New Molecular Entities via Intermolecular *meta* Photocycloaddition

Dennis Piet*[a], Serge de Bruijn[a], Jane Sum[b] and Gerrit Lodder[b]

[a]Specs, Julianalaan 136, 2628 BL Delft, The Netherlands
[b]Leiden University, Leiden Institute of Chemistry, Gorlaeus Laboratories, PO Box 9502, 2300 RA Leiden, The Netherlands

Received July 21, 2004

The intermolecular *meta* photocycloaddition of 1,3-dihydroisobenzofuran and 1,3-dihydroisoindole-2-carboxylic acid methyl ester with cyclopentene and 2,5-dihydrofuran affords two new classes of photoadducts. The photoadducts were identified by the SORT&gen algorithm as New Molecular Entities in two-dimensional scaffold space. The structures of the adducts were established by NMR spectroscopy and the stereo-, regio- and chemoselectivity of the reactions is discussed.

J. Heterocyclic Chem., **42**, 227 (2005).

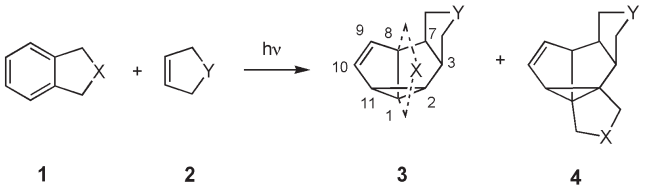
Introduction.

As part of our New Molecular Entities (NME) project the software program SORT&gen was introduced [1]. Using a set of descriptors SORT&gen makes it possible to define molecules in two-dimensional space on the basis of their scaffold ring constructions and the position of various functional groups and heteroatoms. When applied to the available literature databases this two-dimensional scaffold space appears to be remarkably empty. Based on the descriptors defining the empty spaces, all of the corresponding 'missing' scaffolds can be generated. This makes SORT&gen a valuable tool in the search for New Molecular Entities. The aim of the current research is to get from these virtual molecules to real molecules, preferably accessible in a limited number of steps. Out of the thousands of useful NME's we have identified two which serve as a proof of the SORT&gen concept and which are accessible in one single reaction step *i.e.*, the pentacyclo[6.3.0.0^{1,3}.0^{2,6}]tetradec-13-ene and the pentacyclo[6.3.0.0^{2,12}.0^{3,7}]tetradec-13-ene framework. Because the ultimate goal is to obtain novel drug-like molecules, at least one heteroatom must be part of the scaffold.

The *meta* photocycloaddition of benzenes to alkenes is an elegant method to construct, in one single reaction step, complex polycyclic ring systems. Numerous examples of both inter- and intramolecular *meta* photocycloaddition reactions are known [2]. Photochemical reactions of arenes with oxygen-containing alkenes such as 1,3-dioxole, dihydrofurans and -pyrans [3-8] are well documented to give *ortho*, *meta* and *para* adducts. Intramolecular photocycloaddition reactions of pent-4-enylbenzenes with an oxygen atom at the α-, β- or γ position of the side chain give mainly *meta* adducts [9-11]. Photochemical reactions of nitrogen containing arenes in which the nitrogen atom is part of the aromatic ring or adjacent to the ring do not result in *meta* addition but yield fragmentation, *ortho* [12] and/or *para* addition [13] and other 1:1-photoaddition products [13,14]. However, Blackmore and Gilbert reported the successful intramolecular *meta* photocycloaddition of 3-benzylazaprop-1-enes in which the nitrogen atom in the tether was protected with an electron-withdrawing acetyl or carbomethoxy group to give an azatriquinane as the major photoadduct [15,16]. The chemical yield was much larger with carbomethoxy than with acetyl as the N-protecting group.

As part of our NME-program we have investigated the photochemical reaction of 1,3-dihydroisobenzofuran (**1a**), 1,3-dihydroisoindole-2-carboxylic acid methyl ester (**1b**) and indane (**1c**) with 2,5-dihydrofuran (**2a**), 2,5-dihydropyrrole-1-carboxylic acid methyl ester (**2b**) and cyclopentene (**2c**) as shown in Scheme 1. The identity of the novel photoadducts was established and the regio- and chemoselectiviy of the reactions is discussed.

Scheme 1



1 **2** **3** **4**

1a: X = O **2a**: Y = O
1b: X = NCOOMe **2b**: Y = NCOOMe
1c: X = CH_2 **2c**: Y = CH_2

Table 1

Formation of Photoadducts **3** and **4** and their Product Distribution

Arene	Olefin	Adduct [a]
1a	**2a**	**3aa:4aa** (9:4)
1a	**2b**	---
1a	**2c**	**3ac:4ac** (9:4)
1b	**2a**	---
1b	**2b**	---
1b	**2c**	**3bc:4bc** (8:5)
1c	**2a**	---
1c	**2b**	---
1c	**2c**	---

[a] Ratios according to GC in the crude irradiation mixtures prior to workup.

Results and Discussion.

Irradiation of 1,3-dihydroisobenzofuran (**1a**) in acetonitrile in the presence of 2,5-dihydrofuran (**2a**) or cyclopentene (**2c**) at λ_{exc} = 254 nm for 76 h resulted in an about 65% conversion into two regioisomeric photoadducts, the propellane derivatives **3** and the tetraquinanes **4** with 35% of starting arene **1a** left. Under identical circumstances **1b** reacted with **2c** to ca 90% of the adducts **3** and **4** with less than 10% of **1b** remaining. In all cases more **3** than **4** is produced. All other arene-alkene combinations studied only yielded either trace amounts of photoproducts which could not be isolated nor identified or did not react at all. The formation of photoadducts **3** and **4** and their product distribution are summarised in Table 1. After evaporation of the solvent, the irradiation mixtures were taken up in ethylacetate and polymeric material was filtered off. The filtrates were evaporated and purified by preparative GC. The structures of the photoadducts were determined using NMR spectroscopy. The ^{1}H-NMR data of the relevant bridgehead protons of the photoadducts **3** and **4** are presented in Table 2.

Table 2

^{1}H-NMR data of Photoadducts **3** and **4**[a]

Adduct	H-2	H-3	H-7	H-8	H-9	H-10	H-11
3aa	1.84	3.30	3.39	---	5.63	5.88	1.95
3ac	1.81	3.04	3.14	---	5.62	5.81	1.86
4ac	---	2.62	3.56	2.81	5.69	5.76	1.96
3bc	1.80	3.03	3.12	---	5.62	5.75	1.85
4bc	---	2.85	3.71	3.00	5.74	5.80	1.87

[a] No conclusive spectroscopical data of **4aa** could be obtained.

Stereoselectivity.

Cyclic alkenes such as **1a-c** can be oriented towards the arene, when adding, yielding *endo*-adducts, or away from the arene, yielding *exo*-adducts [2,6]. The stereochemical orientation of the addends in the photoadducts **3** and **4** was established with NMR spectroscopy. The degree of coupling between vicinal protons can be predicted on the basis of the magnitude of the dihedral angles. This makes it possible to distinguish between the *endo* or *exo* configuration of the photoadducts. The dihedral angle between H2 and H3 in the PM3-optimised [17] structure of propellane **3** is ca 20° for the *endo* configuration and 110° for the *exo* configuration. The Karplus relation [18,19] predicts medium-sized coupling between H2 and H3 in the case of the *endo* adduct and a small or virtually absent one in the case of the *exo* adduct. The $J_{2,3}$-values of the propellane derivatives were found to be 6.5 Hz, 6.1 Hz and 6.6 Hz for **3aa**, **3ac** and **3bc**, respectively. Therefore photoadducts **3** were assigned the *endo* configuration. This assignment is supported by the chemical shift of H7. Comparison of the available ^{1}H NMR data on *endo* and *exo* adducts shows that this shift is a valuable tool to distinguish between both configurations. In *endo* adducts H7 is found between δ 2.90-3.50 while in *exo* adducts H7 resonates between δ 2.10-2.30 [11]. This profound up-field shift of H7 in *exo* adducts can be attributed to the shielding effect by the C9-C10 double bond [20,21]. The chemical shifts of H7 in the propellane derivatives **3** are all above δ 3.10 (Table 2).

In the case of the tetraquinane photoadducts **4** the dihedral angle between H7 and H8 was PM3-calculated to be ca 40° for the *endo* and ca. 85° for the *exo* configuration. The coupling between H7 and H8 in *exo*-adducts has indeed been shown to be too small to be determined [11]. The $J_{8,7}$-value of adduct **4ac** was found to be 5.9 Hz. Unfortunately the multiplicity of H8 in **4bc** could not be established as it appeared as a broadened singlet in the ^{1}H-NMR spectrum at δ 3.00. The position of H7 in **4bc** coincides with that of the carbomethoxy group thus obscuring its multiplicity. However, a relatively strong correlation between H7 and H8 is observed in the 2D-NOE spectrum of **4bc**. Therefore photoadducts **4** are also assigned the *endo* configuration. The low-field position of H7 of both **4ac** (δ 3.56) and **4bc** (δ 3.70) is consistent with this assignment.

The preferred formation of *endo* adducts has previously been observed in the irradiation of tetralin and xylenes in the presence of various alkenes [22-27]. The preference is the result of an intermolecular hyperconjugation between the allylic CH_2-groups of the alkene and the sp^2 carbon atoms of the aromatic ring [28]. This effect can only occur in the *endo* approach of the reagents despite the increased steric hindrance involved in this mode of addition.

Regioselectivity.

The ratio in which **3** and **4** are produced (~2:1) is similar to that of the *meta*-adducts of *o*-xylene and cyclopentene [22,29]. The preference for production of **3** over **4** is ascribed to the asymmetrical partitioning of complex **I**, formed between the S_1-state of the arene and the S_0-state of the olefin, into adducts **3** and **4** (Figure 1).

The major photoadduct **3** is the result of the formation of the three-membered ring between C1 and C5 while **4** is the result of a C1-C3 closure. The direction of the closure is affected by substituents at the arene [30]. Because there is a certain degree of charge transfer between the addends from the cycloalkene to the excited benzene an electron-accepting substituent at the site of the addition will promote bond formation at the carbon atom to which it is attached. That carbon atom (C2) will attain sp^3 character earlier than the other one (C6) and it will draw its neighbours closer together, thus promoting ring closure on this side. The

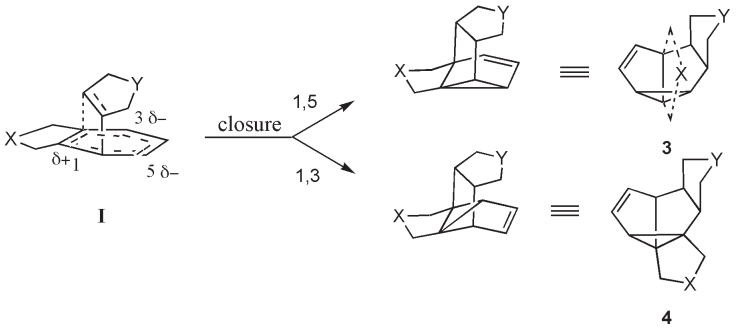


Figure 1

opposite will be true for electron-donating substituents at the arene. Since the $–CH_2XCH_2–$ substituent at the arene (X = O, N(COOMe)) is weakly electron donating [32], C2 will retain its sp^2 character longer, leading to preferred closure of the three-membered ring between C1 and C5 and thus to the preferred formation of **3**.

Chemoselectivity.

Although indane (**1c**) was been reported to undergo *meta* photocycloaddition with vinylacetate [32], it appears unreactive towards alkenes **2a-c**. Tetralin on the other hand, the next homologue of **1c**, has been reported to undergo *meta* photocycloaddition with **2c** [27]. The lower quantum yield of the reaction of tetralin with **2c** compared to the reaction of *o*-xylene with **2c** (ϕ = 0.01 and 0.08, respectively) indicates that an increase in ring strain leads to a decrease in quantum yield. The reluctance of the even more strained **1c** to react with cyclopentenes **2a-c** is in line with this observation. The non-reactivity of **1b** with **2a** remains unexplained at the moment.

Photoadducts were also not detected in the reaction of alkene **2b** with arenes **1a-c**. Efficient quenching of the fluorescence of aromatic compounds by carbamates has been reported by several groups [33,34]. The quenching presumably involves partial electron transfer away from the excited arene, a process that is known to be detrimental to the formation of *meta* photocycloadducts [22,35].

In conclusion, this work shows that new molecules with unique scaffolds can be synthesized in a quite limited number of steps. Thus, in a single reaction step the *meta* photocycloaddition reaction of functionalized indanes and cyclopentenes yields some new molecular entities (NME) which occupy an empty scaffold space as identified by the SORT&gen program. Our research towards the synthesis of NME's continues.

EXPERIMENTAL

The irradiations were carried out using spectroscopic grade acetonitrile as solvent in quartz vessels in a Rayonet Photochemical Reactor RPR 200 fitted with five 254 nm lamps, placed in a room cooled to 4 °C. The progress of the reactions was followed by GC. The analyses of the irradiation mixtures were performed on a Varian 3400 GC (CpSil-5, 25 m x 0.25 mm, d_f 0.40 μ, carrier gas H_2) equipped with a FID. Mass spectra were obtained on a HP 5890 GC with a HP5920 MS detector (DBX-4, 25 m x 0.25 mm, d_f 0.25 μ, carrier gas H_2). Accurate mass measurements were obtained on a VG-70SE mass spectrometer at 50 eV and 70 eV. Isolation by means of preparative gas chromatography was performed on an Intesmat model 120 (10% CP-sil-5, 25 m x 25 mm, carrier gas H_2). ^{1}H- and ^{13}C-NMR spectrometry was performed on a Varian VXR 400S operating at 400 MHz for ^{1}H-NMR and at 100 MHz for ^{13}C-NMR. All spectra were recorded in $CDCl_3$ with TMS as the internal standard.

Starting Materials.

Compounds **1a, 1c, 2a** and **2c** are commercially available (Acros) and were used without further purification.

1,3-Dihydroisoindole-2-carboxylic Acid Methyl Ester (**1b**).

To a suspension of 1,2-bis-bromomethylbenzene (5.00 g, 18.9 mmol) and NaH (60% in mineral oil, 1.65 g, 40.7 mmol) in 10 ml of dry dimethylformamide was added dropwise at 0 ºC a solution of methyl carbamate (1.25 g, 16.7 mmol) in 5 ml of dry dimethylformamide. The reaction mixture was stirred overnight at room temperature and poured on ice. The resulting precipitate was collected and purified by flash chromatography (silica gel, 3:1 petroleum ether (bp 40-60 ºC)/ethylacetate) to yield **1b** (1.46 g, 8.25 mmol, 49%) as light yellow crystals, mp 88-89 ºC (lit 89 ºC) [36]; ^{1}H-NMR δ 7.30 (m, 4H), 4.85 (d, 4H), 3.67 (s, 3H).

2,5-Dihydropyrrole-1-carboxylic Acid Methyl Ester (**2b**).

To a suspension of 2,5-dihydro-1*H*-pyrrole (1.00 g, 14.7 mmol) and potassium carbonate (4.02 g, 29.1 mmol) in 10 ml of water cooled to 0 °C was added dropwise methyl chloroformate (1.40 g, 14.8 mmol). The reaction mixture was stirred for 30 minutes at room temperature and extracted with 3 x 20 ml of ether. The combined organic layers were washed with 25 ml of brine, dried over magnesium sulfate and evaporated to yield **2b** (1.45 g, 11.4 mmol, 78%) as a colorless oil which solidified on standing, mp: 37-38 °C (lit. 37-39 °C) [37]; ^{1}H-NMR δ 5.82 (d, 2H), 4.11 (d, 4H), 3.67 (s, 3H).

Photoproducts.

Mixtures of 0.5 *M* of 1,3-dihydroisobenzofuran (**1a**) and 1.5 *M* of 2,5-dihydrofuran (**2a**), 0.5 *M* of 1,3-dihydroisobenzofuran (**1a**)

and 1.5 *M* of cyclopentene (**2c**) and of 0.5 *M* of 1,3-dihydroisoindole-2-carboxylic acid methyl ester (**1b**) and 1.5 *M* of cyclopentene (**2c**) were irradiated for 76 h followed by the removal of the solvent. Irradiation of **1a** in the presence of **2a** and **2c** resulted in a ca 65% conversion into the two photoadducts **3** and **4** in a 9:4 ratio with 35% of starting arene **1a** left. Under identical circumstances **1b** reacted with **2c** to ca 90% of the adducts **3** and **4** in an 8:5 ratio with less than 10% of **1b** remaining. The resulting mixtures were taken up in ethylacetate and polymeric material was filtered off. The filtrates were evaporated and purified by preparative GC.

6,10-Dioxapentacyclo[6.3.0^{1,3}.0^{2,6}]tetradec-13-ene (**3aa**).

The irradiation and purification procedure yielded 17 mg of **3aa** and 4 mg of a mixture of **3aa** and **4aa**. From the later mixture no conclusive spectroscopic data could be obtained. **Adduct 3aa** ^{1}H-NMR: ($CDCl_3$) δ 5.88 (dd, 1H, H-10, $J_{10,9}$ = 5.2 Hz, $J_{10,11}$ = 2.1 Hz), 5.63 (d, 1H, H-9, $J_{9,10}$ = 5.2 Hz), 4.19 (d, 1H, H-12, $J_{12,12'}$=9.1 Hz), 3.96 (d, 1H, H-13, $J_{13,13'}$ = 9.1 Hz), 3.92 (d, 1H, H-12', $J_{12',12}$ = 9.1Hz), 3.73 (dd, 1H, H-4, $J_{4,3}$ = 10.0 Hz, $J_{4,4'}$ = 8.1Hz), 3.72 (d, H1, H-6, $J_{6,6'}$ = 9.5 Hz), 3.60 (dd, 1H, H-4', $J_{4',4}$ = 8.1 Hz, $J_{4',3}$ = 6.2 Hz), 3.53 (dd, 1H, H-6', $J_{6',6}$ = 9.5 Hz, $J_{6',7}$ = 5.5 Hz), 3.49 (d, 1H, H-13', $J_{13',13}$ = 9.1 Hz), 3.39 (dd, 1H, H-7, $J_{7,3}$ = 10.0 Hz, $J_{7,6'}$ = 5.5 Hz), 3.30 (tt, 1H, H-3, $J_{3,4}$ = 10.0 Hz, $J_{3,7}$ = 10.0 Hz, $J_{3,2}$ = 6.2Hz, $J_{3,4'}$ = 6.2Hz), 1.95 (dd, 1H, H-11, $J_{11,2}$ = 6.5 Hz, $J_{11,10}$ = 2.1 Hz), 1.84 (broadened t, 1H, H-2, $J_{2,3}$ = 6.5 Hz, $J_{2,11}$ = 6.5 Hz). ^{13}C-NMR: δ 133.26 (d), 131.45 (d), 74.45 (t), 72,68 (s), 70.90 (t), 68.00 (t), 68.22 (d), 68.17 (t), 63.24 (s), 49.54 (d), 34.20 (d), 33.07 (d). MS (m/e): 190 (0), 142 (3), 131 (8), 130 (22), 129 (100), 128 (42), 117 (13), 115 (67), 92 (22), 91 (40), 77 (14). HRMS: Calcd. for 190.0994, found 190.0988.

10-Oxapentacyclo[6.3.0^{1,3}.0^{2,6}]tetradec-13-ene (**3ac**) and 3-Oxapentacyclo[6.3.0^{2,12}.0^{3,7}]tetradec-13-ene (**4ac**).

The irradiation and purification procedure yielded 22 mg of **3ac** and 16 mg of **4ac**, both as colourless oils. **Adduct 3ac** ^{1}H-NMR: ($CDCl_3$) δ 5.81 (dd, 1H, H-10, $J_{10,9}$ = 5.2 Hz, $J_{10,11}$ = 2.0 Hz), 5.62 (dd, 1H, H-9, $J_{9,10}$ = 5.2 Hz, $J_{9,11}$ = 0.7 Hz), 4.16 (d, 1H, H-12, $J_{12,12'}$ = 9.0 Hz), 3.89 (2d, 2H, H-12', H-13, $J_{12',12}$ = 9.0 Hz, $J_{13,13'}$ = 9.0 Hz), 3.51 (d, 1H, H-13', $J_{13',13}$ = 9.0 Hz), 3.14 (m, 1H, H-7), 3.04 (m as broadened dq, 1H, H-3, $J_{3,4}$ = 9.1 Hz, $J_{3,7}$ = 9.1 Hz, $J_{3,2}$ = 6.1 Hz, $J_{3,4'}$ = 6.1 Hz), 1.86 (dd, 1H, H-11, $J_{11,2}$ = 7.0 Hz, $J_{11,10}$ = 2.0 Hz), 1.81 (dd, 1H, H-2, $J_{2,11}$ = 7.0 Hz, $J_{2,3}$ = 6.1 Hz), 1.70-1.40 (m, 6H, H-4, H-5, H-6). ^{13}C-NMR: δ 134.76 (d), 132.76 (d), 75.24 (t), 73.00 (s), 69.30 (t), 66.35 (d), 63.22 (s), 51.55 (d), 36.02 (d), 33.61 (d), 30.50 (t), 29.82 (t), 25.97 (t). MS(m/e): 188 (15), 159 (11), 157 (13), 143 (14), 130 (36), 129 (100), 128 (39), 119 (16), 117 (18), 116 (23), 115 (56), 92 (34), 91 (55), 77 (18), 67 (15), 65 (16), 51 (14). HRMS: Calcd. for 188.1201, found: 188.1212. **Adduct 4ac** ^{1}H-NMR: ($CDCl_3$) δ 5.76 (ddd, 1H, H10, $J_{10,9}$ = 5.7 Hz, $J_{10,11}$ = 2.3 Hz, $J_{10,8}$ = 0.9 Hz), 5.69 (ddd, 1H, H-9, $J_{9,10}$ = 5.2 Hz, $J_{9,8}$ = 2.8 Hz, $J_{9,11}$ = 0.7 Hz), 4.12 (d, 1H, H-12, $J_{12,12'}$ = 7.9 Hz), 3.98 (d, 1H, H-13, $J_{13,13'}$ = 8.5 Hz), 3.89 (d, 1H, H-12', $J_{12',12}$ = 7.9 Hz), 3.72 (d, 1H, H-13', $J_{13'13}$ = 8.6 Hz), 3.56 (m, 1H, H-7), 2.81 (dd, 1H, H-8, $J_{8,7}$ = 5.9 Hz, $J_{8.9}$ = 2.8 Hz), 2.62 (ddd as q, 1H, H-3, $J_{3,7}$ = 9.6 Hz, $J_{3,4}$ = 9.6 Hz, $J_{3,4'}$ = 9.6 Hz), 1.96 (m, 1H, H-11), 1.70-1.40 (m, 6H, H-4, H-5, H-6). ^{13}C-NMR: δ 136.88 (d), 131.04 (d), 77.40 (t), 69.93 (d), 69.07 (t), 66.46 (s), 52,12 (d), 51.97 (d), 49.41 (s), 42.80 (d), 30.79 (t), 30.20 (t), 26.75 (t). MS(m/e): 188 (17), 158 (15), 157 (15), 143 (210, 142 (16), 130 (37), 129 (84), 128 (36), 119 (43), 117 (25), 115 (57), 92 (75), 91 (100), 78 (21), 77 (28), 68 (23), 65 (30). HRMS: Calcd. for 188.1201, found: 188.1200.

10-Azapentacyclo[6.3.0^{1,3}.0^{2,6}]tetradec-13-ene 10-Carboxylic Acid Methyl Ester (**3bc**) and 3-Azapentacyclo[6.3.0^{2,12}.0^{3,7}]-tetradec-13-ene 10-Carboxylic Acid Methyl Ester (**4bc**).

The irradiation and purification procedure yielded 19 mg of **3bc** and 7 mg of **4bc**, both as colourless oils. **Adduct 3bc** ^{1}H-NMR: ($CDCl_3$) δ 5.75 (dd, 1H, H-10, $J_{10,9}$ = 5.3 Hz, $J_{10,11}$ = 2.1 Hz), 5.62 (d, 1H, H-9, $J_{9,10}$ = 5.0 Hz), 3.88 (m, 1H, H-12), 3.65 (s, 3H, -CH_3), 3.60 (m, 2H, H-12', H-13), 3.20 (m, 1H, H-13'), 3.12 (m, 1H, H-7), 3.03 (m, 1H, H-3), 1.87 (m, 1H, H-4), 1.85 (m, 1H, H-11), 1.80 (broadened t, 1H, H-2, J = 6.6 Hz), 1.60-1.45 (m, 5H, H-4', H-5, H-6). ^{13}C-NMR [38]: δ 155.73 (s), 135.67/135.42 (2d), 131.84/131.81 (2d), 69.68/68.66 (2s), 67.94 (d), 60.62/59.81 (2s), 53.89/53.49 (2t), 52.34 (q), 50,69 (d), 48.27/47.88 (2t), 36.47 (d), 35.71 (d), 30.05 (t), 29.53 (t), 25.67 (t). MS (m/e): 245 (55), 230 (14), 216 (10), 176 (40), 162 (99), 158 (24), 157 (26), 156 (27), 143 (24), 129 (75), 128 (53), 118 (49), 117 (36), 116 (27), 115 (62), 102 (31), 91 (48), 77 (27), 67 (23), 59 (100). HRMS: Calcd. for 245.1416, found 245.1416. **Adduct 4bc** ^{1}H-NMR: δ 5.80 (dd, 1H, H-10, $J_{10,9}$ = 5.6 Hz, $J_{10,11}$ = 2.4 Hz), 5.74 (ddd, 1H, H-9, $J_{9,10}$ = 5.6 Hz, $J_{9,8}$ = 2.7 Hz, $J_{9,11}$ = 0.7 Hz) 3.90 (d, 1H, H-12. J=10.5Hz), 3.75-3.50 (m, 3H, H-7, H-12', H-13), 3.64 (s, 3H, -CH_3), 3.40 (d, 1H, H-13', $J_{13',13}$ = 11.0 Hz), 3.00 (broadened t, 1H, H-8), 2.85 (m, 1H, H-3), 1.90 (m, 1H, H-4), 1.87 (m, 1H, H-11), 1.65-1.50 (m, 5H). ^{13}C-NMR [38]: δ 155.34 (s), 136.41/136.34 (2d), 130.22/130.16 (2d), 68.56 (d), 63.17/62.35 (2s), 56.53/56.02 (2t), 53.31 (d), 52.94 (d), 52.22 (q), 49.23/48.73 (2t), 47.48/46.59 (2s), 43.74 (d), 30.12 (t), 29.49 (t), 25.97 (t). MS (m/e): 245 (30), 177 (17), 176 (51), 163 (10), 162 (100), 158 (19), 157 (14), 143 (12), 130 (21), 129 (42), 128 (27), 118 (39), 117 (30), 116 (18), 115 (36), 102 (10), 91 (36), 89 (11), 78 (11), 77 (18), 67 (16), 59 (72). HRMS: Calcd. for 245.1416, found 245.1418.

Acknowledgment.

We thank Dr. R.V.A. Orru and Mr. R. Schmitz of the Free University of Amsterdam, The Netherlands for their hospitality and help with the preparative GC. We also appreciate the fruitful discussions with Prof. Dr. J. Cornelisse of Leiden University.

REFERENCES AND NOTES

* Corresponding author. tel.: +31-15-2577930; fax: +31-15-2566090; e-mail: dennis.piet@specs.net

[1] A. De Laet, J. J. Hehenkamp and R. L. Wife, *J. Heterocyclic Chem*. **37**, 669 (2000).

[2] For comprehensive reviews see: [a] P. A. Wender, L. Siggel and J. M. Nuss, in Comprehensive Organic Synthesis, Vol **5**, B.M. Trost, I. Fleming and L. A. Paquette, eds. Pergamon, Elmsford, New York, 1991, pp 357-473; [b] J. Cornelisse, *Chem. Rev*. **93**, 615-669 (1993); [c] P. A. Wender and T. M. Dore, in Handbook of Organic Photochemistry and Photobiology; W. S. Horspool and P.-S. Son, eds. CRC Press Inc, Boca Raton, FL. 1995, pp 280-290; [d] N. Hoffmann, *Synthesis*, 481 (2004).

[3] R. J. Atkins, G. I. Fray, M. G. B. Drew, A. Gilbert and G. N. Taylor, *Tetrahedron Lett*. 2945 (1978).

[4] J. Mattay, H. Leismann and H.-D. Scharf, *Chem. Ber*., **112**. 577 (1979).

[5] J. Mattay, J. Runsink, H. Leismann and H.-D. Scharf,

Tetrahedron Lett., **23**, 4919 (1982).

[6] A. Gilbert, *Pure & Appl. Chem*., **52**, 2669 (1980).

[7] A. W. H. Jans, B. van Arkel, J. J. van Dijk-Knepper, H. Mioch and J. Cornelisse, *Tetrahedron*, **40**, 5071 (1984).

[8] A. Gilbert, G. N. Taylor, and M. W. bin Samsudin, *J. Chem. Soc., Perkin Trans. 1*, 869 (1980).

[9] A. Gilbert and G. N. Taylor, *J. Chem. Soc., Chem. Commun*., 229 (1979).

[10] A. Gilbert and G. N. Taylor., *J. Chem. Soc., Perkin Trans. 1*, 1761 (1980).

[11] E. M. Osselton, Ph.D. Thesis, Leiden (1987).

[12] J. Cornelisse and R. de Haan in Molecular and Supramolecular Photochemistry, Vol **8**, V. Ramamurthy and K. S. Schante, eds, Marcel Dekker: New York, 2001, pp 1-126.

[13] M. Bellas, D. Bryce-Smith, M. T. Clarke, A. Gilbert, G. Klunkin, S. Krestonosich, C. Manning and S. Wilson, *J. Chem. Soc., Perkin Trans 1*, 2571 (1977).

[14] A. Gilbert, S. Krestonosich and S. Wilson, *Tetrahedron Lett*., 4061 (1982).

[15] D. C. Blackmore and A. Gilbert, *Tetrahedron Lett*., **35**, 5267 (1994).

[16] D. C. Blackmore and A. Gilbert, *Tetrahedron Lett*., **36**, 2307 (1995).

[17] J. P. P. Steward, *J. Comput. Chem*., **10**, 209 (1989).

[18] M. Karplus, *J. Chem. Phys*., **30**, 15 (1959).

[19] M. Karplus, *J. Am. Chem. Soc*., **85**, 2870 (1963).

[20] J. A. Pople, *J. Chem. Phys*. **37**, 53 (1962).

[21] A. A. Bothner-By and J. A. Pople, *Ann. Rev. Phys. Chem*., 43 (1965).

[22] D. Bryce-Smith, A. Gilbert, B. Orger, and H. Tyrrell, *J. Chem. Soc., Chem. Commun.*, 334 (1974).

[23] J. Cornelisse, V. Y. Merritt and R. Srinivasan, *J. Am. Chem. Soc*. **95**, 6197 (1973).

[24] R. Srinivasan, *J. Am. Chem. Soc*. **93**, 3555 (1971).

[25] J. Cornelisse and R. Srinivasan, *Chem. Phys. Lett*. **20**, 278 (1973).

[26] D. Bryce-Smith, W. M. Dadson, A. Gilbert, B. H. Orger and H. M. Tyrrell, *Tetrahedron Lett*. 1093 (1978).

[27] C. S. Angadiyavar, J. Cornelisse, V. Y. Merritt and R. Srinivasan, *Tetrahedron Lett*., 4407 (1973).

[28] D. Bryce-Smith, M. G. B. Drew, G. A. Fenton and A. Gilbert, *J. Chem. Soc., Chem. Commun.*, 607 (1985).

[29] P. de Vaal, G. Lodder and J. Cornelisse, *J. Phys. Org. Chem*. **5**, 581 (1992).

[30] E. M. Osselton, E. S. Krijnen, E. L. M. Lempers and J. Cornelisse, *Recl. Trav. Chim. Pays-Bas*, **105**, 375 (1986).

[31] C. Hansch, A. Leo and R. W. Taft, *Chem. Rev*. **91**, 165 (1991).

[32] P. A. Wender and G. B. Dreyer, *J. Am. Chem. Soc*., **104**, 5805 (1982).

[33] F. Fang, S. Kanan, H. H. Patterson and C. S. Cronan, *Anal. Chim. Acta*, **373**, 139 (1998)

[34] A. Krebs, V. Ludwig, O. Boden, M. W. Göbel, *ChemBioChem*., **4**, 972 (2003)

[35] J. Mattay, *Tetrahedron*, **41**, 2405 (1985).

[36] R. Bonnett, S. A. North, R. F. Newton and D. I. C. Scopes, *Tetrahedron*, **39**, 1401 (1983).

[37] J. C. Lapierre Armande and U. K. Pandit, *Recl. Trav. Chim. Pays-Bas*, **99**, 87 (1980).

[38] It is worthy to note that *syn*/*anti* isomerism around the amide bond is observed in both photoadducts **3bc** and **4bc**. Especially in the ^{13}C-NMR spectra double resonances were observed for the vinylic carbons as well as the secondary and quaternary carbons of the pyrrolidine ring.