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Synthesis of biomimetic light-driven molecular switches via a cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction

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Abstract—A cyclopropyl ring-opening/nitrilium ion ring-closing tandem reaction has been conveniently used in an expeditious synthetic approach to light-driven *Z*/*E* molecular switches featuring an imine function conjugated to olefin groups that mimics natural protonated Schiff bases.

1. Introduction

The fascinating idea of casting single molecules capable to convert light-energy into 'mechanical' motion prompted chemists to develop, in different contexts, systems capable of undergoing light-driven structural changes. Currently, the design and preparation of molecular switches (i.e., molecules that can interconvert among two or more states) based on photochemical *E*/*Z* isomerization constitutes an attractive research target to obtain novel materials for nanotechnology.[1] Indeed, switches based on the photoisomerization of the azobenzene chromophore have been used to control ion complexation,[2] electronic properties[3] and catalysis,[4] or to trigger folding/unfolding of oligopeptide chains.[5] Most remarkably, a sophisticated application of the above principle led to the preparation of light-driven molecular rotors[6] where chirality turned out to be an essential feature to impose unidirectional rotation. In these systems helical bis-arylidene scaffolds featuring a single exocyclic double bond have been employed to achieve photoinduced unidirectional rotary motion.

The retinal protonated Schiff base (PSB) chromophores of rhodopsin proteins,[7] a class of trans-membrane photoreceptors, constitute examples of natural *E*/*Z* switches undergoing unidirectional isomerization motion. In previous reports[8,9] we have shown, through combined computational and experimental studies, that conformationally locked PSBs provide a novel class of potential molecular switches capable to mimic the photoisomerization of the retinal PSBs of rhodopsins. In that context, we prepared a small set of molecules featuring a poly-conjugated iminium system (Fig. 1). The low $E \rightarrow Z$ isomerization quantum yield measured for the initially prepared *p*-substituted-4-benzylidene-3,4-dihydro-2*H*-pyrrolinium salts **PSB^{I}** (first generation PSBs)[8] prompted us to look at related structures with the aim of increasing the photoisomerization efficiency. We envisaged the development of a second generation PSB switches by decreasing the number of torsional degrees of freedom of the **PSB^{I}** backbone and especially the potential competitive rotation around the benzylic single bond. We translated these concepts into a simple working hypothesis for the synthesis of a novel unnatural protonated Schiff base (**PSB^{II}**) system[9] where the carbon–carbon exocyclic double bond appears to be the only conformationally free site in the excited state electronic structure.

We disclose herein the results of our investigation to achieve an effective preparation of **PSB^{II}**, a molecule featuring a pyrrolinium moiety conjugated to an aromatic ring, the latter being embedded in a conformationally locked indanylidene nucleus. We addressed this compound through different pathways. As we will discuss below one of these pathways not only provides a flexible synthetic route but also opens the way to the preparation of chiral **PSB^{II}** systems and therefore to novel light-powered and biomimetic single-molecule rotors.

Keywords: Light-driven molecular switches; Tandem reaction; Nitrilium ion cyclization; Cyclopropylcarbinyl cation.
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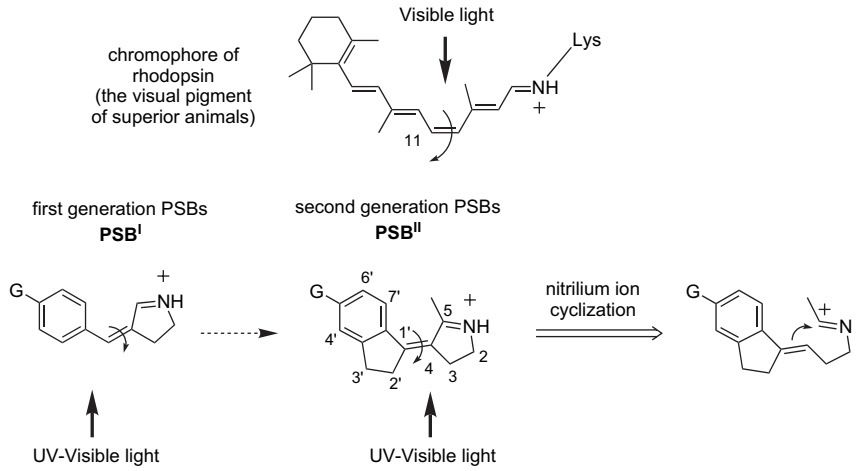


Figure 1.

2. Results and discussion

Among the possible retrosynthetic approaches to **PSB^{II}**, we initially selected the intramolecular capture of a nitrilium ion by a suitably located olefin group as the most promising one (Fig. 1). Nitrilium salts undergo various types of reactions, being key intermediates in a number of named reactions,[10] including ring-closing reactions to form five- and six-membered nitrogen heterocycles.[11] These interesting reagents are usually prepared by N-alkylation of nitriles with relatively stable carbocations, in turn generated by a plethora of reagents,[12] a common drawback being the unavoidable formation of mixtures of nitrilium species[13] derived from the rearrangement of initially formed carbocations.

A rather different approach to nitrilium ions entailed a Beckmann rearrangement of oximes,[14] but the efficiency of the process is seriously limited by the low stereospecificity, a single geometric isomer of the oxime being required to obtain the desired nitrilium ion. This hurdle seems to be overcome in the protocol introduced by Gawley and Chemburkar,[15] the nitrilium ions being generated by the action of trimethylsilyl polyphosphate (PPSE) on secondary amides. Recently, Angelastro et al.[16] described a vinylogous Bischler–Napieralski approach to quinolizidines by employing the PPSE protocol, showing that the *p*-methoxy substituted styryl group was the terminator of choice for the cationic cyclization.

The **PSB^{II}** retrosynthetic analysis led us to identify the commercially available 5-methoxy-1-indanone **1** as a convenient starting material, bearing a suitably located methoxy group able to favour the pivotal cationic cyclization (Fig. 2). Thus, the synthesis called for the installation of the homoallyl acetamido group at the C-1 carbon of the 5-methoxy-1-indanone scaffold.

To this end, the well-established acid-catalyzed cyclopropylcarbinol ring-opening, also called the homoallyl transposition, a widely exploited strategy to prepare 3-halo-*n*-propylidene derivatives by treatment of cyclopropylcarbinols with HX in acetic acid, could be a convenient starting step.[17]

Thus, we turned our attention to the protocol successfully employed to prepare 1-(3-chloro-propylidene)-1,2,3,4-tetrahydro-naphthalene from 1-cyclopropyl-1-tetralol by Perrone et al.,[18] who stressed the importance of a short reaction time in the treatment with 15% HCl in AcOH in order to obtain the kinetically favoured isomer rather than the thermodynamically favoured one having an endocyclic double bond. Consequently, the crude adduct resulting from addition of cyclopropylmagnesium bromide to the indanone **1** was treated with HCl in acetic acid for 1 h at room temperature. Unfortunately, only the undesired thermodynamically favoured indenyl derivative **2** *endo* could be isolated in low

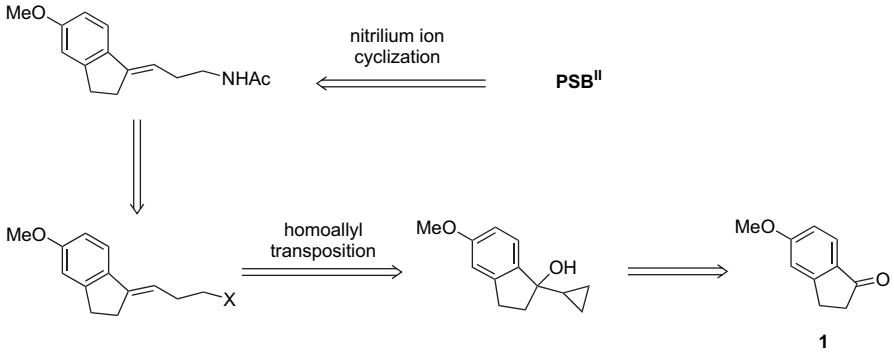
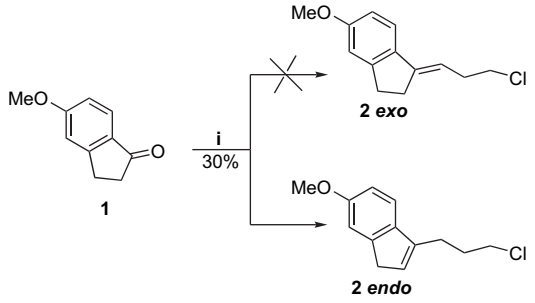


Figure 2.

yield from the reaction mixture, a result, which could be explained in the presence of mobile protons in position C-2 leading to a dominant [1,3] shift (Scheme 1).



Scheme 1. Reagents and conditions: (i) 1, Mg, cyclopropyl bromide, THF, reflux, 3 h and 2, HCl, AcOH, rt, 1 h.

Given the vital role played by the *exo*-olefin function in the nitrilium ion cyclization, we were forced to modify our original plan by removing the α-hydrogen atoms of the starting 5-methoxy-1-indanone **1**. This operation was easily achieved via exhaustive methylation[19] of the indanone **1** to give the bis-methyl derivative **1a**, which on treatment with cyclopropylmagnesium bromide afforded the cyclopropylcarbinol derivative **3a**. Its exposure to the action of HBr in AcOH promoted the expected rearrangement with the formation of the bromopropylidene derivative **4a** as a 3:1 mixture of diastereomers for which the *Z/E* descriptors were not assigned (Scheme 2).

Conversion of **4a** to **6a** was obtained in high yield through bromide displacement with sodium azide followed by the one-pot transformation of the corresponding azido group to acetamide by chemoselective hydrogenation in the presence of acetic anhydride.[20] The resulting secondary amide was eventually submitted to Gawley's protocol: a CCl_4 solution containing an excess of PPSE was added to the acetamide **6a** and the resulting mixture heated at reflux for 2 h. After aqueous work up the desired pyrroline derivative **7a** was isolated as the main product in 71% yield.

The ^{1}H NMR spectrum of **7a** showed the presence of two diastereomers in 92:8 ratio, the respective geometry being inferred on the basis of NOE difference spectroscopy. In detail, a positive NOE between the proton at the aromatic C-7′

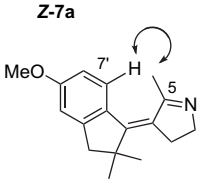


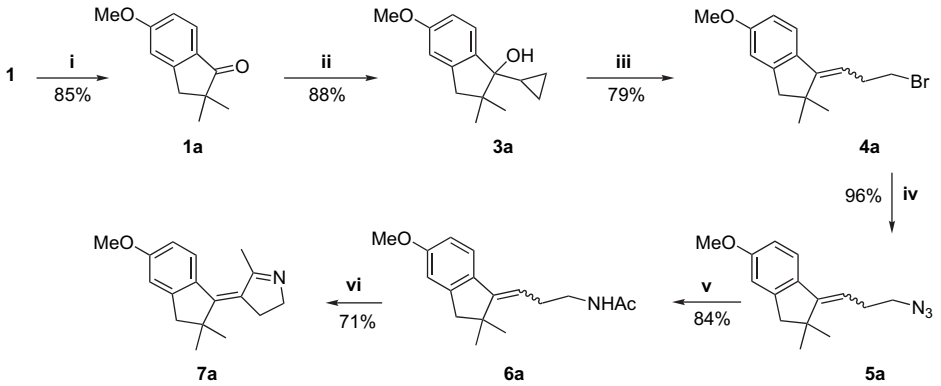
Figure 3.

carbon (d, δ=7.2) and the methyl at the C-5 of the pyrroline ring (m, δ=2.2) was observed for the predominant isomer to which *Z* configuration could be assigned (Fig. 3).

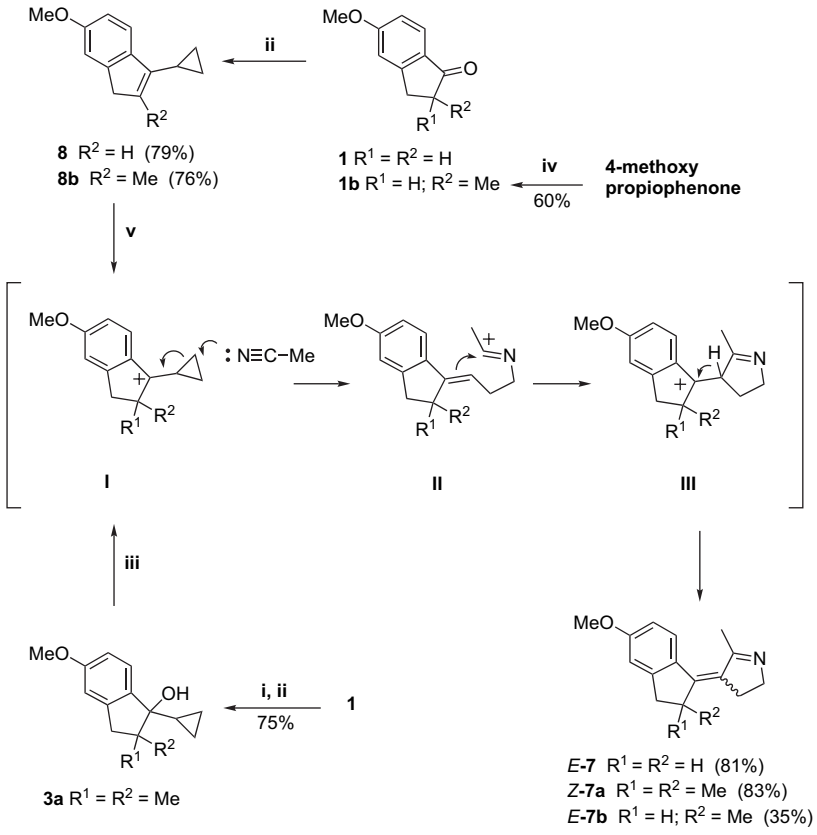
Conversion of the imine function of **7a** to an iminium ion, initially accomplished by protonation with HCl, was subsequently effected by N-methylation with methyl triflate, a more stable compound being produced. Their photochemical characterization has shown[9] that they constitute prototypes for the development of a novel class of light-driven biomimetic switches featuring a rigid molecular framework and a fully selective *Z/E* photoisomerization.

In view of this, the rather long (six-step) and low-yielding (33%) synthetic pathway described above (Scheme 2) prompted us to devise a new and more convenient synthesis, taking advantage of the alternative possibilities to generate nitrilium ions i.e., through direct N-alkylation of acetonitrile. Thus, the direct transformation of alcohols into secondary amides[21] provides a nice example of the use of alkyl triflates as electrophilic species able to react with nitriles. Moreover, Shi and Huang[22] have recently reported the one-pot reaction of nitriles, disubstituted methylenecyclopropanes (MCPs) and triflic acid (TfOH) to yield [3+2] cycloaddition products. The two interesting processes have in common the in situ generation of nitrilium ions, in the first case quenched with water, in the second one intercepted by the olefin group originating from the cyclopropyl ring-opening.

The chemistry described above supports the conjecture that the triflate ester of compound **3a** could be the precursor of the cyclopropylcarbinyl cation **I**, which, according to Shi's domino process, would lead to compound **7a** via the nitrilium ion **II** and the tertiary-benzylic carbocation **III** (Scheme 3). Accordingly, treatment of the cyclopropylcarbinol **3a** with acetonitrile in presence of Tf_2O smoothly furnished compound **7a** together with trace amounts of the



Scheme 2. Reagents and conditions: (i) MeI, *t*-BuOK, *t*-BuOH, Et_2O, reflux, 7 h; (ii) Mg, cyclopropyl bromide, THF, reflux, 3 h; (iii) HBr, AcOH, <10 °C, 10 min; (iv) NaN_3, DMF, 60 °C, 2.5 h; (v) Lindlar catalyst, Ac_2O, AcONa, 60 psi H_2, 6 h and (vi) P_2O_5, HMDSO, CCl_4, reflux, 2 h.



Scheme 3. Reagents and conditions: (i) MeI, *t*-BuOK, *t*-BuOH, Et_2O, reflux, 7 h; (ii) Mg, cyclopropyl bromide, THF, reflux, 3 h; (iii) Tf_2O, CH_3CN, 3 h; (iv) 1, morpholine, aqueous formaldehyde, AcOH, reflux, 5 h and 2, H_2SO_4, 60 °C, 1 h and (v) TfOH, CH_3CN, rt, 3 h.

amide **6a**. In such a way, a more direct and fruitful approach to **7a** was obtained (three steps from **1** with a 62% overall yield). The relief of the cyclopropyl ring strain associated with the installation of an extended π-system on the backbone of the final compound provided the driving force for this transformation.

The possibility that the transformation described in Scheme 3 would prove to be insensitive to the presence of protons at C-2 of indanone **1** (in contrast with the synthetic route of Scheme 2), opened the way to the preparation of switches **7** and **7b** featuring a decreased steric encumbrance in the proximity of the exocyclic carbon–carbon double bond. Accordingly, both the indanone **1** and its monomethyl derivative **1b**, in turn obtained from 4-methoxypropiophenone via Mannich α-methylenation followed by acid catalyzed cyclization of the resulting acrylophenone,[23] were submitted to reaction with cyclopropylmagnesium bromide.

Surprisingly, in both cases the indenyl dehydrated derivatives **8** and **8b** were isolated in high yields after silica gel column chromatography of the crude reaction mixtures instead of the expected Grignard adducts. Compounds **8** and **8b** may be considered as the conjugated bases of cyclopropylcarbinyl cations that could potentially trigger the domino process described above.

At this stage, we were confident that the regioselective protonation of the indenyl derivatives **8** and **8b** in the presence of acetonitrile would promote the cyclopropyl ring-opening/nitrilium ion ring-closing sequence.

Accordingly, treatment of **8** and **8b** with 1 equiv of TfOH in CH_3CN solution at room temperature yielded the desired cyclic imines **7** and **7b** as single geometric isomers. Photochemical studies are currently being undertaken on the iminium salts obtained by N-methylation of compounds **7** and **7b**.

With the aim of defining the spatial relationships throughout the new molecules, once again we resorted to NOE difference spectroscopy as outlined below (Fig. 4). For compound **7**, irradiation of the signal at δ=2.3 (the methyl at C-5 of pyrroline) showed a NOE to the hydrogens at the C-2′ carbon of the indane. In addition, irradiation of the signal at δ=7.4 (the hydrogen at C-7′ of indane) showed a NOE to the hydrogens at the C-3 carbon of the pyrroline ring. For compound **7b**, irradiation of the signal at δ=1.1 (the methyl at C-2′ of indane) showed a NOE to the methyl at C-5 of pyrroline and vice versa. Moreover, the hydrogen at C-2′ of indane showed NOE enhancements to the methyl at C-5 of pyrroline nucleus. The data collected for compounds **7** and **7b** support an *E* geometry that is opposite to that observed for compound **7a**.

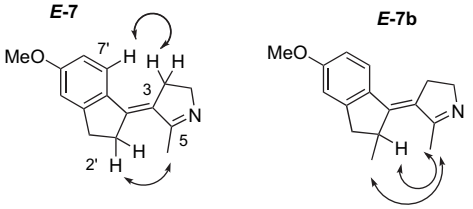


Figure 4.

Moreover, the presence of a stereogenic centre adjacent to the photoisomerizable carbon–carbon double bond in **7b** can induce a helical molecular framework, consistent with computational results previously reported by us.[8] Thus, the photoinduced isomerization of the iminium salt of **7b** may occur with control over the direction of rotation, as for Feringa's second generation light-driven molecular rotors.[6a] We were confident that compound **7b** may provide a precursor of a new class of single-molecule light-powered motors able to mimic rhodopsin both in terms of photoisomerization mechanism and unidirectionality of the rotation.

3. Conclusion

We described an intriguing sequential cyclopropyl ring-opening/nitrilium ion ring-closing reaction, which allowed for the development of a convenient synthesis of the conformationally locked molecular switches **PSB^{II}** featuring a polyene protonated Schiff base framework. The formation of compounds such as **7**, **7a** and **7b** is likely to involve a cyclopropylcarbinyl cation triggering the domino process. In particular, the electrophilic carbocations were produced via homoallylic rearrangement of the first formed intermediates, generated both by departure of triflate anion from a benzylic and tertiary carbon atoms or by regioselective protonation of 1*H*-indenyl derivatives (Scheme 3). The derived nitrilium ions eventually collapse into an internal olefin affording the required pyrroline heterocycles. The new structures constitute biomimetic light-driven *Z*/*E* molecular switches that promise to be an attractive alternative (e.g., with high polarity and reduced molecular size) to the widely used azobenzene switch. Moreover, the chiral compound **7b** constitutes the first example of a potential light-driven biomimetic single-molecule rotor whose $Z \rightarrow E$ and $E \rightarrow Z$ rotation directions are ultimately determined by the absolute configuration of the stereogenic centre at C-2′.

4. Experimental

4.1. General methods

Solvents were distilled prior to use, following standard procedures, and reactions were performed under nitrogen or argon atmosphere. Silica gel 60 F_{254} plates were used to monitor synthetic transformations, visualization being done under UV light or using 2% $KMnO_4$ solution. Organic solutions were dried over anhydrous magnesium sulfate and evaporated with a rotary evaporator. Chromatographic purifications were carried out using 70–230 mesh silica gel. Melting points were determined on a Büchi–Tottoli apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FTIR Paragon 500 spectrometer. Light petroleum refers to the fractions boiling in the range 40–60 °C and ether to diethyl ether. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Mercury Plus spectrometer at 400 MHz and 100 MHz, respectively. Chemical shifts (δ values) are given in parts per million downfield from tetramethylsilane as the internal standard. Elemental analyses were effected by the microanalytical laboratory of Dipartimento di Chimica, University of Ferrara.

4.1.1. 3-(3-Chloro-propyl)-6-methoxy-1*H*-indene (2-*endo*). To magnesium turnings (0.24 g, 9.8 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.8 mL, 9.8 mmol) in dry THF (5 mL) was added dropwise with mild reflux. After the addition was completed, a solution of **1** (0.8 g, 4.9 mmol) in dry THF (8 mL) was added dropwise and the mixture was heated at 60 °C for 3 h. Saturated NH_4Cl solution (20 mL) was added and the mixture was extracted with ether (3×20 mL). The organic phases were combined, dried and concentrated in vacuo. The crude residue was stirred with 15% HCl solution in acetic acid (10 mL) for 1 h at room temperature, then 10% NaOH was added until pH 8. The mixture was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were dried and evaporated. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether 3:7) to give **2**-*endo* (0.33 g, 30%) as a yellow oil. R_f (CH_2Cl_2/petroleum ether 3:7) 0.55; IR (film): ν 2954, 1742, 1606, 1492, 1255, 732 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.04–2.23 (2H, m, $CH_2CH_2CH_2Cl$), 2.67–2.78 (2H, m, $CH_2CH_2CH_2Cl$), 3.34 (2H, d, *J* 1.8 Hz, ArCH_2), 3.65 (2H, t, *J* 6.4 Hz, $CH_2CH_2CH_2Cl$), 3.87 (3H, s, *Me*O), 6.14 (1H, m, $ArCH_2CH$═), 6.90 (1H, dd, *J* 8.4, 2.4 Hz, Ar), 7.10 (1H, d, *J* 2.4 Hz, Ar), 7.29 (1H, d, *J* 8.4 Hz, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 30.87, 37.73, 44.8, 55.6, 110.4, 111.6, 119.1, 126.4, 138.2, 142.4, 146.3, 158.0. Anal. Calcd for $C_{13}H_{15}ClO$: C, 70.11; H, 6.79. Found: C, 70.14; H, 6.75.

4.1.2. 5-Methoxy-2,2-dimethyl-indan-1-one (1a). A solution of *t*-BuOK (3.4 g, 30.36 mmol) in *t*-BuOH (20 mL) was added dropwise to a cooled (0 °C) solution of **1** (1.5 g, 9.3 mmol) and methyl iodide (2.9 mL, 46.2 mmol) in ether (40 mL). The mixture was heated at reflux for 7 h, then water (10 mL) was added. The organic phase was separated, and the aqueous phase was extracted with ether (3×50 mL). After the combined organic phases were dried, the solvent was removed in vacuo. The residue was purified by column chromatography (ether/petroleum ether 3:7) to give **1a** (1.5 g, 85%) as a colourless oil. R_f (ether/petroleum ether 3:7) 0.41; IR (film): ν 2960, 2926, 1704, 1599, 1264, 1089 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (6H, s, Me_2C), 2.89 (2H, s, ArCH_2C), 3.81 (3H, s, *Me*O), 6.80–6.85 (2H, m, Ar), 7.62 (1H, d, *J* 8.4 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3 (2C), 42.9, 45.6, 55.6, 109.7, 115.4, 125.9, 128.4, 155.1, 165.4, 209.6. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.69; H, 7.47.

4.1.3. 1-Cyclopropyl-5-methoxy-2,2-dimethyl-indan-1-ol (3a). To magnesium turnings (0.2 g, 8.4 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.67 mL, 8.4 mmol) in dry THF (5 mL) was added dropwise with mild reflux. A solution of **1a** (0.8 g, 4.2 mmol) in dry THF (8 mL) was then added dropwise and the mixture heated at 60 °C for 3 h. Saturated NH_4Cl solution was added (20 mL) and the mixture was extracted with ether (3× 20 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography (ether/petroleum ether 3:7) to furnish **3a** (0.86 g, 88%) as a colourless oil. R_f (ether/petroleum ether 3:7) 0.39; IR (film): ν 3514, 2959, 2870, 1607, 1490, 1268, 1142, 1032, 808 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.10–0.20 (1H, m, cyclopropyl), 0.35–0.47 (3H, m, cyclopropyl), 1.04 (3H, s, MeC*Me*), 1.20 (3H, s, *Me*CMe), 1.53 (1H, s, cyclopropyl),

2.63 (1H, d, *J* 15.6 Hz, ArCH_aH_bC), 2.71 (1H, d, *J* 15.6 Hz, ArCH_aH_bC), 3.76 (3H, s, *Me*O), 6.70–6.72 (2H, m, Ar), 7.18–7.23 (1H, m, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ −0.5, −0.2, 15.3, 23.6, 23.7, 45.5, 48.5, 55.2, 83.0, 110.2, 111.7, 124.6, 138.8, 143.6, 159.7. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.60; H, 8.65.

4.1.4. 1-(3-Bromo-propyliden)-5-methoxy-2,2-dimethyl-indan (4a). A cooled (<10 °C) solution of 33% HBr in acetic acid (2.5 mL) and acetic acid (10 mL) was poured into a flask containing **3a** (0.45 g, 1.94 mmol) and stirring was continued for 10 min with ice bath cooling. After evaporation under reduced pressure, the residue was partitioned between H_2O (20 mL) and ether (20 mL). The aqueous phase was extracted with ether (3×20 mL), the combined organic extracts were dried and evaporated. The residue was purified by column chromatography (ether/petroleum ether 5:95) to afford **4a** (*Z*/*E* mixture, 0.45 g, 79%) as a yellow oil. R_f (ether/petroleum ether 5:95) 0.68; IR (film): ν 2956, 2836, 1604, 1487, 1308, 1263, 1034 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (isomeric ratio 3:1) 1.24 (6H, s, *Me*$_2$C, major), 1.39 (6H, s, *Me*$_2$C, minor), 2.81 (2H, s, Ar*CH*$_2$C, major), 2.84 (2H, s, Ar*CH*$_2$C, minor), 2.95 (2H, q, *J* 7.2 Hz, CH*CH*$_2$CH$_2$Br, minor), 3.03 (2H, q, *J* 7.2 Hz, CH*CH*$_2$CH$_2$Br, major), 3.45 (2H, t, *J* 7.2 Hz, CHCH$_2$*CH*$_2$Br, minor), 3.53 (2H, t, *J* 7.2 Hz, CHCH$_2$*CH*$_2$Br, major), 3.82 (3H, s, *Me*O, minor), 3.84 (3H, s, *Me*O, major), 5.30 (1H, t, *J* 7.2 Hz, C=*CH*CH$_2$-CH$_2$Br, major), 5.72 (1H, t, *J* 7.2 Hz, C=*CH*CH$_2$CH$_2$Br, minor), 6.74–6.85 (4H, m, Ar, major and minor), 7.32 (1H, d, *J* 8.6 Hz, Ar, minor), 7.48 (1H, d, *J* 9.2 Hz, Ar, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 29.4 (2C), 32.0, 32.6, 43.9, 46.9, 55.3, 110.3, 112.7, 115.1, 125.6, 132.4, 146.5, 151.80, 159.7. Anal. Calcd for $C_{15}H_{19}BrO$: C, 61.03; H, 6.49. Found: C, 61.08; H, 6.44.

4.1.5. 1-(3-Azido-propylidene)-5-methoxy-2,2-dimethyl-indan (5a). Sodium azide (1.66 g, 25.5 mmol) was added to a solution of **4a** (1.5 g, 5.1 mmol) in DMF (25 mL) and the mixture was heated at 60 °C for 2.5 h. After addition of water (100 mL), the solution was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were washed with water (100 mL), dried and evaporated. Purification of the residue by column chromatography (ether/petroleum ether 5:95) afforded **5a** (*Z*/*E* mixture, 1.25 g, 96%) as a yellow oil. R_f (ether/petroleum ether 5:95) 0.68; IR (film): ν 2957, 2096, 1604, 1487, 1464, 1262, 1034, 849 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (isomeric ratio 3:1) 1.21 (6H, s, *Me*$_2$C, major), 1.37 (6H, s, *Me*$_2$C, minor), 2.69 (2H, q, *J* 7.6 Hz, CH*CH*$_2$CH$_2$N$_3$, minor), 2.75 (2H, q, *J* 7.2 Hz, CH*CH*$_2$CH$_2$N$_3$, major), 2.78 (2H, s, Ar*CH*$_2$C, major), 2.85 (2H, s, Ar*CH*$_2$C, minor), 3.34–3.47 (4H, m, CHCH$_2$*CH*$_2$N$_3$, major and minor), 3.79 (3H, s, *Me*O, minor), 3.82 (3H, s, *Me*O, major), 5.25 (1H, t, *J* 7.2 Hz, C=*CH*CH$_2$CH$_2$N$_3$, major), 5.71 (1H, t, *J* 7.6 Hz, C=*CH*CH$_2$CH$_2$N$_3$, minor), 6.61–6.82 (4H, m, Ar, major and minor), 7.31 (1H, d, *J* 8.8 Hz, Ar, minor), 7.48 (1H, d, *J* 8.0 Hz, Ar, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 28.4, 29.4 (2C), 43.9, 47.0, 51.3, 55.3, 110.4, 112.6, 113.9, 125.7, 132.5, 146.5, 151.9, 159.7. Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.06; H, 7.40; N, 16.30.

4.1.6. *N*-[3-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-propyl]-acetamide (6a). A solution of **5a** (0.26 g, 1 mmol), NaOAc (0.11 g, 1.2 mmol) and Ac_2O (0.12 mL, 1.2 mmol) in EtOAc (20 mL) was stirred under 60 psi of hydrogen, in the presence of Lindlar catalyst (0.04 g), for 6 h at room temperature. The catalyst was removed by filtration and the filtrate was washed with water (15 mL) and brine (15 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to give **6a** (*Z*/*E* mixture, 0.23 g, 84%) as a yellow oil. R_f (EtOAc) 0.37; IR (film): ν 3290, 3084, 2956, 1651, 1487, 1262, 1033, 816 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ (isomeric ratio 3:1) 1.13 (6H, s, *Me*$_2$C, major), 1.30 (6H, s, *Me*$_2$C, minor), 1.91 (3H, s, *Me*C=O, major), 1.92 (3H, s, *Me*C=O, minor), 2.51 (2H, q, *J* 7.2 Hz, CH*CH*$_2$CH$_2$NHAc, minor), 2.59 (2H, q, *J* 7.2 Hz CH*CH*$_2$CH$_2$NHAc, major), 2.73 (2H, s, Ar*CH*$_2$C, major), 2.79 (2H, s, Ar*CH*$_2$C, minor), 3.31–3.42 (4H, m, CHCH$_2$*CH*$_2$NHAc, major and minor), 3.75 (3H, s, *Me*O, minor), 3.76 (3H, s, *Me*O, major), 5.17 (1H, t, *J* 7.2 Hz, C=*CH*CH$_2$CH$_2$NHAc, major), 5.64 (1H, t, *J* 7.2 Hz, C=*CH*CH$_2$CH$_2$NHAc, minor), 6.15 (2H, br, Ac*NH*, major and minor), 6.63–6.76 (4H, m, Ar, major and minor), 7.25 (1H, d, *J* 8.8 Hz, Ar, minor), 7.48 (1H, d, *J* 8.4 Hz, Ar, major); ^{13}C NMR (100 MHz, $CDCl_3$): δ (major isomer) 23.2, 29.3 (2C), 39.6, 43.8, 46.9, 49.3, 55.3, 110.1, 112.5, 114.9, 125.7, 132.6, 146.3, 151.5, 159.5, 170.4. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.72; H, 8.45; N, 5.08.

4.1.7. 4-(5-Methoxy-2,2-dimethyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2*H*-pyrrole (7a). *Pathway A* (step vi in Scheme 2): A trimethylsilyl polyphosphate (PPSE) solution, prepared by heating at reflux for 1.5 h a mixture of P_2O_5 (1.6 g, 11 mmol) and hexamethyldisiloxane (HMDSO, 3.3 mL, 15.4 mmol) in CCl_4 (15 mL), was added at room temperature to **6a** (0.3 g, 1.1 mmol). The reaction mixture was heated at reflux for 2 h, cooled to room temperature and quenched with water (5 mL). The organic phase was separated and washed with 10% HCl (2×30 mL). The combined aqueous layers were cooled to 0 °C, brought to pH 9 by treatment with 6 N NaOH solution, and extracted with CH_2Cl_2 (2×60 mL). The combined organic layers were washed with water (100 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/Et_3N 9:1:0.2) to give **7a** (92:8 *Z*/*E* mixture, 0.2 g, 71%) as a yellow oil.

Pathway B (step iii in Scheme 3): To a stirred solution of triflic anhydride (0.15 mL, 0.9 mmol) in CH_3CN (2 mL), a solution of **3a** (0.21 g, 0.9 mmol) in CH_3CN (1 mL) was added dropwise at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 3 h. The solution was washed with 10% NaOH (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography (EtOAc/MeOH/Et_3N 9:1:0.2) to afford **7a** (0.19 g, 83%) as a yellow oil.

Compound **7a**: R_f (EtOAc/MeOH/Et_3N 9:1:0.2) 0.32; IR (film): ν 1702, 1600, 1576, 1291 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (6H, s, *Me*$_2$C), 2.22 (3H, m, *Me*C=N), 2.77–2.80 (4H, m, *CH*$_2$CH$_2$N and Ar*CH*$_2$C), 3.82–3.84 (5H, m, *Me*O and CH$_2$*CH*$_2$N), 6.70 (1H, dd,

J 8.4, 2.0 Hz, Ar), 6.75 (1H, d, *J* 2.0 Hz, Ar), 7.20 (1H, d, *J* 8.4 Hz, Ar). A positive NOE between signal at δ 2.22 (methyl at C-5 of 3,4-dihydro-2*H*-pyrrole) and signal at δ 7.24 (H-7 on the aromatic ring) could be detected; ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.7, 25.1, 42.9, 49.0, 49.4, 55.5, 56.8, 109.9, 111.7, 126.1, 128.9, 131.4, 131.7, 148.0, 160.5, 174.6. Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.93; H, 8.22; N, 5.54.

4.1.8. 5-Methoxy-2-methyl-indan-1-one (1b). Aqueous formaldehyde solution 36% (5.5 mL, 68.6 mmol) was added dropwise over 5 h to a refluxing mixture of 4-methoxypropiophenone (2 g, 12.2 mmol) and morpholine (0.53 mL, 6.1 mmol) in glacial acetic acid (20 mL). The mixture was refluxed overnight, then acetic acid was stripped off under reduced pressure and the residue was diluted with EtOAc (30 mL). The organic layer was washed successively with 10% HCl (15 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL), and then dried. The solvent was evaporated in vacuo and the residue was used in the next step without further purification.

The crude product was poured slowly into concentrated H_2SO_4 (10 mL) and the solution heated at 60 °C for 1 h. After being cooled at room temperature, the mixture was poured into water (50 mL) and extracted with ether (3×50 mL). The organic layer was washed with 10% $NaHCO_3$, dried and evaporated. The residue was purified by column chromatography (ether/petroleum ether 2:8) to afford **1b** (1.3 g, 60%) as a white solid, mp 66–68 °C. R_f (ether/petroleum ether 2:8) 0.29; IR (KBr): ν 1701, 1595, 1253, 1086, 851 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.28 (3H, d, *J* 7.0 Hz, *Me*CH), 2.62–2.72 (2H, m, Ar*CH*$_2$), 3.27–3.40 (1H, m, Me*CH*), 3.87 (3H, s, *Me*O), 6.85–6.90 (2H, m, Ar), 7.67 (1H, d, *J* 8.8 Hz, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 16.6, 35.1, 42.2, 55.7, 109.7, 115.4, 125.7, 129.6, 156.5, 165.4, 207.8. Anal. Calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 74.93; H, 6.90.

4.1.9. 3-Cyclopropyl-6-methoxy-1*H*-indene (8) and 3-cyclopropyl-6-methoxy-2-methyl-1*H*-indene (8b). To magnesium turnings (0.23 g, 9.8 mmol) in dry THF (8 mL), a solution of cyclopropyl bromide (0.78 mL, 9.8 mmol) in dry THF (5 mL) was added dropwise with mild reflux. After the addition was completed, a solution of ketone **1** or **1b** (4.9 mmol) in dry THF (8 mL) was added dropwise and the mixture was heated at 60 °C for 3 h. Saturated NH_4Cl solution was added (20 mL) and the mixture was extracted with ether (3×20 mL). The combined organic solutions were dried and evaporated. The residue was purified by column chromatography (CH_2Cl_2/petroleum ether 3:7) to yield **8** or **8b**.

Compound **8**: white solid (0.72 g, 79%), mp 42–45 °C. R_f (CH_2Cl_2/petroleum ether 3:7) 0.68; IR (KBr): ν 3447, 2960, 1604, 1258, 1073, 1015, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63–0.69 (2H, m, cyclopropyl), 0.85–0.92 (2H, m, cyclopropyl), 1.78 (1H, m, cyclopropyl), 3.28 (2H, s, Ar*CH*$_2$CH═), 3.86 (3H, s, *Me*O), 5.91 (1H, m, ArCH$_2$*CH*═), 6.90 (1H, dd, *J* 8.4, 2.4 Hz, Ar), 7.07 (1H, d, *J* 2.4 Hz, Ar), 7.42 (1H, d, *J* 8.4 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 6.2 (2C), 8.5, 37.4, 55.6, 110.3, 111.6, 119.3, 123.0, 139.0, 146.2, 146.4, 157.9. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.87; H, 7.53.

8b: colourless oil (0.74 g, 76%). R_f (CH_2Cl_2/petroleum ether 3:7) 0.65; IR (film): ν 3000, 2906, 1478, 1266, 1037, 809 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.62–0.67 (2H, m, cyclopropyl), 0.83–0.89 (2H, m, cyclopropyl), 1.57–1.63 (1H, m, cyclopropyl), 2.12 (3H, s, *Me*C═), 3.22 (2H, s, Ar*CH*$_2$CMe), 3.82 (3H, s, *Me*O), 6.81 (1H dd, *J* 8.4, 2.6 Hz, Ar), 6.97 (1H, d, *J* 2.6 Hz, Ar), 7.28 (1H, d, *J* 8.4 Hz, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 4.4 (2C), 7.3, 14.5, 42.7, 55.7, 10.1, 111.3, 119.0, 136.4, 138.3, 140.3, 144.1, 157.1. Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.92; H, 8.11.

4.1.10. 4-(5-Methoxy-indan-1-ylidene)-5-methyl-3,4-dihydro-2*H*-pyrrole (7) and 4-(5-methoxy-2-methyl-indan-1-ylidene)-5-methyl-3,4-dihydro-2*H*-pyrrole (7b). To a stirred and cooled (0 °C) solution of triflic acid (115 μL, 1.3 mmol) in CH_3CN (2 mL), a solution of indene **8** or **8b** (1.3 mmol) in CH_3CN (1 mL) was added dropwise. The reaction mixture was slowly warmed to room temperature and stirring was continued for 3 h, before quenching with 10% NaOH (5 mL). The aqueous phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic phases were dried and concentrated in vacuo. The residue was purified by column chromatography (EtOAc containing 2% Et_3N) to give **7** or **7b**.

Compound **7**: brown solid (0.24 g, 81%), mp 58–60 °C. R_f (EtOAc containing 2% Et_3N) 0.33; IR (KBr): ν 3434, 2921, 1583, 1293, 1248, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (3H, m, *Me*C═N), 2.88–2.92 (2H, m, *CH*$_2$CH$_2$N), 3.01–3.07 (2H, m, Ar*CH*$_2$CH$_2$), 3.10–3.16 (2H, m, ArCH$_2$*CH*$_2$), 3.83 (3H, s, *Me*O), 3.91–3.99 (2H, m, CH$_2$*CH*$_2$N), 6.79 (1H, dd, *J* 8.4, 2.6 Hz, Ar), 6.84 (1H, d, *J* 2.6 Hz, Ar), 7.47 (1H, d, *J* 8.4 Hz, Ar); a positive NOE between signal at δ 2.37 (methyl at C-5 of pyrroline ring) and signal at δ 3.15 (hydrogens at C-2′ carbon of indane nucleus) was detected as well as between signal at δ 7.47 (hydrogen at C-7′ of indane nucleus) and signal at δ 2.91 (hydrogen at C-3 carbon of pyrroline ring). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 31.0, 31.1, 31.8, 55.5, 57.8, 109.9, 113.2, 1260, 135.1, 139.7, 147.3, 150.8, 160.4, 173.2. Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.21; H, 7.57; N, 6.21.

Compound **7b**: brown solid (0.10 g, 35%), mp 61–63 °C. R_f (EtOAc containing 2% Et_3N) 0.31; IR (KBr): ν 3390, 2930, 1600, 1583, 1486, 1249, 1031 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (3H, d, *J* 6.8 Hz, *Me*CH), 2.42 (3H, m, *Me*C═N), 2.56 (1H, d, *J* 16.0 Hz, Ar*CH*^{I}H^{II}), 2.79 (1H, ddd, *J* 3.2, 8.0, 16.8 Hz, *CH*^{I}H^{II}CH$_2$N), 2.99 (1H, ddd, *J* 3.2, 8.0, 16.8 Hz, CH^{I}*H*^{II}CH$_2$N), 3.19 (1H, dd, *J* 7.2, 16.0 Hz, ArCH^{I}*H*^{II}), 3.61–3.70 (1H, m, Me*CH*), 3.82 (3H, s, *Me*O), 3.84–3.89 (1H, m, CH$_2$*CH*^{I}H^{II}N), 3.95–4.47 (1H, m, CH$_2$CH^{I}*H*^{II}N), 6.80 (1H, dd, *J* 8.4, 2.6 Hz, Ar), 6.85 (1H, d, *J* 2.6 Hz, Ar), 7.45 (1H, d, *J* 8.4 Hz, Ar); a positive NOE between signal at δ 1.10 (methyl at C-2′ of indane nucleus) and signal at δ 2.56 (methyl at C-5 of pyrroline ring) was detected. ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.73, 23.96, 32.17, 36.88, 39.8, 55.4, 57.9, 110.6, 112.8, 126.5, 132.4, 133.9, 144.4, 148.5, 160.2, 171.9. Anal. Calcd for

$C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.60; H, 7.98; N, 5.84.

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References and notes

1. (a) *Structure & Bonding*; Amendola, V., Ed.; Springer: Berlin, 2001; Vol. 99; (b) Drexler, K. E. *Nanosystems: Molecular Machinery, Manufacturing and Computation*; John Wiley & Sons: New York, NY, 1992; (c) Balzani, V.; Credi, A.; Venturi, M. *Molecular Devices and Machines. A Journey into the Nanoworld*; Wiley-VCH: Weinheim, 2003.
2. (a) Shinkai, S.; Kusano, Y.; Manabe, O.; Nakaji, T.; Nishida, Y.; Ogawa, T. *J. Am. Chem. Soc.* **1980**, *102*, 5860; (b) Shinkai, S.; Minami, T.; Kusano, Y.; Manabe, O. *J. Am. Chem. Soc.* **1983**, *105*, 1851.
3. Jousselme, B.; Blanchard, P.; Gallego-Planas, N.; Delaunay, J.; Allain, M.; Richomme, P.; Levillain, E.; Roncali, J. *J. Am. Chem. Soc.* **2003**, *125*, 2888.
4. Cacciapaglia, R.; Stefano, S. D.; Mandolini, L. *J. Am. Chem. Soc.* **2003**, *125*, 2224.
5. (a) 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; (b) Ulysse, L.; Cubillos, J.; Chmielewski, J. *J. Am. Chem. Soc.* **1995**, *117*, 8466; (c) 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.
6. (a) Koumura, N.; Geertsema, E. M.; van Gelder, M. B.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2002**, *124*, 5037; (b) Koumura, N.; Zijistra, R. W. J.; van Delden, R. A.; Harada, N.; Feringa, B. L. *Nature* **1999**, *401*, 152; (c) Koumura, N.; Geertsema, E. M.; Meetsma, A.; Feringa, B. L. *J. Am. Chem. Soc.* **2000**, *122*, 12005; (d) Feringa, B. L. *Acc. Chem. Res.* **2001**, *34*, 504.
7. (a) Mathies, R. A.; Lugtenburg, J. *Handbook of Biological Physics*; Stavenga, D. G., de Grip, W. J., Pugh, E. N., Eds.; Elsevier Science B.V.: Amsterdam, 2000; Vol. 3, pp 56–90; (b) Kandori, H.; Shichida, Y.; Yoshizawa, T. *Biochemistry (Moscow)* **2001**, *66*, 1483; (c) Teller, D. C.; Okada, T.; Behnke, C. A.; Palczewski, K.; Stenkamp, R. E. *Biochemistry* **2001**, *40*, 7761.
8. Sampedro, D.; Migani, A.; Pepi, A.; Busi, E.; Basosi, R.; Latterini, L.; Elisei, F.; Fusi, S.; Ponticelli, F.; Zanirato, V.; Olivucci, M. *J. Am. Chem. Soc.* **2004**, *126*, 9349.
9. Lumento, F.; Zanirato, V.; Fusi, S.; Busi, E.; Latterini, L.; Elisei, F.; Sinicropi, A.; Andruniow, T.; Ferré, N.; Basosi, R.; Olivucci, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 414.
10. (a) Henninger, J.; Polborn, K.; Mayr, H. *J. Org. Chem.* **2000**, *65*, 3569; (b) Al-Talib, M.; Zaki, M.; Hehl, S.; Stumpf, R.; Fischer, H.; Jochims, J. C. *Synthesis* **1996**, 1115; (c) Jochims, J. C.; Glocker, M. O. *Chem. Ber.* **1990**, *123*, 1537.
11. Moustafa, A. H. *Synthesis* **2003**, 837 and references cited therein.
12. Shrestha-Dawadi, P. B.; Jochims, J. C. *Synthesis* **1993**, 426 and references cited therein.
13. (a) Bach, R. D.; Taaffee, T. H.; Rajan, S. J. *J. Org. Chem.* **1980**, *45*, 165; (b) Olah, G. A.; Gupta, B. G. B.; Narang, S. C. *Synthesis* **1979**, 274.
14. Gawley, R. E.; Termine, E. J. *J. Org. Chem.* **1984**, *49*, 1946.
15. Gawley, R. E.; Chemburkar, S. R. *Heterocycles* **1989**, *29*, 1283.
16. Marquart, A. L.; Podlogar, B. L.; Huber, E. W.; Demeter, D. A.; Peet, N. P.; Weintraub, H. J. R.; Angelastro, M. R. *J. Org. Chem.* **1994**, *59*, 2092.
17. Julia, M.; Julia, S.; Guégan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072.
18. Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Oliati, V.; Ghiglieri, A.; Govoni, S. *J. Med. Chem.* **1995**, *38*, 942.
19. Nishio, T.; Okuda, N.; Kashima, C. *Liebigs Ann.* **1996**, 117.
20. Chen, L.; Zhang, X.; Schultz, A. *Tetrahedron Lett.* **2002**, *43*, 4711.
21. Garcia Martinez, A.; Martinez Alvarez, R.; Teso Vilar, E.; Garcia Fraile, A.; Hanack, M.; Subramanian, L. R. *Tetrahedron Lett.* **1989**, *30*, 581.
22. Huang, J.-W.; Shi, M. *Synlett* **2004**, 2343.
23. (a) Siqueira Filho, E. P.; Rodrigues, J. A. R.; Moran, P. J. S. *Tetrahedron: Asymmetry* **2001**, *12*, 847; (b) Bhattacharya, A.; Segmuller, B.; Ybarra, A. *Synth. Commun.* **1996**, *26*, 1775.