JOC Articles

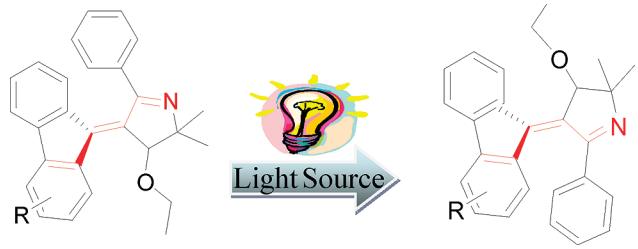
# Fluorenylidene−Pyrroline Biomimetic Light-Driven Molecular Switches

Laura Rivado-Casas,[†] Diego Sampedro,*[,†] Pedro J. Campos,[†] Stefania Fusi,[§] Vinicio Zanirato,[‡] and Massimo Olivucci[§,||]

*Departamento de Química, Universidad de La Rioja, Grupo de Síntesis Química de La Rioja, Unidad Asociada al C.S.I.C., Madre de Dios, 51, 26006 Logroño, Spain, Dipartimento di Scienze Farmaceutiche, Università di Ferrara, via Fossato di Mortara 17-19, I-44100 Ferrara, Italy, Dipartimento di Chimica, Università di Siena, via Aldo Moro 2, I-53100 Siena, Italy, and Chemistry Department, Bowling Green State University, Bowling Green 43403, Ohio*

*diego.sampedro@unirioja.es*

*Received January 2, 2009*




A new family of biomimetic photoactivated molecular switches based in the retinal chromophore is described. Expedient synthesis allows a library of compounds with a different substitution pattern, including chiral substituents, to be obtained. The effect of substitution, solvent, and light source on the photoisomerization step has been assessed. The absorption maximum has been red-shifted ca. 50 nm with respect to related systems and rotation is now easily achieved by using visible light.

## Introduction

Molecular switches based on photochemical *E*/*Z* isomerizations have been employed in different contexts to convert light energy into "mechanical" motion at the molecular level.[1−3] For instance, switches based on azobenzene have been used to control ion complexation,[4,5] electronic properties,[6] and catalysis[7] or to trigger folding/unfolding of oligopeptides.[8−13] In this context, preparation of novel switches differing from azobenzene in size, polarity, and isomerization mechanism represents an attractive target yielding alternative building blocks that could

[†] Universidad de La Rioja.
[§] Università di Siena.
[‡] Università di Ferrara.
[||] Bowling Green State University.

(1) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines. A journey into the nanoworld*; Wiley-VCH: Weinheim, Germany, 2003.
(2) Drexler, K.-E. *Nanosystems: Molecular Machinery, Manufacturing and Computation*; John Wiley: New York, 1992.
(3) Sauvage, J.-P. *Molecular Machines and Motors*; Springer Verlag: Heidelberg, Germany, 2001.
(4) Shinkai, S.; Kusano, Y.; Manabe, O.; Nakaji, T.; Nishida, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1980**, *102*, 5860–5865.
(5) Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1983**, *105*, 1851–1856.
(6) Jousselme, B.; Blanchard, P.; Gallego-Planas, N.; Delaunay, J.; Allain, M.; Richomme, P.; Levillain, E.; Roncali, J. *J. Am. Chem. Soc.* **2003**, *125*, 2888–2889.
(7) Cacciapaglia, R.; Stefano, S. D.; Mandolini, L. *J. Am. Chem. Soc.* **2003**, *125*, 2224–2227.
(8) Behrendt, R.; Renner, C.; Schenk, M.; Wang, F.; Wachtveitl, J.; Oesterhelt, D.; Moroder, L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2771–2774.
(9) Bredenbeck, J.; Helbing, J.; Sieg, A.; Schrader, T.; Zinth, W.; Renner, C.; Behrendt, R.; Moroder, L.; Wachtveitl, J.; Hamm, P. *Proc. Natl. Acad. Sci. U.S.A.* **2003**, *100*, 6452–6457.
(10) Renner, C.; Behrendt, R.; Spörlein, S.; Wachtveitl, J.; Moroder, L. *Biopolymers* **2000**, *54*, 489–500.
(11) Rudolph-Böhner, S.; Krüger, M.; Oesterhelt, D.; Moroder, L.; Nägele, T.; Wachtveitl, J. *J. Photochem. Photobiol. A* **1997**, *105*, 235–248.
(12) Spörlein, S.; Carstens, H.; Satzger, H.; Renner, C.; Behrendt, R.; Moroder, L.; Tavan, P.; Zinth, W.; Wachtveitl, J. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 7998–8002.
(13) Ulysse, L.; Cubillos, J.; Chmielewski, J. *J. Am. Chem. Soc.* **1995**, *117*, 8466–8467.



10.1021/jo802792j CCC: $40.75 
Published on Web 06/01/2009

expand the applicability of the switch concept to diversified molecular environments. A sophisticated application of the above principle led to the preparation of chiral diarylidenes, featuring a single isomerizable bond. These systems constitute examples of light-driven molecular rotors[14−18] where the chiral framework imposes a preferential direction (either clockwise or counterclockwise) of isomerization.

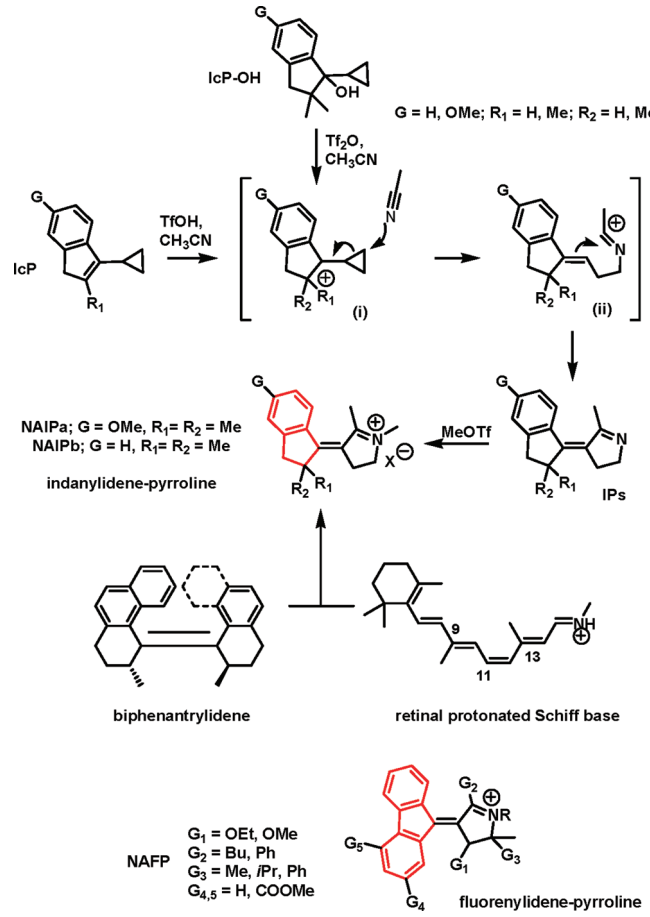
The retinal protonated Schiff base chromophore of rhodopsins[19−21] constitutes an example of an *E*/*Z* switch shaped by biological evolution that can be modeled with quantitative computations.[22] In bovine rhodopsin (Rh) a selective photoisomerization of the 11-cis chromophore (PSB11) occurs via evolution of a single $\pi \rightarrow \pi^*$ excited state ($S_1$) that survives for only 150 fs and yields, upon decay, the *all-trans* ground state ($S_0$) product with a 67% quantum yield.[19,20] While these properties make Rh an excellent reference for the design of *E*/*Z* switches, irradiation of PSB11 in solution features an unselective isomerization and a picosecond excited state lifetime[20] prompting a search for artificial Rh-mimetic molecules.

Recently, we have been able to demonstrate that it is possible to prepare and characterize[23] an *N*-alkylated indanylidene−pyrroline Schiff base (NAIP) that displays, in methanol solution, excited state properties similar to those of Rh-embedded PSB11. The synthetic strategy we have developed to set up the polyconjugated iminium chromophore features a high-yielding heterocyclization as the key step. We have shown that 4-indanylidene pyrroline derivatives (IPs) are the products of an intriguing multistep one-pot process we named "cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction".[24] In detail, when 1-cyclopropylindenium intermediates (**i**) react with acetonitrile they undergo homoallyl rearrangement yielding the corresponding nitrilium ions (**ii**). Then, the transient electrophilic species collapse onto the internal olefine generating the desired pyrroline derivatives IPs.

We could trigger the heterocyclization step both by treating 1-cyclopropylindanols IcP−OH in $CH_3CN$ with $Tf_2O$ and by regioselective protonation with TfOH of indenyl cyclopropane derivatives IcP in $CH_3CN$. The effectiveness and versatility of the synthetic approach permitted the access to several NAIPs, structure NAIPa and NAIPb included (Scheme 1).

NAIPs are "chimerical" switches that incorporate into the Feringa's biarylidenes skeleton a protonated or alkylated Schiff base function (see Scheme 1) that could potentially replicate the dynamics of the PSB11 isomerization in Rh. This protein features a $S_1$ lifetime of ≈150 fs, a $S_0$ transient (photorhodopsin)

**SCHEME 1. NAIP and NAFP Switches**



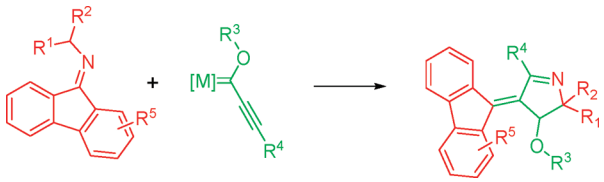

appearance time of 180 fs, and a primary photoproduct (bathorhodopsin) appearance time of ≈6 ps. Very recently we have shown, through a highly interdisciplinary research effort,[25] that a *p*-methoxy NAIP derivative (**NAIPa**, Scheme 1) is a photochromic compound completing its $Z \rightarrow E$ and $E \rightarrow Z$ photocycle in picoseconds. These time scales (ca. 0.3 ps for Z-**a**) suggest that NAIP-based motors may complete a half-rotary cycle in less than 10 ps,[25] i.e., a few orders of magnitude faster than the fastest (≈6 ms for half-cycle) known biarylidene.[25,26]

In spite of the remarkable properties of NAIPs, these switches display absorption maxima in the near-UV region. Thus, the parent compound NAIPb has an absorption maximum of 343 nm that is red-shited to 377 nm for NAIPa due to the electron-releasing effect of its *p*-MeO group. Indeed, electron releasing groups in the para and ortho position are predicted to stabilize the spectroscopic (charge-transfer) state with respect to the ground state and therefore lead to a red-shift.[23] Unless derivatives of this switch can be prepared that span absorption maxima in the 343−420 nm range one still seeks homologues where the absorption maximum of the parent (unsubstituted) system is clearly in the visible. With this idea in mind we have pointed to a replacement of the indanylidene unit of NAIPs with moieties displaying a more expanded $\pi$-system.

In the present report we focus on switches where the indanylidene unit has been replaced by a fluorenylidene unit.

(14) Feringa, B. L. *Acc. Chem. Res.* **2001**, *34*, 504.
(15) Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 6635–6652.
(16) Koumura, N.; Geertsema, E. M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 12005.
(17) Koumura, N.; Geertsema, E. M.; van Gelder, M. B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 5037.
(18) Koumura, N.; Zijistra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152.
(19) Kandori, H.; Shichida, Y.; Yoshizawa, T. *Biochemistry (Moscow)* **2001**, *66*, 1483–1498.
(20) Mathies, R. A.; Lugtenburg, J. In *Handbook of Biological Physics*; Stavenga, D. G., de Grip, W. J., Pugh, E. N., Eds.; Elsevier: Amsterdam, The Netherlands, 2000; Vol. 3, pp 56−90.
(21) Teller, D. C.; Okada, T.; Behnke, C. A.; Palczewski, K.; Stenkamp, R. E. *Biochemistry* **2001**, *40*, 7761–7772.
(22) Andruniow, T.; Ferré, N.; Olivucci, M. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 17908–17913.
(23) Lumento, F.; Zanirato, V.; Fusi, S.; Busi, E.; Latterini, L.; Elisei, F.; Sinicropi, A.; Andruniów, T.; Ferré, N.; Basosi, R.; Olivucci, M. *Angew. Chem., Int. Ed.* **2007**, *47*, 414–420.
(24) Zanirato, V.; Pollini, G. P.; De Risi, C.; Valente, F.; Melloni, A.; Fusi, S.; Barbetti, J.; Olivucci, M. *Tetrahedron* **2007**, *63*, 4975–4982.
(25) Sinicropi, A.; Martin, E.; Ryasantsev, M.; Helbing, J.; Briand, J.; Sharma, D.; Léonard, J.; Haacke, S.; Canizzo, A.; Chergui, M.; Zanirato, V.; Fusi, S.; Santoro, F.; Basosi, R.; Ferré, N.; Olivucci, M. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 17642–17647.
(26) Vicario, J.; Walko, M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 5127–5135.

**SCHEME 2. Synthetic Route to NAFPs**



Through the preparation of a library of *N*-alkylated fluorenylidene−pyrroline switches (NAFPs), we show that it is possible to achieve biomimetic light-driven switches where the absorption maxima of an unsubstituted system has been red-shifted by >50 nm with respect to that of the NAIPs. We also show that, similar to NAIPs, NAFPs undergo $Z \rightarrow E$ and $E \rightarrow Z$ photoisomerization displaying a photomodulable stationary state.

Several approaches were considered for the synthesis of the polyconjugated iminium chromophore. The main synthetic task was an expeditious entry to a small library of compounds, the synthetic route was required to be amenable to the preparation of derivatives in which functional groups with different electronic nature could serve to tune the photochemical behavior. Another goal was the production of chiral molecular switches potentially acting as molecular rotors. With these considerations in mind, we believed of particular usefulness the already reported[28] reaction of alkynyl Fischer carbene complexes with fluorenone imines leading directly to compounds featuring the pivotal chromophore embedded into a conformationally locked structure. As shown in Scheme 2, different substituents could be introduced with ease in almost every point of the molecule, thus allowing the tuning of the properties of the system.

## Synthesis

In the original paper,[28] the nonenolizable imine partners of the pentacarbonyl(1-ethoxy-3-phenyl-2-propyn-1-ylidene)tungsten were restricted to a couple of examples and no further efforts have appeared in the literature to extend this intriguing reactivity. A rapid entry to a small library of NAFP photoswitches was envisaged simply by combining different alkynyl Fischer carbene complexes with proper imines, both preparable by conventional chemistry.

Embarking on the synthetic work we prepared imines from fluorenone as well as from the C-2 and C-4 carbomethoxy derivatives. Regarding the amine moiety with the required C−H bond adjacent to the primary nitrogen atom, we used four different substrates. Importantly, starting from commercially available enantiopure primary amines chirality was easily introduced in the imine reactants. Eventually, structural diversity also could be introduced at the Fischer carbene complex by modifying the metal, the alkoxy, and alkynyl substituents (see Chart 1).

Our next step was to optimize the reaction conditions: best results were obtained by heating the imines at 90 °C in a toluene solution 0.5 M in carbene complexes. The main side reactions consisted of carbene complexes decomposition (specially for **2d**) and imine hydrolysis followed by amine addition to carbene complexes. These drawbacks could be mitigated by avoiding higher temperatures, employing 1.5 equiv of carbene complexes and using anhydrous conditions. The presence in the reaction mixture of pyrrolium complexes as reported by Aumann[28] was not investigated. Both tungsten and chromium carbene complexes were synthesized (**2a** and **2e**) and tested. Although both compounds yield the same product **3b**, better results were obtained for the tungsten compound (58% from **2a** and 40% from **2e**). Following the optimized protocol, a set of compounds shown in Table 1 could be prepared in modest to good yields in all but one entry.

In the case that chiral nonracemic fluorenone imines **1b** and **1c** were the substrates, a certain degree of diastereoselection was observed, instead reacting **1d**, a single diastereoisomer, was isolated from the reaction mixture. However, we were not able to appreciate optical activity for **3j**, and chiral GC/MS analysis, in order to evaluate its ee, revealed to be impracticable. On the other hand, when a sample containing **3j** in $CDCl_3$ was doped[27] with $Eu(hfc)_3$ the $^1H$ NMR signals moved downfield showing coupling but no splitting, a result suggesting a ≥90% ee (see the Supporting Information for details). As far as both (possible) enantiomers showing exactly the same displacements, further experiments will be needed for a comprehensive exploration of the stereochemical outcome of the Aumann's reaction.[28] As expected, the carbomethoxy fluorenone imines gave rise to the corresponding fluorenylidene−pyrrolines as a mixture of geometric isomers. All attempts to prepare the 5-TMS derivatives failed and only the substitution product **4** could be isolated. Apparently, the TMS group hampers the Michael-type addition of the imine nitrogen atom to the alkyne $\beta$ carbon and, as expected,[29] the isopropylamine in the reaction medium gives substitution at the carbene carbon atom.

Once the compounds featuring a fluorene nucleus conjugated to the cyclic imine were prepared, what remained to do in order to obtain biomimetic[20] switches was the quaternization of the imine nitrogen atom. Several methods were tried to alkylate the imine moiety ($Me_2SO_4$, MeI, $Et_3OBF_4$) but best results were obtained with methyl triflate in dry toluene. Under these conditions, the triflate salts precipitated in pure form and the free bases could be easily recovered from the filtrate. Alternatively, iminium ions (**5e**, **5f**) were quantitatively obtained following protonation with $HBF_4$ of the corresponding imines in $CDCl_3$ solution. Chart 2 shows the NAFP switches formed and used in the photochemical study, while Figure 1 depicts the structure of **5c** as obtained from X-ray diffraction data. Complete delocalization of the $\pi$ system is clearly shown by long double bond distances (C═N, 1.31 Å, central C═C, 1.37 Å) and short single bond distances (C−C between 1.45 and 1.49 Å). This will be reflected in the low-energy UV absorption bands. Besides, the structure is not planar as the dihedral angle between the fluorenyl and pyrroline moieties is 19.5°.

## Spectroscopic Studies

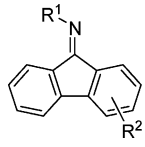
First, we studied the effect in the UV spectrum of the imine methylation. As stated before, previous results suggest that the presence of a positive charge in the nitrogen atom would contribute to an increase in the isomerization rate. Of course, a fast activation process is a desirable feature of a molecular switch, but the positive charge also can cause a direct effect on the absorbance of these compounds. To check this effect, we recorded the UV−visible spectrum for **3a** and **5a** shown in Figure 2.

(27) Parker, D. *Chem. Rev.* **1991**, *91*, 1441–1457.

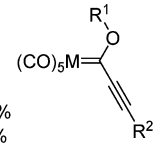
(28) Aumann, R.; Yu, Z.; Fröhlich, R.; Zippel, F. *Eur. J. Inorg. Chem.* **1998**, *11*, 1623–1629.

(29) Dörwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 1999.

**CHART 1. Imines and Carbene Complexes Used in the Synthesis of Molecular NAFP Switches**



**1a** $R^1$= $CH(CH_3)_2$ $R^2$= H 94%
**1b** $R^1$= (*R*)-$CHPhCH_3$ $R^2$= H 78%
**1c** $R^1$= (*S*)-$CHPhCH_3$ $R^2$= H 94%
**1d** $R^1$= (*S*)-$CH(i\text{-}Pr)CH_3$ $R^2$= H 91%
**1e** $R^1$= $CH(CH_3)_2$ $R^2$= 4-$CO_2$Me 80%
**1f** $R^1$= $CH(CH_3)_2$ $R^2$= 2-$CO_2$Me 70%



**2a** M=W, $R^1$=Et, $R^2$=Ph 93%
**2b** M=W, $R^1$=Me, $R^2$=Ph 49%
**2c** M=W, $R^1$=Me, $R^2$=TMS 69%
**2d** M=W, $R^1$=Et, $R^2$=Bu 71%
**2e** M=Cr, $R^1$=Et, $R^2$=Ph 53%

As can be seen, the main difference between both spectra is the red-shift of the low-energy band of the salt with respect to that of the neutral compound. Although this behavior is common in the chemistry of iminium salts, it becomes important in this particular case as far as the displacement of ca. 70 nm implies that these compounds will absorb in the visible region. This feature greatly increases the interest in these compounds as far as no UV-light will be needed to activate the switches.

We first explored the photochemical behavior of the simplest switch structures, i.e., **3a** and **3b**. Irradiation of **3a** with a medium-pressure Hg lamp at room temperature was followed by $^1$H NMR. Different spectra were recorded every 90 min and no change was noticed after 18 h of irradiation. Similar results were obtained after irradiation of **3b**. Methylated compound **5a** was also tested under the same reaction conditions and the compound remained unaltered after irradiating for 60 h. These values are also important because they denote the high photostability of these compounds, a key feature of any potential technological application. Although **3a** and **3b**, together with other examples shown in Table 1, have the symmetrical fluorenone moiety, they could present two different stereoisomers due to steric constraints around the central double bond. This feature has also been used before in the preparation of molecular switches and motors.[30] This was also shown in the X-ray diffraction structure for **5c** (Figure 1) where the dihedral angle around the central double bond is 19.5°. These two isomers were studied by means of DFT theoretical calculations (Figure 3). The main geometrical change between both structures is the dihedral angle connecting the fluorenyl and pyrroline moieties. The most stable structure for **3b** shows a dihedral angle of 23.3° (close to the value of 19.5° for **5c**), while the isomer presents a dihedral angle of −26.5°. However, only a very small energy difference was found between both isomers.

To clarify this point, a careful NMR analysis of **3c** was carried out. We chose this compound due to the absence of the phenyl ring bonded to the imine, which simplifies the NMR spectrum in the relevant region of aromatic hydrogen atoms. The presence of unresolved aromatic signals at 298 K suggested the possibility of different isomers in fast equilibrium. To check the possibility of equilibrium between the two stereoisomers shown in Figure 3 we registered the NMR spectrum at low temperatures. Temperature-dependent NMR spectra enabled the measurement of the energy barrier between isomers, by determining experimentally the coalescence temperature for the signals (Figure 4). The relation between the coalescence point, the difference in the chemical shift, and the rate constant is well-known.[31] Using these data we were able to obtain a value of 11.6 kcal/mol for the dynamic energy barrier from a coalescence temperature of 253 K. It should be noted that the equilibration between these two stereoisomers is fast at room temperature and it will not hamper the photoactivated *Z*−*E* isomerization, but this equilibrium should be controlled in the case of chiral molecules behaving as molecular motors.

## Photoisomerization of Neutral Compounds

We chose for this part of the study **3m** and **3n**, as far as they are separable isomers with distinctive $^1$H NMR signals. We started from pure samples of the two isomers **3m** and **3n** and followed the photoisomerization process by $^1$H NMR. We used a 125-W medium-pressure Hg lamp and pyrex filter to ensure absorption of the low-energy band (see Figure 2). We recorded the spectra at different times to follow the isomerization process. Results can be seen in Figure 5.

As can be seen, fast isomerization takes places and the photostationary state is reached within 30 min starting from **3m** (Figure 5, top) and 60 min starting from **3n**. In both cases the same equilibrium is reached (ca. 55:45) with a majority of the mixture formed by **3n**. This equilibrium remains unaltered with further irradiation or heating. To check the photochemical nature of the process, we carried out a comparative experiment heating isolated isomers **3m** and **3n** at 50 °C in the dark. Results are shown in Figure 6.

Clearly, although thermal isomerization also takes place, heating at 50 °C for more than 18 h is needed to reach the equilibrium. These data should be compared with the 30 min necessary to photochemically equilibrate the mixture. Thus, the photochemical isomerization is much faster than the thermal one, and the latter can be completed at short times. Once we assessed the feasibility of the fast photoisomerization process we aimed for the effect the reaction conditions could have on the isomerization speed. In order to do this, we carried out similar experiments as those described above with different solvents, switches, and light sources. To determine the performance of the switches, we measured the initial rate constant for the isomerization process, $k_i$. To permit direct comparison we carried out a series of experiments in which we varied only one variable at a time. This will allow us to obtain precise information on the effect of the variable, but comparison between different runs should be taken with care. We first measured by $^1$H NMR the isomerization process of neutral compounds and these data will used as a benchmark for the cationic species.[32] Results are summarized in Table 2.[33]

Several conclusions can be drawn from the data presented in Table 2. First, the solvent has some influence on the isomerization ratio for both **3m** and **3n**. Polar solvents such as acetonitrile contribute to a faster isomerization but the effect is stronger in **3m** (the relative ratio in $CD_3CN$ is twice that with $CDCl_3$) than in **3n** (relative ratio 1:1.1). Comparing **3m** vs. **3n** with $CD_3CN$ as solvent, faster isomerization takes place for **3m**. This could be linked to the relative stability of both compounds as far as DFT calculations show that **3m** is 1.2 kcal/mol less stable than **3n** (see the Supporting Information for details).

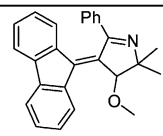
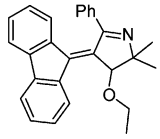
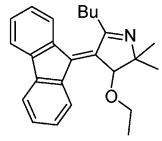
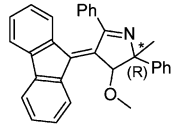
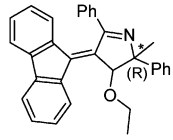
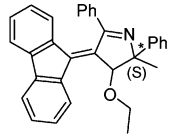
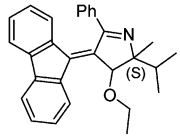
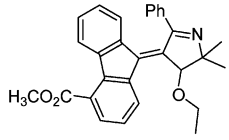
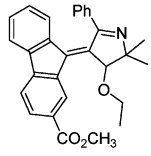
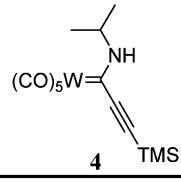
(30) For a recent example see: Katsonis, N.; Minoia, A.; Kudernac, T.; Mutai, T.; Xu, H.; Uji-i, H.; Lazzaroni, R.; DeFeyter, S.; Feringa, B. L. *J. Am. Chem. Soc.* **2008**, *130*, 386–387.

(31) Williams, D. H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry*; 4th ed.; McGraw-Hill: New York, 1984.

(32) A typical experiment was carried out with a concentration of 0.010 M, but concentrations between 0.004 and 0.15 M were also tested with similar results.

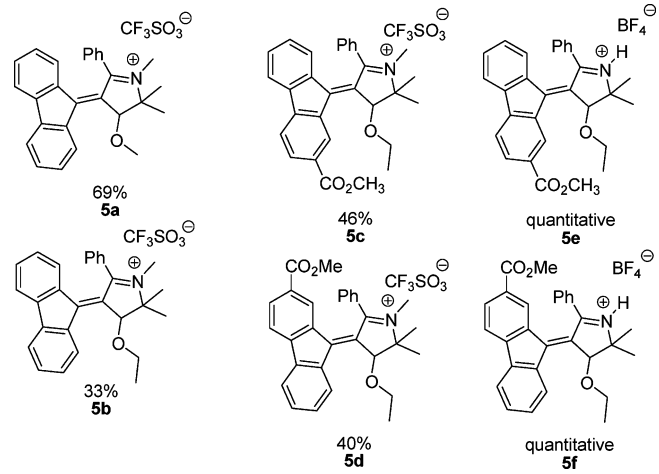
(33) Several experiments were performed for each entry. Data shown correspond with the mean value and error was determined to be <8%.

**TABLE 1. Fluorenylidene−pyrroline Derivatives**

| Imine | Complex | Product | Yield |
|---|---|---|---|
| **1a** | **2b** |  **3a** | 23 |
| **1a** | **2a** |  **3b** | 58 |
| **1a** | **2d** |  **3c** | 9 |
| **1b** | **2b** |  **3d + 3e** | 34[a] |
| **1b** | **2a** |  **3f + 3g** | 41[a] |
| **1c** | **2a** |  **3h + 3i** | 33[a] |
| **1d** | **2a** |  **3j** | 20[b] |
| **1e** | **2a** |  **3k + 3l** | 24[c] |
| **1f** | **2a** |  **3m + 3n** | 30[d] |
| **1a** | **2c** |  **4** | 30 |

[a] Two separable diastereoisomers were obtained in a 6:1 ratio. [b] One only diastereoisomer was found in the reaction crude. [c] As an inseparable mixture of two isomers. [d] As a separable mixture of two isomers.

**CHART 2. NAFP Molecular Switches Used in the Photochemical Study**




## Photoisomerization of Biomimetic Switches

**Methylated Compounds.** The next step was to study the photoisomerization of switches **5c** and **5d**. In this case, one more factor should be taken into account as far as these compounds also absorb in the visible. So, the light source could also affect the isomerization rate. The results obtained in this series of experiments are shown in Table 3.

As can be seen, the solvent used has little influence on the rate of isomerization, at least in the cases studied. The only exception was **5d** in CDCN, which gave a mixture of **5c** and **5d** from the very beginning avoiding the measurement of the isomerization rate. However, methylated analogues **5c** and **5d** are more soluble in polar solvents like acetonitrile and concentration in less polar solvents like chloroform or toluene always must be lower to avoid precipitation. When both cationic compounds are compared, little difference in the photoisomerization rate is observed (1:1.1). However, it should be noted that **5d** isomerizes slightly faster than **5c**. This result is opposed to the one found for the neutral compounds, but also in this case the difference in the relative stability can explain these rates. Our DFT calculations show that **5d** is less stable than **5c** by 0.5 kcal/mol. As expected, nitrogen atom methylation contributes not only to simulate the retinal chromophore, but also to speed up the isomerization process. In the case of **5c**,

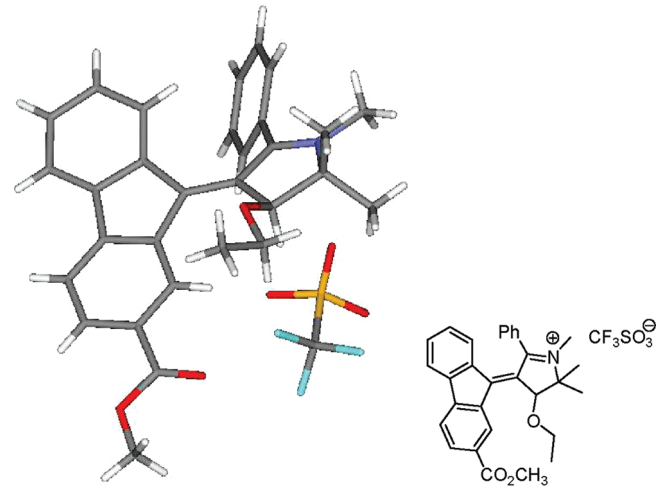


**FIGURE 1.** X-ray diffraction structure for NAFP switch **5c**.

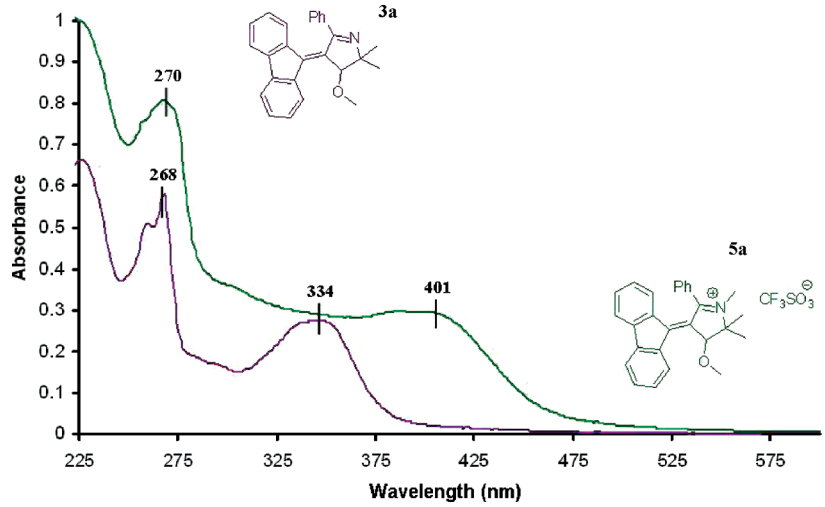



**FIGURE 2.** UV−visible spectrum in $CH_3CN$ for compounds **3a** (neutral, $7.25 \times 10^{-5}$ M) and **5a** (methylated, $4.84 \times 10^{-5}$ M).

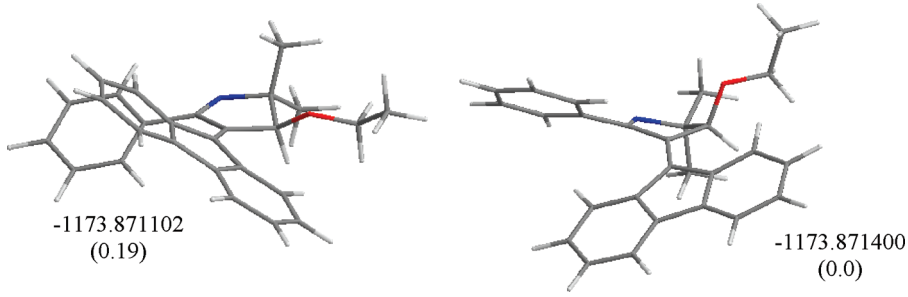



**FIGURE 3.** BP86/6-31G* structures and absolute and relative energies for the two stereoisomers available for **3b**.

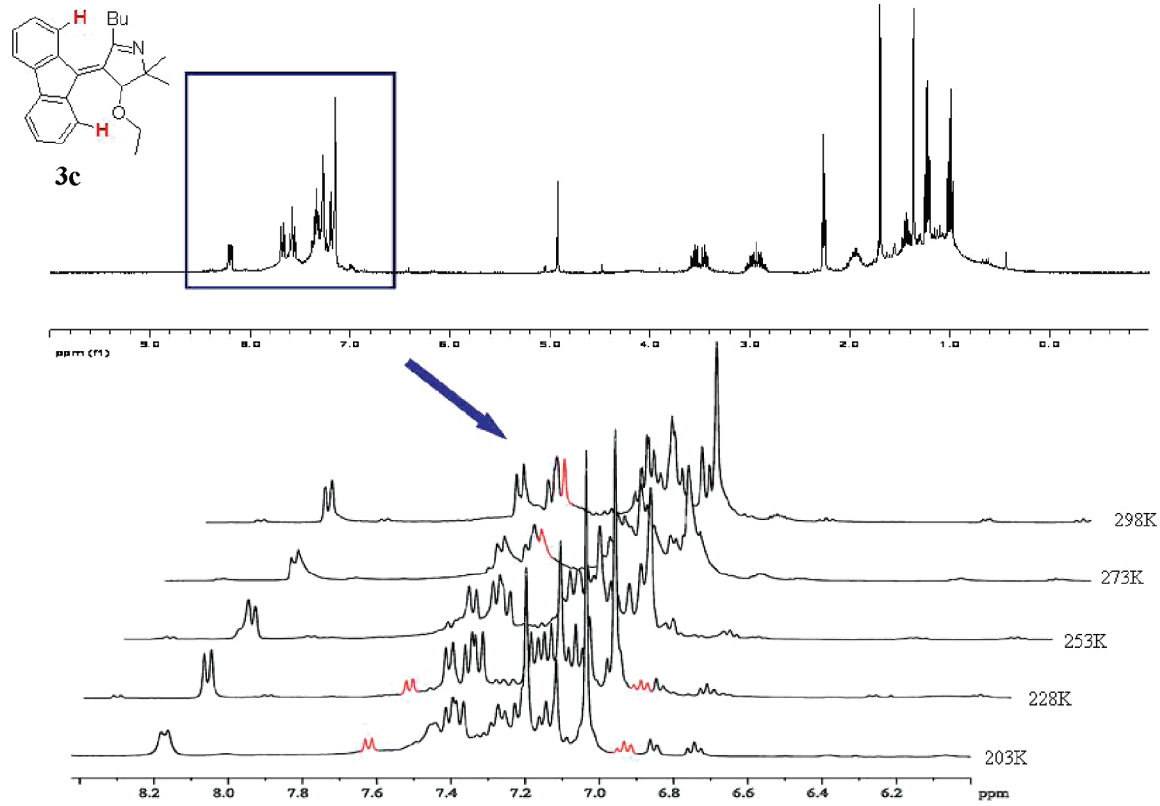



**FIGURE 4.** $^1$H NMR spectra for **3c** in $d_8$-toluene at the temperatures shown.

photoisomerization takes place almost four times faster than for **3m**, while **5d** isomerizes almost three times faster than **3n**. Finally, the effect of the light source was assessed. For both switches **5c** and **5d**, higher relative rates were found when using

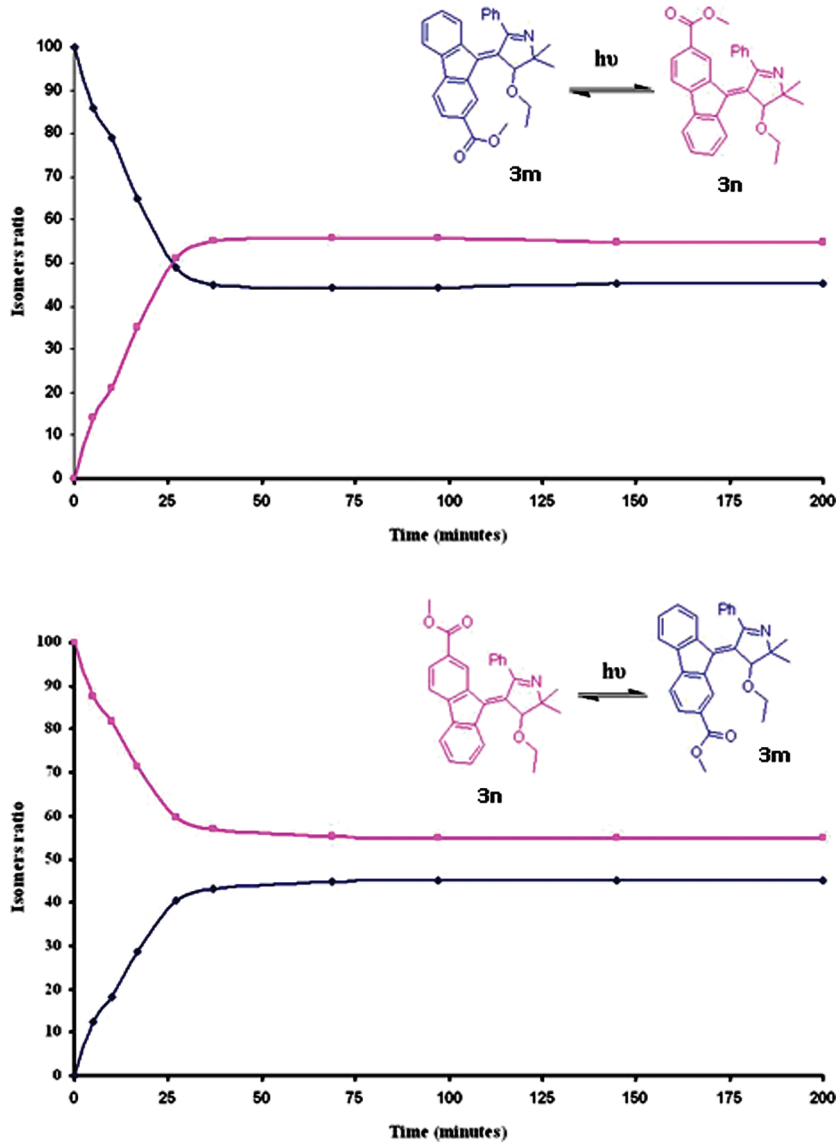



**FIGURE 5.** Photoisomerization process for **3m** and **3n** with use of pyrex-filtered UV light.

the medium-pressure Hg lamp compared to ambient light. This effect is clearly due to the different intensities of the light sources. However, the small differences in the reaction rates indicate the usefulness of these switches as far as no UV light is needed to trigger the photoisomerization. This fact, far from being trivial, constitutes an important feature of these switches and constitutes an improvement over the majority of switches based in overcrowded alkenes[15] which usually need UV light to rotate. The use of low-energy light in the presence of a complex matrix and sunlight exploitation are important features for technological applications of molecular switches. To further explore the effect of the light source, we explored the wavelength dependence in the photoisomerization of **5c**. Using monochromatic light, we followed the photoisomerization process at 330 and 433 nm. We chose those wavelengths because they have the same extinction coefficient ($\varepsilon = 1060$) at both sides of the absorption band (see Figure 2 for the UV spectrum of a related compound). Under these conditions, solutions of the same concentration (0.02 M) will absorb exactly the same amount of light. We found the same kinetic constants and composition of the photostationary state (57% of **5c** and 43% of **5d**) for the irradiation at these two wavelengths for 6 h. This fact emphasizes the usefulness of these compounds under low-energy irradiation.

We also checked the thermal isomerization of these compounds. An equivalent experiment as the one shown in Figure 6 was carried out for **5c** and **5d**, with similar results. After 22 h at 50 °C an equilibrium formed by 59% **5c** and 41% **5d** was reached. Interestingly, the main isomer in this case (**5c**) is the opposite of the one mainly obtained when the neutral compounds are used (**3n**). This means that methylation causes a change in the relative stabilities of the different isomers. This is confirmed by the DFT calculations carried out for both pairs of compounds as discussed above (see the Supporting Information for details).

**Protonated Compounds.** Finally, we decided to explore the effect of protonation instead of methylation in the nitrogen atom. This was first carried out with $HBF_4$ to generate the cationic species **5e** and **5f**. A series of experiments was then performed to determine how this modification affects the isomerization outcome. Results are shown in Table 4.

Although protonation in the nitrogen atom also contributes to faster photoisomerization rates, the accelerating effect is smaller than that in the methylated analogues. However, light absorption takes place also in the visible and preparation of the

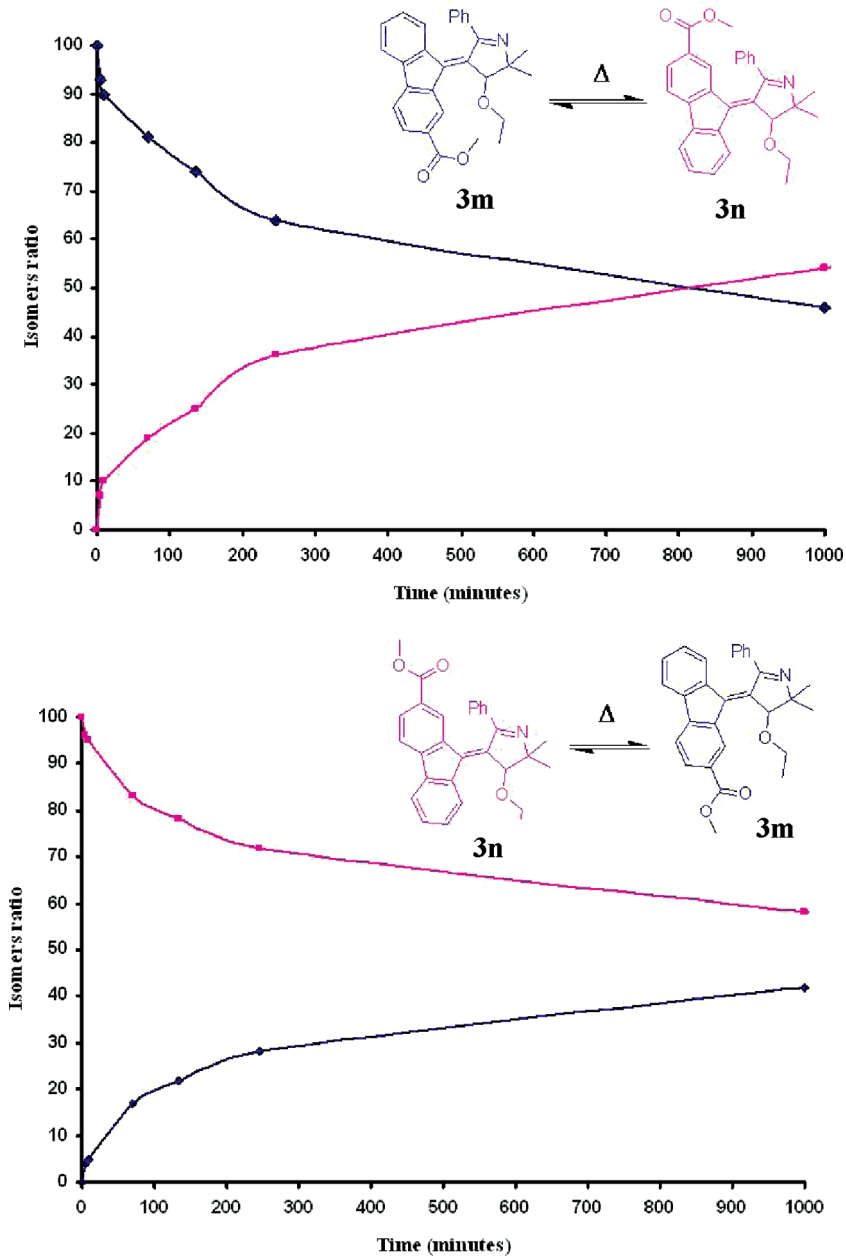



**FIGURE 6.** Thermal isomerization process for **3m** and **3n**.

**TABLE 2. Photochemical Isomerization of 3m and 3n**

| compd | solvent | $k_i$[a] |
|---|---|---|
| **3m** | $CDCl_3$ | 1 |
| **3m** | $CD_3CN$ | 1.9 |
| **3n** | $CDCl_3$ | 1 |
| **3n** | $CD_3CN$ | 1.1 |
| **3m** | $CD_3CN$ | 1.8 |
| **3n** | $CD_3CN$ | 1 |

[a] Relative rate constants.

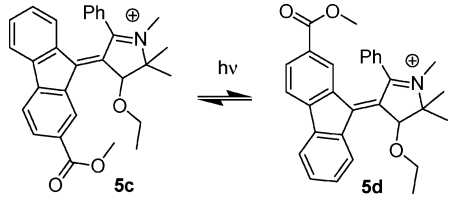
protonated compounds **5e** and **5f** can be obtained in situ in quantitative yields. Thus, these compounds could also be useful in practical applications. It should also be noted that the counterion is different in pairs **5c**−**5d** and **5e**−**5f** and it is known that the counterion affects the reaction rate in related photoisomerizations.[34]

Protonation can also be carried out with HCl. Here 4.6 μL of a solution containing HCl obtained with $CH_3COCl$ in anhydrous $CH_3OH$ (179 μL) was added in the dark and at room temperature to a solution of **3n** (8 mg (0.018 mmol) in 1.5 mL of $CD_3OD$). The solution was divided into two equal parts and transferred into two NMR tubes and the $^1H$ NMR spectra was recorded immediately. One NMR tube is kept in the dark, while the other is irradiated at 420 nm with a monochromator. The progress of the isomerization, both thermal and photochemical, was monitored by $^1H$ NMR spectroscopy, recording different spectra at different times. The results are reported in Table 5.

Again, isomerization can be easily achieved by in situ formation of the protonated switches and using an ambient light source. As in previous experiments, it can be seen that the photoisomerization proceeds much faster than the thermal one.

(34) Cembran, A.; Bernardi, F.; Olivucci, M.; Garavelli, M. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6255–6260.

**TABLE 3. Photochemical Isomerization of 5c and 5d**




| compd | solvent | light source | $k_i$[a] |
|---|---|---|---|
| **5c** | $CDCl_3$ | UV | 1 |
| **5c** | $CD_3CN$ | UV | 1.01 |
| **5d** | $CDCl_3$ | UV | 1 |
| **5d** | $CD_3CN$ | UV | —[b] |
| **5c** | $CDCl_3$ | UV | 1 |
| **5d** | $CDCl_3$ | UV | 1.1 |
| **3m** | $CDCl_3$ | UV | 1 |
| **5c** | $CDCl_3$ | UV | 3.9 |
| **3n** | $CDCl_3$ | UV | 1 |
| **5d** | $CDCl_3$ | UV | 2.8 |
| **5c** | $CDCl_3$ | UV | 1.61 |
| **5c** | $CDCl_3$ | visible | 1 |
| **5d** | $CDCl_3$ | UV | 1.92 |
| **5d** | $CDCl_3$ | visible | 1 |
| **5c** | $CDCl_3$ | visible | 1 |
| **5d** | $CDCl_3$ | visible | 1.01 |

[a] Relative rate constants. [b] A mixture of compounds **5c** and **5d** was obtained from the beginning.

**TABLE 4. Photochemical Isomerization of 5e and 5f**

| compd | solvent | $k_i$[a] |
|---|---|---|
| **5e** | $CDCl_3$ | 1.6 |
| **5f** | $CDCl_3$ | 1 |
| **3m** | $CDCl_3$ | 1 |
| **5e** | $CDCl_3$ | 1.3 |
| **3n** | $CDCl_3$ | 1 |
| **5f** | $CDCl_3$ | 1.2 |

[a] Relative kinetic constants.

**TABLE 5. Photochemical and Thermal Isomerization after Protonation of 3n with HCl**

| time (min) | $h\nu$[a] | $\Delta$[a] |
|---|---|---|
| 30 | 1/0.52 | 1/0.40 |
| 60 | 1/0.73 | 1/0.52 |
| 90 | 1/0.73 | 1/0.56 |

[a] *E*/*Z* ratio.

## Conclusions

Fischer carbene complexes have been used to synthesize a new family of photochemical switches based in the retinal chromophore (NAFP switches). Optimization of the overall yield allows the synthesis of a set of compounds acting as photoactivated molecular switches. The synthetic route has been explored to allow the formation of compounds with a different substitution pattern. Chosen compounds have been used to determine the structure and characterize the different stereoisomers available. Thermal and photochemical stability have been checked to validate the use of these compounds as useful switches. Kinetic measures of the photoisomerization allow quantitative exploration the effect of the modifications in the basic structure. Fast photochemical isomerization can be achieved through irradiation of pure samples of neutral or cationic forms. The effect of substitution, solvent, methylation, and light source has been investigated in order to control the switch behavior prior to its use in practical applications. In contrast with most of switches based in overcrowded alkenes, NAFP switches presented here can use visible light to rotate. This constitutes a clear improvement over previous results and makes retinal-based molecular switches interesting candidates for technological applications.

## Experimental Section

**Typical Procedure for the Synthesis of Fluorenylidene−Pirroline Derivatives.** To a pentacarbonyl(ethoxyalkynylcarbene)tungsten complex (**2a**) (482 mg, 1.00 mmol) solution in dried and degassed toluene (2 mL) was added (fluoren-9-ylidene)isopropilamine (**1a**) (221 mg, 1.00 mmol) under Ar at room temperature. The reaction mixture was stirred for 36 h at 90 °C until the complex disappeared. The solvent was removed and the solid residue was disolved in ethyl acetate and solution was filtered through a Buchner funnel. Solvents were then removed with a rotary evaporator, and the products were separated by column chromatography. Elution with hexane/ethyl acetate affords a brown fraction with compound **3b** ($R_f$ 0.3, in hexane/ethyl acetate, 4:1, 220 mg, 58%).

**3-Ethoxy-4-(9*H*-fluoren-9-ylidene)-3,4-dihydro-2,2-dimethyl-5-phenyl-2*H*-pyrrole (3b):** brown oil; yield 220.10 mg, 58%; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.31−8.25 (m, 1H), 7.84−7.70 (m, 1H), 7.66 (dd, $J$ = 6.58, 1.70 Hz, 1H), 7.57 (d, $J$ = 7.50 Hz, 1H), 7.45−7.27 (m, 6H), 7.13 (t, $J$ = 7.45, 7.45 Hz, 1H), 6.75−6.64 (m, 1H), 6.55 (d, $J$ = 7.93 Hz, 1H), 5.07 (s, 1H), 3.66 (td, $J$ = 13.85, 6.94, 6.94 Hz, 1H), 3.54−3.43 (m, 1H), 1.61 (s, 3H), 1.25 (d, $J$ = 4.99 Hz, 3H), 1.20 (d, $J$ = 6.91 Hz, 3H) ppm; $^{13}$C NMR (300 MHz, $CDCl_3$) $\delta$ 171.1, 141.6, 141.5, 139.0, 135.3, 130.8, 129.9, 129.1, 128.9, 128.7, 128.6, 127.9, 126.4, 126.3, 119.6, 119.3, 90.1, 62.2, 27.7, 22.0, 15.5 ppm; UV−vis $\lambda$ 224 ($\varepsilon$ 29 922 $M^{-1}$ $cm^{-1}$), $\lambda$ 257 ($\varepsilon$ 24 457 $M^{-1}$ $cm^{-1}$), $\lambda$ 339 ($\varepsilon$ 7981 $M^{-1}$ $cm^{-1}$); exact mass ($C_{27}H_{25}NO$ + H) calcd 380.2009, found 380.2000.

**Acknowledgment.** We thank the Spanish MEC (CTQ2007-64197) for financial support. D.S. is financed by the Ramón y Cajal program from the MEC. L.R. thanks the Comunidad Autonoma de La Rioja for his fellowship. M.O., V.Z. and S.F. are grateful to MIUR for the Grant PRIN 2006 In silico design, synthesis and photochemical reactivity of cyclic phototunable peptidomimetics containing the RGD sequence.

**Supporting Information Available:** Experimental procedures, characterization data for new compounds, X-ray structure details for compound **5c** in CIF format, and Cartesian coordinates for the calculated geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802792J