed with potent cytotoxic activities toward cancer cells.[29,30] Clearly, a new synthesis route, avoiding the nitrilium cyclization, was required.

Compound **15** (see Figure 4), featuring a polyconjugated aldimine system, was selected as the target chemically stable NAIP amino acid precursor. We considered the retrosynthetic analysis of **15** disconnecting the indan and heterocycle moieties. After adjusting the oxidation state as in **14**, the N-protected pyrrolidone could be disconnected from the indanone derivative **7**. Accordingly, we conceived a synthesis route relying on the reactivity of the electrophile **7** with a nucleophile obtained via *α*-deprotonation of a suitable *γ*-lactam.[31]

In order to test the feasibility of the proposed pivotal aldol reaction, we started employing the known indanone derivative **16** and the commercially available N-protected *γ*-lactam **A**. We found that the lithium enolate of **A** adds to the BF$_3$-activated[32] carbonyl group of **16** giving the corresponding aldol **17**, which then yields **18** by spontaneous dehydration in CHCl$_3$ (see

Scheme 6). The structure of compound **18E** was confirmed by RX diffraction analysis (see the Supporting Information). The next step led to the one-pot formation of the desired polyconjugated aldimine **19**, by reduction, cleavage of the N-Boc group and condensation to yield the *E* isomer.[33] The free base **19E** provided the NAIP **20E** through N-quaternarization performed with methyl triflate. The geometry of the exocyclic double bond of **20E** was inferred by NOESY experiment.

The successful preparation of **19** and **20** prompted the extension of the aldolic approach to the indanone derivative **7** so as to obtain a photomodulable *α*-cycloalkyl amino acid precursor potentially useful, after deprotection, for peptide synthesis (Scheme 7). We found that **7** features a diminished electrophilic character of the indanone carbonyl, maybe due the presence of the secondary trifluoroacetamide group and/or steric congestion around the reactive center which renders partially incisive the BF$_3$-activating role. However, apart from a lower yield in the aldolic reaction and the need of promoting dehydration with the use of a Tf$_2$O—DMAP system, we smoothly reproduced all steps. Interestingly, we observed that, for both **14** and **18**, the multistep one-pot process leading to the cyclic aldimine **15** and **19** yielded a single geometric isomer. The pure free base **15Z**, treated with methyl triflate, gave the NAIP switch **5Z** whose geometry was ascertained by NOESY experiment.

Spectral and Photochemical Characterization. The UV spectra of a mixture of **3E/Z**, **13E/Z**, and **20E** were recorded, and their photochemical behavior was explored. The solution has been irradiated at room temperature in an NMR Pyrex tube at different wavelength until reach the photostationary state. The *E/Z* isomer ratio at the photostationary state has been calculated by integration of distinctive ^{1}H NMR signals. All compounds undergo *Z*→*E* and *E*→*Z* photo-isomerization displaying a photomodulable stationary state. Below we report the photostationary states achieved using three different wavelength in the 350—450 nm range for NAIP **3**, **5** and **20**. Notice that in all cases (see Tables 1—3) we were able to invert the *E/Z* isomer ratio which resulted in a dominant *E* isomer for **3** and **5** and a dominant *Z* isomer for **20** upon irradiation with low wavelength values (ca. 350 nm). This indicates that the λ_{max} value of the **3Z**, **5Z**, and **20E** must be

Table 1. Changes of the Photostationary-State Composition for Compound 3

λ (nm)	Z	E
350	1	1.37
400	1	0.93
450	1	0.34

Table 2. Changes of the Photostationary-State Composition for Compound 20

λ (nm)	E	Z
365	1	1.60
394	1	1.05
440	1	0.00

Table 3. Changes of the Photostationary-State Composition for Compound 5

λ (nm)	Z	E
360	1	0.80
400	1	0.69
440	1	0.00

blue-shifted with respect to the λ_{max} value of the alternative isomer. (Notice that the backbone and, consequently, the π-system geometry of **3Z**, **5Z**, and **20E** are consistent. The *E* label for the dominating isomer of compound **20** is only due to a change in the substituent priorities). NAIP **13** featuring the bulk phenyl group at C5 has also been irradiated at room temperature in a NMR pyrex tube at different wavelength (λ = 380, 430, 480 nm) and the reaction followed by ^{1}H NMR. After irradiation at 380 nm we see a photostationary state containing only one of two geometric isomers (the one already presents in greater amount in the initially mixture). The irradiation at 480 nm shifts the mixture equilibrium toward the other geometric isomer indicating that the bulk phenyl group does not represents an impediment to the photoisomerization. This result is consistent with the demonstrated ability of crowded alkenes to photoisomerize.[34]

As expected, in contrast with compound **3**, the **13**, **20**, and **5** *E/Z* ratio achieved after 24 h irradiation in CDCl$_3$ is stable when the solution was maintained in the dark and at room temperature.

Difficulties in Achieving a Deprotected α-Cycloalkyl Amino Acid with a NAIP Side Chain. The simultaneous and selective cleavage of the protective groups of the NAIP switch **5Z** to obtain the corresponding α-amino acid was attempted via both hydrolysis or reaction with different nucleophiles. Regrettably, the attempted hydrolysis in acid (HCl, triflic acid) and basic (LiOH, K$_2$CO$_3$, NaOH) conditions at 0 °C and room temperature using various solvents mixture (THF/H$_2$O, MeOH/H$_2$O, CH$_3$CN/H$_2$O) highlighted an unusual stability of the protective groups which did not react. During the same treatment, we observed no change in the structure of compound **5Z**. However, a total decomposition of the starting material was observed when using reflux conditions. The same lack of reactivity was demonstrated with nucleophiles (NH$_3$ solution in methanol, MeNH$_2$ solution in methanol, hydrazine hydrate) at 0 °C, room temperature and, in contrast to acid and basis conditions, also in refluxing conditions pointing to a considerable stability of compound **5** framework.

CONCLUSIONS AND PERSPECTIVES

The *Z/E* photoisomerization of NAIPs provides the basis for the development of electrostatic light-driven switches to be inserted in specific positions of a synthetic peptide or protein backbone in the form of unnatural residues featuring a quaternary α-carbon and, consequently, a conformationally rigid (with respect to the local backbone) side chain. The change in the local electrostatic field following the photo-chemically driven ca. 180° rotation of the pyrroline unit could, in principle, be exploited to control different structural interactions such as salt bridges, protonation states and hydrogen bonds in nearby residues (for a recent study of the effect of the change in electrostatic field on protein functions see ref 35). At the same time, these changes may be followed by looking at the fluorescence or absorption of an internal reporter (e.g., the 3-methylindole side chain of tryptophan) as previously proposed.[14]

Until now, no NAIP-based compounds had been reported featuring both thermally stable states (i.e., constant *Z/E* isomer ratios) at room temperature and the presence of functional groups allowing for the incorporation of the switch in a peptide chain. We have demonstrated above that it is indeed possible to achieve such desired structures in the form of protected α-cycloalkyl amino acids (structure **5**). Because of the similarity between the quaternary carbon environment of **5** and a local peptide backbone, the data of Table 3 indicate that the control of the *Z/E* ratio via irradiation with light of different wavelength should also be effective in a protein environment. Further studies aiming to uncover an effective protocol for removing the protecting groups are presently being carried out in our laboratory.

EXPERIMENTAL METHODS

Synthesis and Structure Analysis. *Experimental Data.* General: melting points were measured with a hot-stage apparatus. The ^{1}H and ^{13}C NMR spectra were recorded with an instrument operating at 200.13 and at 50.33 MHz, respectively, or with an instrument operating at 400.13 and at 100.62 MHz, respectively. Chemical shifts are reported in part per million from internal TMS. Mass spectra were recorder in the positive or negative ion mode with an instrument by using electrospray ionization. All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F254 plates. Flash column chromatography was carried out on silica gel 60 (0.040–0.063 mm). Irradiation was made with a Rayonet apparatus.

Ethyl 2-Bromo-5-methoxy-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (6). A solution of 5-MeO-1-indanone (5.00 mmol, 810 mg) in diethyl carbonate (20 mL) was added dropwise to a stirred suspension of NaH (11.00 mmol, 60% in mineral oil, 440 mg) in diethyl carbonate (2 mL) at rt. Heating at 100 °C in an oil bath yielded a solid spongy which, after cooling to rt, was diluted in CH$_2$Cl$_2$ and treated with aqueous 1N HCl. The aqueous phase was separated and extracted with CH$_2$Cl$_2$. The combined organic extracts were dried (Na$_2$SO$_4$) and concentrated under reduced pressure.

The crude residue (5.00 mmol), *N*-bromosuccinimide (5.25 mmol, 935 mg), and Amberlyst-15 (3.75 g) in ethyl acetate (50 mL) was stirred at rt for 30 min. After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with ethyl acetate. The combined organic extracts were dried over anhydrous Na$_2$SO$_4$ and concentrated in vacuo, and the residue was purified by chromatography (3:7, ethyl acetate/petroleum ether) to afford 1450 mg (93%) of compound **6** as a yellow oil. ^{1}H NMR (CDCl$_3$, 400 MHz) δ_H: 1.17 (t, *J* = 7.2 Hz, 3H), 3.52 (d, *J* = 18.4 Hz, 1H), 3.81 (s, 3H), 4.06 (d, *J* = 18.0 Hz, 1H), 4.16 (q, *J* = 7.2 Hz, 2H), 6.81–6.88 (m, 2H), 7.64 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ_C:

13.89, 43.80, 55.89, 59.35, 63.34, 109.45, 116.68, 125.04, 127.43, 153.38, 166.62, 167.05, 193.17. ESI-MS, m/z: $[M + H^+]$ = 313−315, $[M + Na^+]$ = 335−337, $[2M + Na^+]$ = 648. Anal. Calcd for $C_{13}H_{13}BrO_4$: C, 49.86; H, 4.18. Found: C, 49.70; H, 4.19.

Ethyl 5-Methoxy-1-oxo-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (7). Sodium azide was added (4.36 mmol, 283 mg) to a solution of **6** (2.18 mmol, 680 mg) in dry DMF (3 mL) under nitrogen atmosphere, and the resulting mixture was stirred at room temperature for 1 h. After addition of H_2O, the aqueous layer was extracted in Et_2O. The combined organic layers were washed with brine and then dried over Na_2SO_4. Removal of solvents gave a crude which dissolved in dry THF (40 mL) under nitrogen atmosphere, and Ph_3P (6.54 mmol, 1713 mg) was added. After 10 min at 0 °C, the cooling bath was removed and the clear solution was stirred at rt overnight. Trifluoroacetic anhydride (4.14 mmol, 1.21 mL) was added and the mixture stirred for 1 h before adding H_2O and Et_2O. The organic layer dried over Na_2SO_4 and concentrated under reduced pressure gave a residue which was purified by flash chromatography (4:6, ethyl acetate/petroleum ether) to afford 1430 mg (95%) of the corresponding pure product **7** as a white solid (mp 106−108 °C). ^1H NMR (CDCl$_3$, 400 MHz) δ_H: 1.09 (t, J = 6.0 Hz, 3H), 3.37 (d, J = 17.2 Hz, 1H), 3.73 (d, J = 17.2 Hz, 1H), 3.84 (s, 3H), 4.13 (q, J = 7.2 Hz, 2H), 6.88−6.92 (m, 2H), 7.66−7.70 (m, 2H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ_C: 13.70, 37.99, 55.78, 63.39, 68.16, 109.40, 115.37 (q, J^1 = 286 Hz), 116.35, 126.75, 127.01, 155.00, 156.54 (q, J^2 = 37 Hz), 166.62, 167.60, 193.66. ESI-MS, m/z: $[M + H^+]$ = 346, $[M − H^+]$ = 344, $[M + Na^+]$ = 368, $[2M + Na^+]$ = 712, $[2M + K^+]$ = 729. Anal. Calcd for $C_{15}H_{14}F_3NO_5$: C, 52.18; H, 4.09; N, 4.06. Found: C, 52.09; H, 4.07; N, 4.07.

Ethyl 1-Hydroxy-5-methoxy-2-(2,2,2-trifluoroacetamido)-1-cyclopropyl-2,3-dihydro-1H-indene-2-carboxylate (8). Cyclopropylmagnesium bromide solution (0.5 M in THF dry, 24.00 mL) was added to a cooled (0 °C) solution of **7** (4.00 mmol, 1380 mg) in dry THF (40 mL). After 30 min at 0 °C, NH_4Cl (s.s.) was added and the mixture extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography (1:9, ethyl acetate/petroleum ether) to afford 1200 mg (78%) of compound **8** as a white solid (mp 92−95 °C). ^1H NMR (CDCl$_3$, 400 MHz) δ_H: 0.08 (m, 1H), 0.40−0.48 (m, 3H), 0.91−0.98 (m, 1H), 1.29 (t, J = 7.2 Hz, 3H), 2.32 (bs, 1H), 3.35 (d, J = 16.8 Hz, 1H), 3.78 (s, 3H), 3.86 (d, J = 16.8 Hz, 1H), 4.18−4.36 (m, 2H), 6.71−6.79 (m, 2H), 7.13 (d, J = 8.4 Hz, 1H), 7.72 (bs, 1H). ^{13}C NMR (CDCl$_3$, 50 MHz) δ_C: 0.30, 1.11, 13.79, 16.63, 37.99, 55.17, 61.89, 73.25, 84.51, 109.72, 113.21, 115.38 (q, J^1 = 286 Hz), 125.14, 132.33, 140.59, 156.89 (q, J^2 = 36 Hz), 160.64, 169.73. ESI-MS, m/z: $[M − H^+]$ = 386, $[M + Na^+]$ = 410. Anal. Calcd for $C_{18}H_{20}F_3NO_5$: C, 55.81; H, 5.20; N, 3.62. Found: C, 55.61; H, 5.21; N, 3.61.

Ethyl 1-(3-Acetamidopropylidene)-5-methoxy-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (9). Compound **8** (0.26 mmol, 100 mg) was added to a cooled (0 °C) solution of trifluoromethanesulfonic anhydride (0.26 mmol, 43 μL) in dry CH_3CN (3 mL) under nitrogen atmosphere. The mixture was stirred for 30 min at rt, diluted with CH_2Cl_2, and quenched with 2 N NaOH. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (ethyl acetate) to give 90 mg (81%) of the pure product **9** as a yellow solid (mp 46−48 °C). ^1H NMR (CDCl$_3$, 400 MHz) δ_H: 1.14 (t, J = 7.2 Hz, 3H), 1.70 (s, 3H), 2.38−2.44 (m, 1H), 2.83−2.88 (m, 1H), 3.11−3.16 (m, 1H), 3.34 (d, J = 17.2 Hz, 1H), 3.50−3.55 (m, 1H), 3.71 (d, J = 17.2 Hz, 1H), 3.78 (s, 3H), 4.13−4.17 (m, 2H), 5.47 (dd, 1H, J_1 = 6.4 Hz, J_2 = 9.6 Hz), 6.04 (m, 1H), 6.75−6.78 (m, 2H), 7.54 (d, J = 8.4 Hz, 1H), 7.96 (bs, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ_C: 13.77, 22.81, 28.65, 38.65, 41.40, 55.32, 62.52, 67.54, 109.48, 113.83, 115.53 (q, J^1 = 286 Hz), 120.56, 125.52, 130.01, 141.13, 145.34, 156.60 (q, J^2 = 38 Hz), 160.42, 170.83, 171.14. ESI-MS, m/z: $[M + H^+]$ = 429, $[M − H^+]$ = 427, $[M + Na^+]$ = 451. Anal. Calcd for $C_{20}H_{23}F_3N_2O_5$: C, 56.07; H, 5.41; N, 6.54. Found: C, 56.25; H, 5.39; N, 6.55.

(E/Z)-Ethyl 5-Methoxy-1-(5-methyl-2H-pyrrol-4(3H)-ylidene)-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-indene-2-carboxylate (10). A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5 h a mixture of P_2O_5 (3.50 mmol, 497 mg) and hexamethyldisiloxane (4.91 mmol, 1.04 mL) in CCl_4 (5 mL), was added to **9** (0.35 mmol, 150 mg) at rt. The reaction mixture was heated at reflux for 5 h, cooled to room temperature, diluted with CH_2Cl_2, and quenched with NaOH 2 N. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel conditioned with TEA and ethyl acetate as eluent to give 90 mg (63%) of product **10** as yellow oil. ^1H NMR (CDCl$_3$, 400 MHz) δ_H: 1.06 (t, J = 7.2 Hz, 3H, *E* isomer), 1.14 (t, J = 7.2 Hz, 3H, *Z* isomer), 2.13 (s, 3H, *Z* isomer), 2.27 (s, 3H, *E* isomer), 2.51−2.64 (m, 2H, mix *E/Z*), 3.00−3.06 (m, 2H, mix *E/Z*), 3.36−3.66 (m, 4H, mix *E/Z*), 3.72−4.08 (m, 4H, mix *E/Z*), 3.78 (s, 6H, mix *Z/E*), 4.13 (q, J = 7.2 Hz, 2H, *E* isomer), 4.21 (q, J = 7.2 Hz, 2H, *Z* isomer), 6.73−6.84 (m, 4H, *E/Z* mix), 7.31 (d, J = 8.4 Hz, 1H, *E* isomer), 7.50 (d, J = 8.8 Hz, 1H, *Z* isomer), 7.75 (s, 1H, *E* isomer), 7.92 (s, 1H, *Z* isomer). ESI-MS, m/z: $[M + H^+]$ = 411, $[M + Na^+]$ = 433, $[M − H^+]$ = 409. Anal. Calcd for $C_{20}H_{21}F_3N_2O_4$: C, 58.53; H, 5.16; N, 6.83. Found: C, 58.71; H, 5.17; N, 6.63.

(E/Z)-4-(2-(Ethoxycarbonyl)-5-methoxy-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-inden-1-ylidene)-1,5-dimethyl-3,4-dihydro-2H-pyrrolium trifluoromethanesulfonate (3). Methyl trifluoromethanesulfonate (0.22 mmol, 25 μL) was added to a solution of **10** (0.22 mmol, 90 mg) in anhydrous benzene (5 mL). The product of reaction was recovered quantitatively as a yellow-orange oil. ^1H NMR (CDCl$_3$, 400 MHz) (mix 1:1 *Z/E*) δ_H: 1.11 (t, J = 7.2 Hz, 3H, *Z*), 1.11 (t, J = 7.5 Hz, 3H, *E*), 2.56 (s, 3H, *E*), 2.72 (s, 3H, *Z*), 3.13 (d, J = 16.6 Hz, 1H, *E*), 3.18−3.30 (m, 4H, mix *E/Z*), 3.40 (d, J = 16.6 Hz, 1H, *Z*), 3.52 (s, 3H, *E*), 3.54 (s, 3H, *Z*), 3.77 (d, J = 16.6 Hz, 1H, *E*), 3.90 (d, J = 16.6 Hz, 1H, *Z*), 4.10−4.30 (m, 8H, mix *E/Z*), 6.83−7.00 (m, 4H, mix *E/Z*), 7.51 (d, J = 9.7 Hz, 1H, *Z*), 7.54 (d, J = 9.2 Hz, 1H, *E*), 8.52 (s, 1H, *E*), 8.90 (s, 1H, *Z*). ^{13}C NMR (CDCl$_3$, 100 MHz) δ_C: 13.51 (*Z/E*), 17.30 (*E*), 17.43 (*Z*), 28.33 (*E*), 32.03 (*Z*), 37.63 (*E*), 37.90 (*Z*), 43.18 (*E*), 45.38 (*Z*), 55.70 (*Z/E*), 57.68 (*Z*), 58.12 (*E*), 63.46 (*E*), 63.57 (*Z*), 69.36 (*Z*), 71.67 (*E*), 109.18 (*Z*), 109.44 (*E*), 114.43 (*E*), 114.84 (*Z*), 115.41 (q, J^1 = 287 Hz, *Z/E*), 127.94 (*E*), 128.12 (*Z*), 129.28 (*E*), 129.63 (*Z*), 130.92 (*E*), 131.31 (*Z*), 149.74 (*Z*), 150.36 (*E*), 151.19 (*Z*), 154.65 (*E*), 156.60 (q, J^2 = 38 Hz, *Z*), 156.70 (q, J^2 = 38 Hz, *E*), 163.57 (*Z*), 164.35 (*E*), 167.65 (*E*), 168.67 (*Z*). ESI-MS, m/z: $[M^+]$ = 425. Anal. Calcd for $C_{22}H_{24}F_6N_2O_7S$: C, 45.99; H, 4.21; N, 4.88. Found: C, 46.14; H, 4.20; N, 4.89.

2,2,2-Trifluoro-N-(8-methoxy-5-oxo-1,2,3,5,5a,6-hexahydroindeno[1,2-e]indol-5a-yl)acetamide (11). Compound **11** was recovered as crystalline yellow solid (mp >210 °C dec) from a solution of **10E/Z** in CDCl$_3$. ^1H NMR (CD$_3$OD, 400 MHz) δ_H: 2.86−2.92 (m, 1H), 2.95 (d, J = 16.2 Hz, 1H), 3.19−3.26 (ddd, J_1 = 12.0 Hz, J_2 = 8.3 Hz, J_3 = 3.5 Hz, 1H), 3.59 (d, J = 16.2 Hz, 1H), 3.78−3.95 (m, 5H), 6.92 (dd, J_o = 8.4 Hz, J_m = 1.6 Hz, 1H), 7.01 (s, 1H), 7.45 (d, J_o = 8.4 Hz, 1H). ^{13}C NMR (CD$_3$OD, 50.33 MHz) δ_C: 25.46, 40.89, 55.99, 67.59, 112.47, 114.98, 116.8 (q, J^1 = 287 Hz), 125.90, 128.59, 131.39, 145.07, 147.07, 157.73 (q, J^2 = 36 Hz), 162.63, 168.79, 192.81. ESI-MS, m/z: $[M + H^+]$ = 365. Anal. Calcd for $C_{18}H_{15}F_3N_2O_3$: C, 59.34; H, 4.15; N, 7.69. Found: C, 59.18; H, 4.16; N, 7.71.

2,2,2-Trifluoro-N-(8-methoxy-3-methyl-5-oxo-1,2,3,5,5a,6-hexahydroindeno[1,2-e]indol-5a-yl)acetamide (4). Compound **4** was obtained after chromatography on SiO$_2$ or treatement with LiOH of mixture of **3E/Z** in CD$_3$OD as yellow solid (mp >200 °C dec). ^1H NMR (CD$_3$OD, 400 MHz) δ_H: 2.85−2.93 (m, 1H), 2.96 (d, J = 16.4 Hz, 1H), 3.12 (s, 3H), 3.17−3.24 (m, 1H), 3.60 (d, J = 16.0 Hz, 1H), 3.76−3.82 (m, 1H), 3.85 (s, 3H), 3.93−4.01 (m, 1H), 5.14 (s, 1H), 6.92 (dd, J_o = 8.8 Hz, J_m = 1.6 Hz, 1H), 7.01 (s, 1H), 7.44 (d, J_o = 8.4 Hz, 1H). ^{13}C NMR (CDCl$_3$, 100 MHz) δ_C: 25.08, 40.89, 56.40, 67.57, 111.95, 114.73, 125.66, 126.00, 129.13, 131.49, 147.03, 162.64, 166.46, 193.18. ESI-MS, m/z: $[M + H^+]$ = 379. Anal. Calcd for $C_{19}H_{17}F_3N_2O_3$: C, 60.32; H, 4.53; N, 7.40. Found: C, 60.53; H, 4.51; N, 7.42.

(1E/Z)-Ethyl 2-(2,2,2-Trifluoroacetamido)-2,3-dihydro-2-phenyl-pyrrol-3-ylidene)-5-methoxy-1H-indene-2-carboxylate (12E/Z). Compound **8** (0.26 mmol, 100 mg) was added to a cooled (0 °C) solution of trifluoromethanesulfonic anhydride (0.26 mmol, 43 μL) in dry PhCN (3 mL) under nitrogen atmosphere. The mixture was stirred for 30 min at rt, diluted with CH_2Cl_2, and quenched with 2 N NaOH. The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to give a mixture of **12a** and **12E/Z**.

A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5 h a mixture of P_2O_5 (2.58 mmol, 367 mg) and hexamethyldisiloxane (3.62 mmol, 769 μL) in CCl_4 (5 mL), was added at room temperature to the previous crude of **12a** and **12E/Z**. The reaction mixture was heated at reflux for 3 h, cooled to room temperature, diluted with CH_2Cl_2, and quenched with NaOH 2 N. The aqueous layer was extracted with CH_2Cl_2, dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (3:7, Et_2O/petroleum ether) to give 80 mg (66%) of the pure product **12E/Z** as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) (mix Z/E) δ_H: 1.08 (t, J = 7.1 Hz, 3H, major), 1.08 (t, J = 7.1 Hz, 3H, minor), 2.64 (dd, J_1 = 14.8 Hz, J_2 = 5.4 Hz, 1H, major), 2.71−2.82 (m, 1H, major), 3.04 (d, J = 16.7 Hz, 1H, minor), 3.16 (dd, J_1 = 14.5 Hz, J_2 = 5.5 Hz, 1H, minor), 3.20−3.26 (m, 1H, minor), 3.29 (d, J = 16.4 Hz, 1H, major), 3.66 (d, J = 16.7 Hz, 1H, minor), 3.68 (s, 3H, major), 3.71−3.82 (m, 3H, major and minor), 4.01−4.08 (m, 2H, minor), 4.11 (q, J = 7.1 Hz, 4H, major and minor), 6.13 (dd, J_o = 8.8 Hz, J_m = 1.5 Hz, 1H, major), 6.21 (d, J_o = 8.8 Hz, 1H, major), 6.61 (s, 1H, major), 6.70 (s, 1H, minor), 6.81−6.88 (m, 2H, minor), 7.20−7.52 (m, 10H, major and minor), 7.88 (s, 2H, major and minor). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 13.51 (minor), 13.68 (major), 34.21 (major), 37.84 (minor), 42.07 (major), 44.78 (minor), 55.19 (major), 55.40 (minor), 58.82 (major), 59.20 (minor), 62.67 (minor), 63.13 (major), 67.45 (minor), 69.54 (major), 108.26 (major), 109.04 (minor), 112.42 (major), 113.67 (minor), 115.58 (q, J^1 = 290 Hz, minor and major), 126.39 (minor), 127.49 (major), 128.50, 129.37, 129.64, 129.75, 130.37, 130.62, 133.76 (minor and major), 133.77 (major), 134.16 (minor), 135.16 (minor), 135.49 (major), 136.74 (major), 137.91 (minor), 144.01 (minor), 145.19 (major), 154.86 (q, J^2 = 37 Hz, minor and major), 160.16 (major), 160.67 (minor), 170.38 (minor), 171.38 (major), 173.34 (minor), 174.06 (major). ESI-MS, m/z: [M + H$^+$] = 473. Anal. Calcd for $C_{25}H_{23}F_3N_2O_4$: C, 63.55; H, 4.91; N, 5.93. Found: C, 63.74; H, 4.92; N, 5.92.

(E/Z)-4-(2-(Ethoxycarbonyl)-2-(2,2,2-trifluoroacetamido)-2,3-dihydro-1H-inden-1-ylidene)-methyl-5-phenyl-3,4-dihydro-2H-pyrrolium (13E/Z). Methyl trifluoromethanesulfonate (0.19 mmol, 22 μL) was added to a solution of **12E/Z** (0.19 mmol, 90 mg) in anhydrous benzene (5 mL). The product of reaction was recovered quantitatively as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) (mix Z/E) δ_H: 1.07 (t, J = 7.0 Hz, 3H, major), 1.08 (t, J = 7.1 Hz, 3H, minor), 2.97−3.08, 3.12−3.23 (m, 2H, major), 3.00−3.38 (m, 2H, minor), 3.15 (d, J = 17.0 Hz, 1H, major), 3.33 (s, 3H, minor), 3.43 (d, J = 16.3 Hz, 1H, major), 3.54 (d, J = 17.0 Hz, 1H, minor), 3.61 (s, 3H, major), 3.70 (d, J = 16.3 Hz, 1H, major), 3.70 (s, 3H, major), 3.74 (s, 3H, minor), 3.98−4.25 (m, 3H, major), 4.11−4.30 (m, 3H, minor), 4.45−4.60 (m, 1H, minor), 4.72−4.80 (m, 1H, major), 6.12 (dd, J_1 = 8.9 Hz, J_2 = 2.4 Hz, 1H, major), 6.44 (d, J = 8.9 Hz, 1H, major), 6.60 (d, J = 2.4 Hz, 1H, major) 6.76 (d, J = 1.4 Hz, 1H, minor), 6.95−7.03 (m, 3H, minor), 7.40−7.70 (m, 5H, major), 7.63−7.81 (m, 5H, minor), 8.21 (bs, 1H, minor and major). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 13.41 (minor and major), 28.97 (major), 33.25 (minor), 39.01 (minor and major), 42.47 (major), 45.65 (minor), 55.49 (major), 55.78 (minor), 58.91 (minor), 59.24 (major), 63.71 (minor), 64.35 (major), 67.39 (minor), 70.92 (major), 108.34 (major), 109.35 (minor), 113.92 (major), 115.32 (minor), 115.41 (q, J^1 = 288 Hz, minor and major), 125.79 (minor and major), 126.72 (major), 126.82 (minor), 128.72, 129.59, 130.49, 130.66, 131.03 (minor and major), 133.15 (minor), 133.30 (major), 148.21 (minor), 149.56 (major), 155.83 (q, J^2 = 37 Hz, minor and major), 156.07 (minor), 157.33 (major), 163.21 (major), 164.13 (minor), 168.48 (minor and major), 176.59 (minor and major). ESI-MS, m/z: [M$^+$] = 487. Anal. Calcd for $C_{27}H_{26}F_6N_2O_7S$: C, 50.94; H, 4.12; N, 4.40. Found: C, 50.76; H, 4.10; N, 4.41.

tert-Butyl 3-(5-Methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ylidene)-2-oxopyrrolidine-1-carboxylate (18E/Z). A 1 M solution of lithium hexamethyldisilazide (LiHMDS) in anhydrous THF (1.80 mmol, 1.80 mL) was added at −78 °C under nitrogen atmosphere to N-Boc-2-pyrrolidinone **A** (1.50 mmol, 278 mg) dissolved in anhydrous THF (5 mL). After 1 h, a solution of the compound **16** (1.65 mmol, 314 mg) and $BF_3 \cdot Et_2O$ (1.65 mmol, 206 μL) in anhydrous THF (8 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 3 h, NH_4Cl (s.s.) was added, and the crude was extracted in Et_2O. The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure and the residue purified by flash column chromatography on silica gel (3:7, ethyl acetate/petroleum ether). The obtained compound **17** poured in $CHCl_3$ underwent spontaneous dehydration (checked by ESI-MS) to afford **18** (410 mg, 76%) as a white solid (1:1 mixture of E/Z isomers).

(E)-tert-Butyl 3-(5-Methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ylidene)-2-oxopyrrolidine-1-carboxylate (18E). White solid. Mp: 170−173 °C. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.24 (s, 6H), 1.54 (s, 9H), 2.94 (s, 2H), 3.00 (t, J = 7.1 Hz, 2H), 3.76 (t, J = 7.1 Hz, 2H), 3.82 (s, 3H), 6.78−6.80 (m, 2H), 7.42 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 26.74, 27.39, 28.16, 29.66, 43.43, 50.98, 55.38, 82.11, 109.47, 113.47, 119.98, 128.06, 133.53, 143.04, 150.49, 151.05, 161.47, 167.02. ESI-MS, m/z: [M + Na$^+$] = 380, [2M + Na$^+$] = 737. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.64; H, 7.61; N, 3.92. Found: C, 70.79; H, 7.58; N, 3.94.

(Z)-tert-Butyl 3-(5-Methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ylidene)-2-oxopyrrolidine-1-carboxylate (18Z). ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.26 (s, 6H), 1.51 (s, 9H), 2.78 (s, 2H), 2.86 (t, J = 7.0 Hz, 2H), 3.69 (t, J = 7.0 Hz, 2H), 3.76 (s, 3H), 6.65−6.69 (m, 2H), 8.54 (d, J = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 24.66, 26.56, 28.12, 43.34, 47.43, 49.21, 55.25, 82.10, 108.66, 112.54, 119.55, 130.33, 131.38, 149.28, 150.93, 160.43, 161.21, 167.76. ESI-MS, m/z: [M + Na$^+$] = 380, [2M + Na$^+$] = 737. Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.64; H, 7.61; N, 3.92. Found: C, 70.50; H, 7.62; N, 3.94.

(E)-4-(5-Methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ylidene)-3,4-dihydro-2H-pyrrole (19E). Diisobutylaluminum hydride solution in hexanes (0.34 mmol, 0.34 mL) was added dropwise to a cooled (−78 °C) solution of compound **18** (0.22 mmol, 80 mg) in dry THF (5 mL) under nitrogen atmosphere. After being stirred at −78 °C for 1 h (checked by TLC and ESI-MS), the reaction mixture was quenched with H_2O and 1 N HCl and extracted with CH_2Cl_2. Removal of solvents gave a crude which dissolved in CH_2Cl_2 (5 mL) and was cooled at −20 °C followed by treatment with trifluoromethanesulfonic acid (2.24 mmol, 195 μL). The resulting solution was stirred for 1 h at 0 °C, $NaHCO_3$ (s.s.) was added, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated under vacuum to give a residue which was purified by flash column chromatography (Et_2O) on silica gel conditioned with TEA to give 40 mg (74%) of compound **19** as yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.44 (s, 6H), 2.81−2.84 (m, 2H), 2.93 (s, 2H), 3.81 (s, 3H), 4.07−4.10 (m, 2H), 6.77−6.82 (m, 2H), 7.45 (d, J = 8.4 Hz, 1H), 8.45 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 29.85, 30.58, 44.29, 49.90, 55.37, 59.78, 109.71, 113.50, 126.18, 131.57, 133.53, 148.14, 149.45, 160.71, 164.03. ESI-MS, m/z: [M + H$^+$] = 242. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.91; H, 7.91; N, 5.82.

(E)-4-(5-Methoxy-2,2-dimethyl-2,3-dihydro-1H-inden-1-ylidene)-1-methyl-3,4-dihydro-2H-pyrrolium Chloride (20E). Methyl trifluoromethanesulfonate (0.16 mmol, 19 μL) was added to a solution of **19E** (0.16 mmol, 40 mg) in anhydrous benzene (5 mL). The product of reaction was recovered quantitatively as orange oil and was subjected to ion-exchange chromatography on DOWEX 1X8, eluting with water to provide the corresponding chloride salt. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 1.62 (s, 6H), 3.01 (s, 2H), 3.29−3.35 (m, 2H), 3.86 (s, 3H), 4.02 (s, 3H), 4.20−4.26 (m, 2H), 6.83−6.91 (m, 2H), 7.51 (d, J = 8.8 Hz, 1H), 10.23 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 29.09, 30.82, 40.44, 46.78, 50.24, 55.65, 57.44, 109.76, 115.33, 123.48, 128.76, 131.13, 153.02, 163.91, 168.69, 170.75. ESI-MS, m/z: [M$^+$] = 256. Anal. Calcd for $C_{17}H_{22}ClNO$: C, 69.97; H, 7.60; N, 4.80. Found: C, 70.18; H, 7.57; N, 4.81.

tert-Butyl 3-(2-(Ethoxycarbonyl)-5-methoxy-2-(2,2,2-trifluoroace-tamido)-2,3-dihydro-1*H*-inden-1-ylidene)-2-oxopyrrolidine-1-car-boxylate (**14Z**). A 1 M solution of lithium hexamethyldisilazide (LiHMDS) in anhydrous THF (1.80 mmol, 1.80 mL) was added at −78 °C under nitrogen atmosphere to *N*-Boc-2-pyrrolidinone **A** (1.50 mmol, 278 mg) dissolved in anhydrous THF (5 mL). After 1 h, solid compound **7** (1.65 mmol, 569 mg) and BF₃·Et₂O (1.65 mmol, 206 µL) were added, and stirring was continued for 3 h at the same temperature. NH₄Cl (s.s.) was added, and the mixture was extracted with Et₂O. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure, and the residue was purified by flash column chromatography on silica gel (at the first dichloro-methane until starting material was recovered then 1:1 ethyl acetate/petroleum ether). The isolated aldolic compound **21** (240 mg) was then dehydrated by the action of Tf₂O–DMAP system. Thus, trifluoromethanesulfonic anhydride (0.90 mmol, 152 µL) was added to a cooled (0 °C) solution of **21** (0.45 mmol, 240 mg) and DMAP (2.72 mmol, 332 mg) in dry CH₂Cl₂ (5 mL) under nitrogen atmosphere. Stirring was continued overnight at rt, and then the reaction mixture was quenched with H₂O and extracted with CH₂Cl₂. The organic layer, dried over Na₂SO₄ and concentrated under vacuum gave a residue which was purified by flash column chromatography on silica gel (3:7, Et₂O/petroleum ether) to give 213 mg (28% over two steps) of compound **14Z** as white solid. Mp: 157−160 °C. ^{1}H NMR (CDCl₃, 400 MHz) δ_H: 1.22 (t, J = 7.2 Hz, 3H), 1.51 (s, 9H), 3.03−3.07 (m, 2H), 3.41 (d, J = 16.0 Hz, 1H), 3.78−3.83 (m, 3H), 3.83 (s, 3H), 4.21−4.26 (m, 2H), 6.82 (s, 1H), 6.88 (dd, J_o = 8.8 Hz, J_m = 2.0 Hz, 1H), 7.46 (d, J_o = 8.8 Hz, 1H), 8.29 (s, 1H). ^{13}C NMR (CDCl₃, 100 MHz) δ_C: 13.92, 24.19, 28.05, 43.51, 55,50, 62.48, 66.43, 82.85, 108.95, 114.86, 115.93 (q, J^1 = 286 Hz), 120.98, 126.80, 132.44, 147.48, 149.03, 150.20, 155.47 (q, J^2 = 37 Hz), 162.33, 167.44, 170.22. ESI-MS, m/z: [M + Na$^+$] = 535. Anal. Calcd for C₂₄H₂₇F₃N₂O₇: C, 56.25; H, 5.31; N, 5.47. Found: C, 56.05; H, 5.32; N, 5.45.

(*Z*)-Ethyl 5-Methoxy-1-(2*H*-pyrrol-4(3*H*)-ylidene)-2-(2,2,2-trifluor-oacetamido)-2,3-dihydro-1*H*-indene-2-carboxylate (**15Z**). Diisobu-tylaluminum hydride solution in hexanes (0.39 mmol, 0.39 mL) was added dropwise to a cooled (−78 °C) solution of compound **14Z** (0.16 mmol, 80 mg) in dry THF (5 mL) under nitrogen atmosphere. After being stirred at −78 °C for 1 h (checking by TLC and ESI-MS), the reaction mixture was quenched with H₂O and 1 N HCl and extracted with CH₂Cl₂. Removal of solvents gave a crude which dissolved in CH₂Cl₂ (5 mL) and cooled at −20 °C was treated with trifluoromethanesulfonic acid (1.56 mmol, 136 µL). The resulting solution was stirred for 1 h at 0 °C, and then NaHCO₃ (s.s.) was added and the mixture extracted with CH₂Cl₂. The organic layer dried over Na₂SO₄ and concentrated under vacuum gave a residue which was purified by flash column chromatography (Et₂O) on silica gel conditioned with TEA to give 40 mg (64%) of compound **15Z** as yellow oil. ^{1}H NMR (CDCl₃, 400 MHz) δ_H: 1.15 (t, J = 6.8 Hz, 3H), 2.82−2.85 (m, 2H), 3.48 (d, J = 17.2 Hz, 1H), 3.74 (d, J = 17.2 Hz, 1H), 3.82 (s, 3H), 4.07−4.14 (m, 2H), 4.17−4.24 (m, 2H), 6.85−6.88 (m, 2H), 7.45 (d, J = 8.8 Hz, 1H), 8.01 (s, 1H), 8.18 (s, 1H). ^{13}C NMR (CDCl₃, 100 MHz) δ_C: 13.82, 29.67, 43.53, 55.45, 60.92, 63.26, 66.69, 109.25, 114.37, 115.39 (q, J^1 = 289 Hz), 125.50, 131.81, 134.73, 146.02, 155.44 (q, J^2 = 39 Hz), 161.21, 161.50, 171.54. ESI-MS, m/z: [M + H$^+$] = 397. Anal. Calcd for C₁₉H₁₉F₃N₂O₄: C, 57.57; H, 4.83; N, 7.07. Found: C, 57.78; H, 4.90; N, 6.99.

(*Z*)-4-(2-(Ethoxycarbonyl)-5-methoxy-2-(2,2,2-trifluoroacetami-do)-2,3-dihydro-1*H*-inden-1-ylidene)-1-methyl-3,4-dihydro-2*H*-pyr-rolium trifluoromethanesulfonate (**5Z**). Methyl trifluoromethanesul-fonate (0.18 mmol, 20 µL) was added to a solution of **15Z** (0.18 mmol, 70 mg) in anhydrous benzene (1 mL). The product of reaction was recovered quantitatively as yellow oil. ^{1}H NMR (CDCl₃, 400 MHz) δ_H: 1.19 (t, J = 7.2 Hz, 3H), 3.21 (d, J = 18.0 Hz, 1H), 3.25−3.36 (m, 1H), 3.50−3.57 (m, 1H), 3.68 (s, 3H), 3.89 (s, 3H), 4.03−4.31 (m, 2H), 4.35 (d, J = 18.0 Hz, 1H), 4.50−4.54 (m, 2H), 6.88 (s, 1H), 6.94 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 8.8 Hz, 1H), 8.96 (s, 1H), 9.67 (s, 1H). ^{13}C NMR (CDCl₃, 50 MHz) δ_C: 13.79, 28.89, 40.79, 44.68, 55.84, 58.22, 63.57, 69.00, 109.54, 115.38 (q, J^1 = 286 Hz), 116.30, 123.55, 127.57, 128.50, 152.16, 152.77, 158.27 (q, J^2 = 39 Hz),

164.70, 168.16, 169.47. ESI-MS, m/z: [M$^+$] = 411. Anal. Calcd for C₂₁H₂₂F₆N₂O₇S: C, 45.00; H, 3.96; N, 5.00. Found: C, 45.14; H, 3.94; N, 4.99.

Kinetic Measurements. Absorption spectra were recorded on an HP 8453 diode-array spectrophotometer. The sample irradiation was carried out using a Xenon lamp equipped with a monochromator for the selection of the excitation wavelength (380 or 440 nm). The thermal reaction was followed keeping the sample in dark conditions in the range temperature range 276-313 K. An Oxford Instruments (Abingdon, UK) cryostat was used for the temperature control. The chromatographic analysis has been performed by use of a Waters apparatus equipped with analytical Symmetry C18 (4.6 × 250 mm; 5 µm) or Prontosil 200-3-C30 (4.6 × 250 mm; 3 µm) columns and a UV Vis diode array detector.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra for all new compounds and 2D NOESY (400 MHz, CDCl₃, 298 K) for compounds **3**, **5**, **10**, and **20**.This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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