Tetrahedron 65 (2009) 765–770

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Stepwise insertion of carbenes into C–H bonds: the case of foiled carbenes☆

Jean-Luc Mieusset [a], Angelika Schrems [a], Michael Abraham [a], Vladimir B. Arion [b], Udo H. Brinker [a,*]

[a] Chair of Physical-Organic and Structural Chemistry, Faculty of Chemistry, University of Vienna, Währinger Strasse 38, A-1090 Vienna, Austria
[b] Institute of Inorganic Chemistry, Faculty of Chemistry, University of Vienna, Währinger Strasse 42, A-1090 Vienna, Austria

ARTICLE INFO

Article history:
Received 9 October 2008
Received in revised form 11 November 2008
Accepted 20 November 2008
Available online 27 November 2008

Keywords:
Carbenes
Oxadiazolines
DFT calculations
Reaction mechanisms

ABSTRACT

The reactivity of stabilized-nucleophilic carbene tricyclo[6.2.1.0^{2,7}]undec-9-en-11-ylidene (**9**) toward C–H insertions has been investigated. It is shown that **9** can only insert into acidic C–H bonds, for example, in malononitrile. In this case, evidence for a stepwise process has been obtained. Protonation of the carbene leads to an ion pair composed of a carbocation and a carbanion, which subsequently reacts and gives rise to the formal insertion product *anti* **10**.

1. Introduction

During the last years, we have reinvestigated the chemistry of foiled carbenes, which are species with a singlet ground state.[1] Foiled carbenes are 'systems where a stabilization is obtained by the inception of a facile carbene reaction which is foiled by the impossibility of attaining the final product geometry.'[2] We have especially concentrated our efforts on the norbonen-7-ylidene derivative tricyclo[6.2.1.0^{2,7}]undec-9-en-11-ylidene[3–5] (**9**) and focused on its intermolecular reactions in order to obtain experimental evidence for the strength of the intramolecular interactions between the double bond and the carbenic center. We have confirmed that the chemistry of **9** is dominated by its nucleophilic reactivity and that *anti* products are selectively formed. Carbene **9** is able to react with amines[3] and alcohols[4] under formal insertion into the N–H and the O–H bond, respectively. Carbenes are also especially well known for their cyclopropanation reactions. However, **9** was found to be able to only add to alkenes bearing electron-withdrawing groups like fumaronitrile and acrylonitrile.[5] In this work, we report our results about tricycloundecenylidene **9** concerning the signature reaction of carbenes, i.e., the insertion into C–H bonds.

2. Results and discussion

2.1. Insertion into methane

First of all, the reaction was investigated theoretically with methane and norbornenylidene **1** as model compound at the B3LYP/6-31G(d) level of theory. A special orientation is required with the hydrogen pointing toward the lone pair (LP) of the carbenic carbon and the carbon atom placed in the LP* (see Fig. 1, **TS1** and **TS2**).[6] A transition state for the reversed orientation (**TS3** and **TS4**, respectively) with the hydrogen interacting with the empty p-orbital and the carbon with the filled σ-orbital can also be located. However, the extremely high energy of more than 38 kcal/mol necessary to overcome this barrier confirms that this pathway is not meaningful. Interestingly, for the insertion into methane only a minor stereoselectivity is predicted: the barriers toward insertion are high and very similar (21.1 kcal/mol for **TS1** '*anti* to *anti*' vs 22.2 kcal/mol for **TS2** '*syn* to *syn*'). This can be explained by the poor ability of the carbon atom in methane to stabilize a negative charge. Therefore, the transition state is very late, the electron deficiency is quite low, and the bridge carbon atom has not the propensity anymore to interact with the double bond. Moreover, from a steric point of view, the *syn* approach would be preferred; thus reducing the energetic gap between the two transition states even more. However, these barriers are much higher than the barrier calculated for the rearrangement of norbornen-7-ylidene to bicyclo[3.2.0]-hepta-1,6-diene (11.0 kcal/mol).[1a] As a result, the carbene will react intramolecularly and it is not realistic to expect insertion of a foiled carbene into a C–H bond if this bond is not strongly activated.

☆ Carbene rearrangements. Part 76. For part 75 see: Mieusset, J.-L.; Abraham, M.; Brinker, U. H. *J. Am. Chem. Soc.* **2008**, *130*, 14634.

* Corresponding author. Tel.: +43 1 4277 52121; fax: +43 1 4277 52140.
E-mail address: udo.brinker@univie.ac.at (U.H. Brinker).

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doi:10.1016/j.tet.2008.11.063

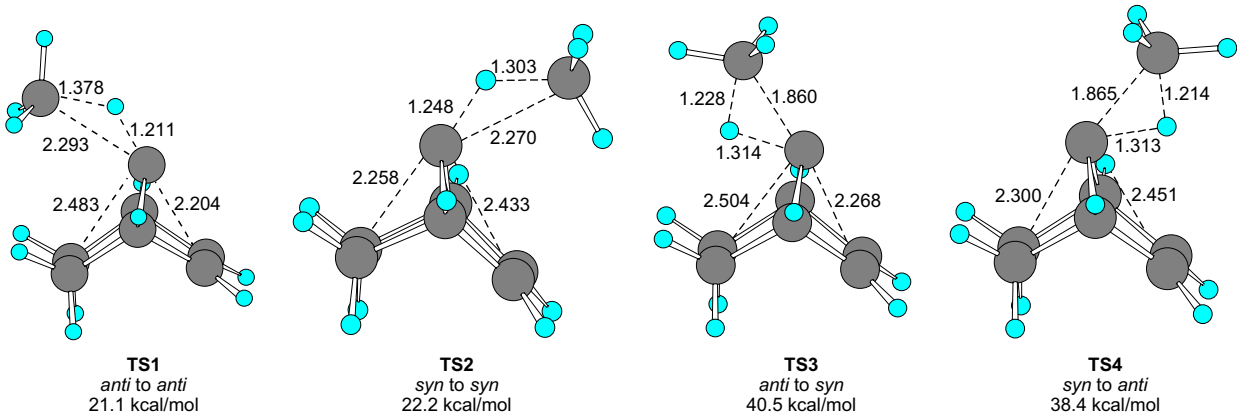


Figure 1. Geometries of the transition states for the insertion of norbornenylidene into methane.

Traditionally, activated bonds for reaction with carbenes are either found in secondary ethers, benzylic compounds, or tertiary hydrocarbons,[7] i.e., compounds with a high hydride transfer potential.[8] The carbon at the breaking C–H bond is then able to stabilize the rising positive charge by resonance. This is especially useful if the carbene is predominantly electrophilic. In fact, for norbornen-7-ylidene, insertion into the tertiary C–H bond of isobutane is only slightly easier: the barrier descends only to 18.9 kcal/mol.[9] This is still not low enough to perform the reaction. However, norbornen-7-ylidene is supposed to be predominantly nucleophilic and there would be a greater chance of success if organic compounds with a carbon atom able to stabilize a rising negative charge efficiently, i.e., a C–H acidic compound, would be used. Indeed, the calculated value for the insertion of norbornen-7-ylidene into acetonitrile (pK_a=31.3 in DMSO)[10] is already quite low (11.5 kcal/mol)[9] but experimentally, no insertion product could be obtained by us. Therefore, a double activation was deemed to be necessary.

With such compounds, a stepwise insertion in which the carbene is protonated and then the ion pair is recombining is quite likely. Indeed, malononitrile (pK_a=11.81 in water[11] and 11.1 in DMSO[10]) and dimethyl malonate (pK_a=13 in water and 15.9 in DMSO[12]) are more acidic than methanol (pK_a=15.54 in water[13] and 29 in DMSO[14]). It has already been shown that norbornenylidene reacts with methanol during solvolysis experiments by formation of the corresponding carbocation.[15]

2.2. Insertion into malononitrile

The results from the computations suggest that malononitrile is an efficient reaction partner for norbornenylidene. However,

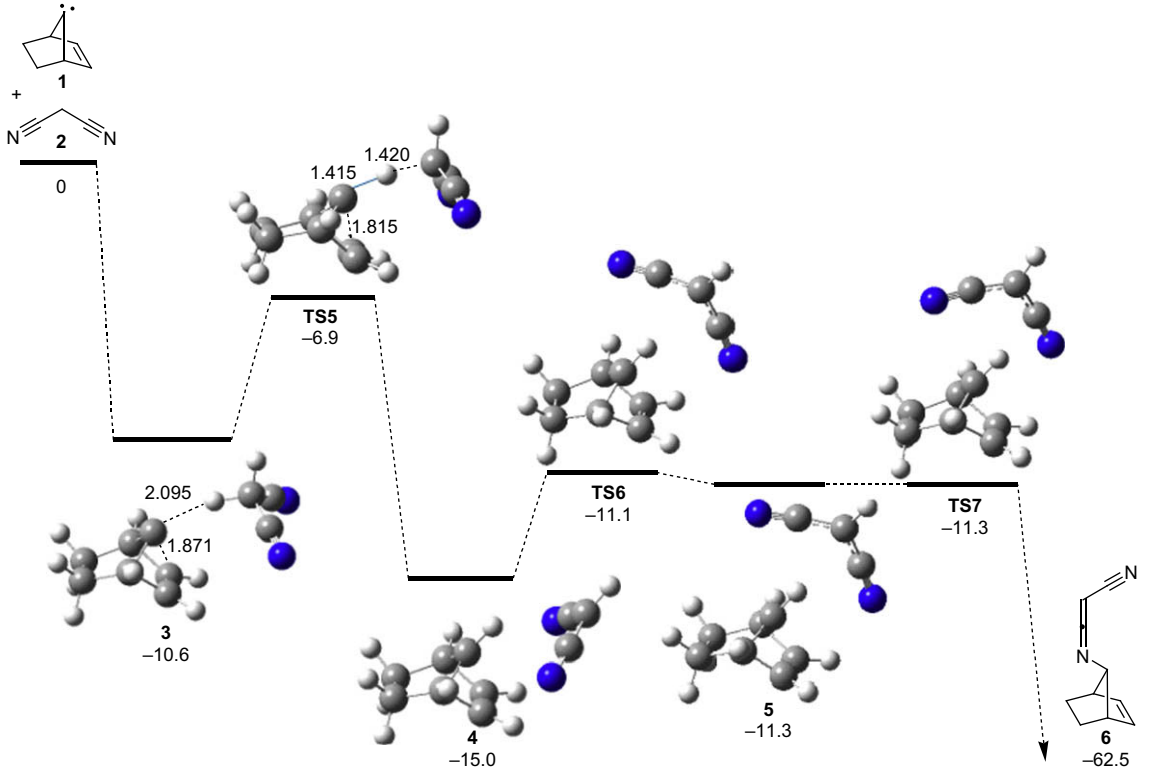
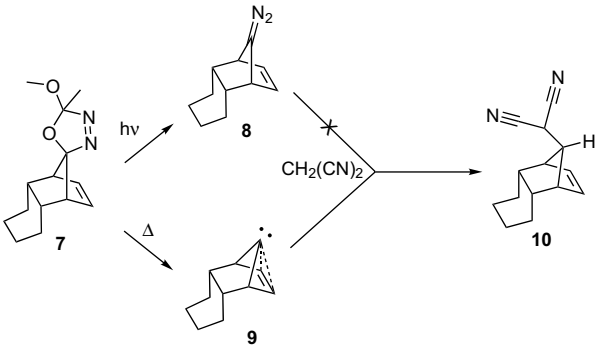


Figure 2. Energy diagram for the insertion of norbornen-7-ylidene (**1**) into malononitrile (**2**). Energies in kcal/mol and distances in angstrom.



Scheme 1. Decomposition of oxadiazoline **7** in malononitrile.

for the C–H insertion, no transition state corresponding to a concerted reaction can be found. Instead, protonation is favored (**TS5**, Fig. 2). All attempts to locate a transition state leading directly to the *anti* insertion product yielded a transition state corresponding to protonation of the carbene. Stepwise C–H insertion has already been postulated to describe the mechanism of the insertion reaction of stable *N*-heterocyclic carbenes.[9,16] The fact that a negative activation energy is found (−6.9 kcal/mol) suggests that this intermolecular reaction should be able to compete with the intramolecular decomposition of the carbene and that significant noncovalent interactions exist between the two reactants. Indeed, protonation is preceded by formation of complex **3** (ΔE=−10.6 kcal/mol, ΔG_{298}=−2.1 kcal/mol) in which the two molecules are hold together through a hydrogen bond and in which dipole–dipole interactions also play a significant role. At this point, it is worth to notice that by the modeling of the insertion of a carbene into the O–H bond of methanol, although solvolysis experiments have shown that the reaction occurs through protonation, the OH insertion is described as a concerted reaction in the gas phase probably because the rising negative charge remains located on the oxygen atom.[4] This is not the case during the insertion into the C–H bond of malononitrile: here, the negative charge is efficiently delocalized and calculations predict the formation of a contact ion pair (CIP) consisting of a carbocation and a carbanion,[17] structure **4**, which is already 15.0 kcal/mol more stable than the reactants. In solution, this strongly stabilized 7-norbornenyl cation is then trapped by another malononitrile anion leading to the formation of the *anti* product. Indeed, the 7-norbornenyl cation is known to show an excellent *anti* selectivity.[18] In order to get an idea about the stability of CIP **4**, we have continued the modeling of the reactivity of **4**. In the gas phase, these calculations lead to the prediction that imine **6** is formed by overcoming a barrier of 3.9 kcal/mol (**TS6**). However, this result shows only that a small but significant barrier exists toward the recombination of the ion pair because it is not very meaningful to model ionic reactions without explicit consideration of solvation. Indeed, the experimental results obtained by the thermal decomposition of oxadiazoline **7** in *p*-xylene in the presence of malononitrile show that no imine is produced. The sole volatile product was *anti*[19] dinitrile **10** (Scheme 1), which was obtained in 29% yield. The reaction has to be performed thermally in order to generate carbene **9** directly; photolytically, the corresponding diazo compound **8** is formed first and leads to different products.[4,20]

2.3. Reaction with esters

These results made us confident that insertion into other acidic bonds also should be possible. To further test the possibility of formation of a C–C bond, we took dimethyl malonate as a test compound with less acidic C–H bonds (pK_a=13 in water, 15.9 in DMSO[12]). Indeed, with this doubly activated compound, the reaction also proceeds stereospecifically to the *anti* compound **11** under photochemical and under thermal conditions as well. However, in the thermolysis, formation of monomethyl ester **12** also is observed. The monoactivated C(2)–H bond of methyl

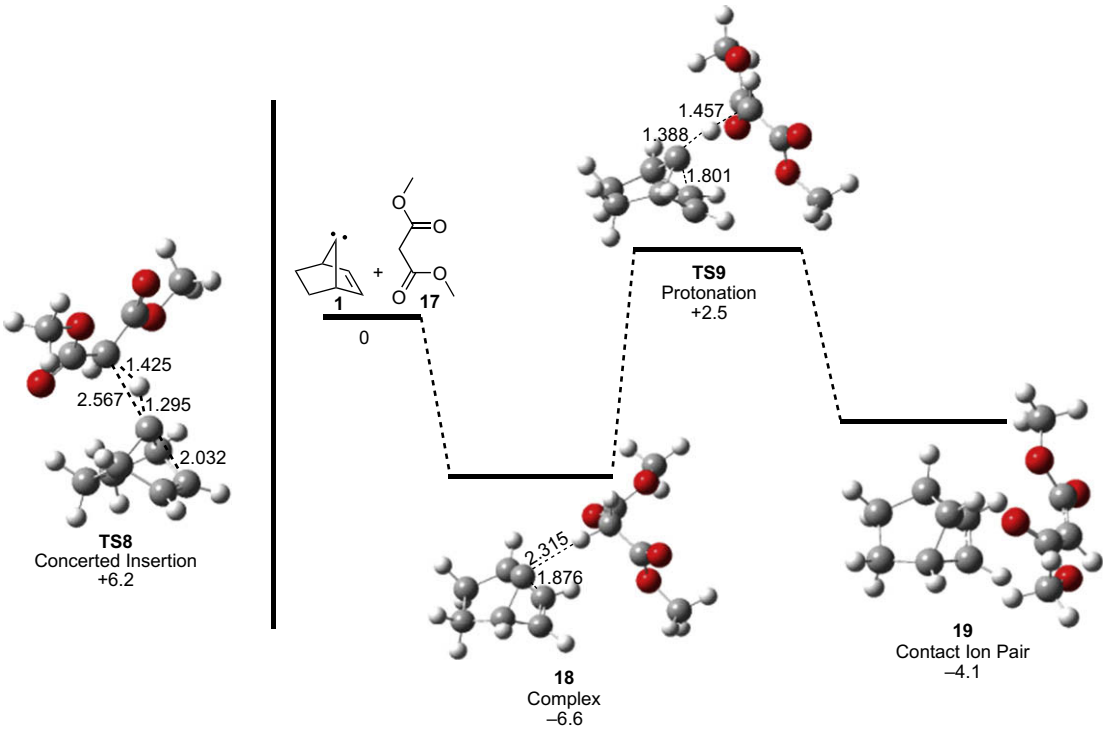
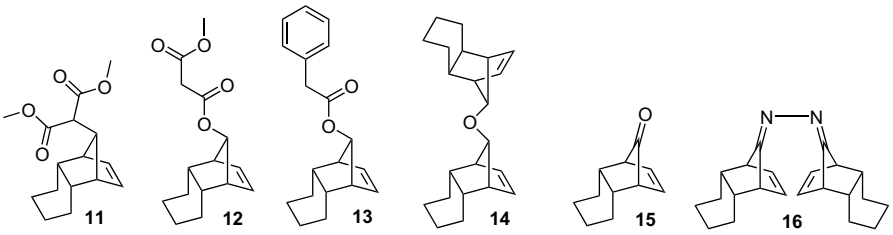


Figure 3. Energy diagram for the insertion of norbornen-7-ylidene into dimethyl malonate. Energies in kcal/mol and distances in angstrom.



phenylacetate with its larger pK_a (22.7 in DMSO for ethyl phenylacetate)[21] was already unreactive. Instead, only phenylacetate **13** was obtained. Also, in solvolysis experiments with ethyl acetate (pK_a=29.5 in DMSO),[22] no reaction with the solvent was observed. Instead, formation of ether **14** resulting from reaction with water traces was the sole intermolecular reaction that took place. In all experiments performed in this study, the reactions resulted in *anti*-substitution; azine formation was never observed. Its absence was confirmed by the synthesis of azine **16** starting from tricycloundecenone **15** and hydrazine hydrate.

2.4. Modeling of the insertion into esters

A picture similar to the insertion into malononitrile is obtained for the insertion reaction of norbornenylidene into the acidic C–H bonds of dimethyl malonate (Fig. 3). Here again, a stepwise process in which the carbene is first protonated (**TS9**, +2.5 kcal/mol) leading to the formation of an ion pair (**19**, −4.1 kcal/mol) is predicted. However, the values are already significantly higher and explain why only poor yields of product **11** (7%) are obtained. It is worth to notice that a transition state leading to the *anti* product (**TS8**) and corresponding to a conventional concerted insertion can be computed. However, with 6.2 kcal/mol (ΔG_{298}=18.3 kcal/mol), the calculated barrier is prohibitively high. Interestingly, the geometries of these transition structures are very different form the transition states of more classical carbene insertion reactions. The reactivity of most carbenes is dominated by their electrophilicity. Therefore, usually, their insertion is initiated by an approach of the empty p-orbital of the carbene to the σ-bond of the attacked C–H bond. This electrophilic phase is then followed by a nucleophilic phase to complete the insertion.[6c–e,23] In contrast, by the reaction between norbornenylidene and slightly acidic C–H bonds, the initial attack occurs from the filled carbene σ-orbital.

Finally, for the insertion into the slightly acidic C–H bond of methyl phenylacetate, a more classical result is obtained (Fig. 4). The reaction is modeled as a concerted process and formation of the *anti* product is unambiguously favored (+7.3 kcal/mol (**TS10**) vs +12.3 kcal/mol (**TS11**) for the formation of the *syn* product). However, the computed barriers are already very high for an alkyl carbene and intramolecular reactions should be preferred. This is in agreement with the experimental non-observation of this insertion.

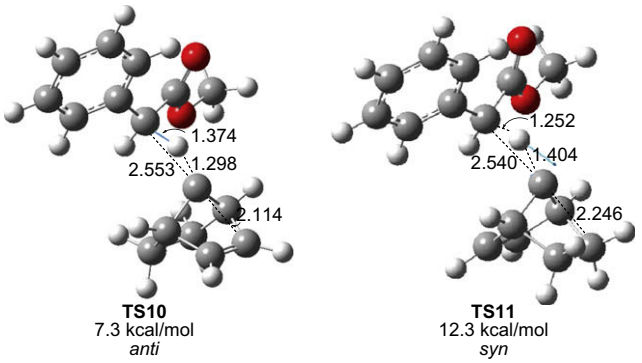


Figure 4. Transition states for the insertion of norbornen-7-ylidene (**1**) into methyl phenylacetate. Energies in kcal/mol and distances in angstrom.

3. Conclusion

We have shown that stabilized-nucleophilic carbene **9** is able to stereoselectively insert into acidic C–H bonds, although until very recently[3–5] foiled carbenes were known to be reluctant to undergo intermolecular reactions at all. Indeed, carbene **9** does not react with solvents like *p*-xylene or ethyl acetate; especially no insertion into the C–H bonds occurs. Moreover, evidence for one of the first stepwise mechanisms of a C–H insertion reaction of an alkyl carbene is presented.

3.1. Computational methods

The Gaussian 03 program[24] was used for density functional theory calculations, employing Becke's[25] three-parameter hybrid method, and the exchange functional of Lee, Yang and Parr (B3LYP).[26] Geometries were optimized at the B3LYP/6-31G(d) level of theory. The stationary points were characterized by vibrational analysis. All reported energies include zero-point corrections. The zero-point vibrational energies (ZPEs) were scaled by a factor of 0.9806 for B3LYP/6-31G(d).[27] The energies reported are results of gas phase calculations. Taking into account that charged species are involved as intermediates, the relative energies are strongly dependant on the reaction conditions and on the solvent. Therefore, the energetic values are purely indicative and should just be considered as a way to help the interpretation of the experimental results.

4. Experimental part

4.1. General experimental methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. The chemical shifts at δ=7.26 ppm and 77.0 ppm of $CHCl_3$ were used as internal standards for ^{1}H and ^{13}C spectra. Conventional 2D COSY, NOESY, HMBC, and HMQC spectra were used to derive proton and carbon assignments. Photolyses were performed using a Heraeus TQ 718 Z4 700-W medium-pressure Hg-arc lamp doped with FeI_2 (λ_{max}=370 nm) at T_{sample}=ca. 15 °C (water bath). The lamp was placed in a water-cooled jacket made of borosilicate glass, which essentially filtered out light below λ=300 nm. The reaction mixtures were placed in sealed flasks, submerged in a water bath, and argon was slowly bubbled in for 10 min before the photolysis was started. The samples were irradiated externally for 12 h, a time sufficient to decompose the oxadiazoline totally. After completion, the composition of the crude product was analyzed by GC–MS and NMR spectroscopy.

4.1.1. 2-(anti,endo-Tricyclo[6.2.1.0^{2,7}]undec-9-en-11-yl)-malononitrile (**10**)

Oxadiazoline **7**[3,4] (112 mg, 0.452 mmol) and malononitrile (60 mg, 0.903 mmol) were dissolved in 4 mL of *p*-xylene and stirred for 24 h at 170 °C in a pressure tube. After removal of the solvent under reduced pressure at 30 °C, the crude product was submitted to column chromatography with hexane/Et_2O 7:3. Yield: 28 mg (29%, 0.132 mmol). Mp 91–92 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.20 (t, J=2.0 Hz, 2H), 3.58 (d, J=11.7 Hz, 1H), 2.87 (br d, J=1.5 Hz, 2H), 2.32 (d, J=11.7 Hz, 1H), 1.84 (br d, J=8.6 Hz, 2H), 1.65 (br d, J=7.5 Hz, 2H), 1.50 (br d, J=14.1 Hz, 2H), 1.38–1.29 (m, 2H), 0.96–0.84 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.0, 112.1, 57.0, 47.6, 35.2, 22.6, 21.8, 19.9 ppm. IR 3065, 2984, 2937, 2867, 2256, 1463, 1450, 1370 cm^{-1}. MS (70 eV) *m*/*z* (%) 212 (M^+, 7), 147 (3), 130 (5), 91 (13), 86 (33), 84 (57), 82 (100), 67 (93), 65 (20). HRMS (70 eV) calculated for $C_{14}H_{16}N_2$ 212.1313, found 212.1315. See also the crystallographic data.[28]

4.1.2. Dimethyl 2-(anti,endo-tricyclo[6.2.1.0^{2,7}]undec-9-en-11-yl)-malonate (**11**)

Oxadiazoline **7**[3,4] (200 mg, 0.807 mmol) was dissolved in 10 mL of malonic acid dimethyl ester and photolyzed (λ >300 nm) overnight. After removal of the solvent under reduced pressure at 30 °C, the crude product was submitted to column chromatography first with hexane/isopropanol 39:1 and then with CH_2Cl_2. Yield: 16 mg (7%) oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (t, J=2.0 Hz, 2H), 3.72 (s, 6H), 3.41 (d, J=12.0 Hz, 1H), 2.60 (br s, 2H), 2.27 (d, J=12.0 Hz, 1H), 1.99–1.92 (m, 2H), 1.62–1.56 (m, 2H), 1.44–1.28 (m, 4H), 0.91–0.79 (m, 2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 136.3, 57.2, 52.4, 50.5, 48.2, 35.8, 23.1, 20.3 ppm. ^{1}H NMR (400 MHz, C_6D_6): δ 6.03 (s, 2H), 3.58 (d, J=11.9 Hz, 1H), 3.31 (s, 6H), 2.75 (s, 2H), 2.70 (d, J=11.9 Hz, 1H), 1.94–1.90 (m, 2H), 1.53–1.48 (m, 2H), 1.40–1.35 (m, 2H), 1.31–1.20 (m, 2H), 0.78–0.76 (m, 2H) ppm. ^{13}C NMR (100 MHz, C_6D_6): δ 169.2, 136.3, 57.2, 52.4, 50.5, 48.3, 35.7, 23.1, 20.2 ppm. IR 3061, 2938, 2864, 1744, 1461, 1437, 1410, 1361, 1332, 1274, 1201, 1152, 1028, 963, 940, 924, 901, 840, 788, 689 cm^{-1}. MS (70 eV) *m*/*z* (%) 247 (M^+−MeO, 2), 196 (100), 164 (4), 121 (12), 136 (78), 105 (26), 83 (97), 59 (19). HRMS (70 eV) calculated for $C_{16}H_{22}O_4$ 278.1518, found 278.1516.

4.1.3. Methyl anti,endo-tricyclo[6.2.1.0^{2,7}]undec-9-en-11-yl malonate (**12**)

Oxadiazoline **7**[3,4] (196 mg, 0.791 mmol) was dissolved in 20 mL of malonic acid dimethyl ester and stirred for 4 h at 150 °C. After removal of the solvent under reduced pressure at 30 °C, the crude product was submitted to column chromatography with hexane/Et_2O 5:1 to separate the ester from unreacted oxadiazoline and polymeric material. Yield: 26 mg (12%) oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.04 (t, J=2.2 Hz, 2H), 4.41 (t, J=1.9 Hz, 1H), 3.75 (s, 3H), 3.35 (s, 2H), 2.79–2.77 (m, 2H), 2.09–2.03 (m, 2H), 1.64–1.58 (m, 2H), 1.46–1.32 (4H), 0.98–0.84 (2H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 166.0, 133.4, 83.7, 52.4, 48.3, 41.6, 35.7, 22.3, 20.3 ppm. MS (70 eV) *m*/*z* (%) 264 (M^+, 1), 183 (6), 164 (11), 146 (100), 131 (14), 118 (14), 101 (52), 91 (40), 82 (92), 67 (32), 59 (28). HRMS (70 eV) calculated for $C_{15}H_{20}O_4$ 264.1362, found 264.1367.

4.1.4. Di(anti,endo-tricyclo[6.2.1.0^{2,7}]undec-9-en-11-yl)ether (**14**)

This product was obtained as the sole volatile product from the photolysis of oxadiazoline **7** in ethyl acetate after column chromatography with hexane. Yield: 8 mg (0.026 mmol, 6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.91 (t, J=2.0 Hz, 4H), 3.15 (t, J=2.0 Hz, 2H), 2.53–2.52 (m, 4H), 2.10–1.97 (m, 4H), 1.53–0.76 (m, 16H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.2, 89.1, 49.7, 36.5, 23.2, 20.9 ppm. IR 3136, 3056, 2934, 2862, 1655, 1570, 1460, 1333, 1243, 1198, 1074, 1056, 1039, 1023, 988, 965, 938, 922, 839 cm^{-1}. MS (70 eV) *m*/*z* (%) 310 (M^+, 0.3), 228 (2), 147 (100), 119 (23), 105 (16), 91 (51), 86 (52), 84 (78), 81 (28), 69 (20). HRMS (70 eV) calculated for $C_{22}H_{30}O$ 310.2297, found 310.2301.

4.1.5. 1,2-Bis(anti,endo-tricyclo[6.2.1.0^{2,7}]undec-9-en-11-ylidene)hydrazine (**16**)

Tricycloundecenone **15**[3,29] (250 mg, 1.54 mmol) and hydrazine hydrate (38.6 mg, 0.77 mmol) were refluxed for 3 h in 4 mL of ethanol. Removal of the solvent gave a crude product, which was recrystallized from methanol. Yield: 214.3 mg (0.67 mmol, 87%). Mp 182–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.40–6.33 (m, 2H), 6.30–6.23 (m, 2H), 3.60 (br s, 2H), 3.01 (t, J=3.3 Hz, 2H), 2.25–2.05 (m, 4H), 1.67–1.55 (m, 4H), 1.47–1.29 (m, 8H), 1.06–0.89 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 179.3, 134.4, 133.1, 133.0, 48.92, 48.90, 44.12, 44.08, 37.2, 37.1, 36.00, 35.98, 21.9, 21.8, 19.7 ppm. IR 2932, 2863, 1699, 1459 cm^{-1}. MS (70 eV) *m*/*z* (%) 320 (M^+, 8), 238 (4), 160 (34), 134 (79), 117 (19), 105 (29), 91 (100), 77 (41), 67 (43). HRMS (70 eV) calculated for $C_{22}H_{28}N_2$ 320.2252, found 320.2245.

Acknowledgements

Calculations were performed on the Schrödinger III cluster at the University of Vienna.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. Cartesian coordinates and energies for all relevant stationary points. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.11.063.

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