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Photochemical, Thermal, and Base-Induced Access to Hydroazulene Derivatives via Two-Carbon Ring-Enlargement Reactions of Condensed Electrophilic Cyclobutenes

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Enamines, silyl enol ethers, and β-keto ester anions derived from bicyclo[3.3.0]octan-2-one efficiently underwent a formal [2 + 2] cycloaddition reaction with DMAD and ethyl propynoate leading to a large variety of electrophilic cyclobutenes. The latter were transformed into polyfunctionalized bicyclo[5.3.0]decane (or hydroazulene) ring systems in high yields by fragmentation of the cyclobutene moiety. These two-carbon ring-enlargement reactions were utilized as a synthetic tool for the construction of a polyfunctionalized hydroazulene derivative that represents a potential precursor of the tricyclic framework of ingenol.

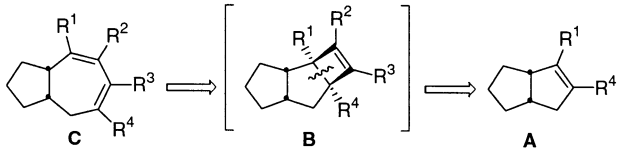
Introduction

Numerous new bioactive natural products present a bicyclo[5.3.0]decane (or hydroazulene) skeleton. To achieve the construction of such a skeleton, many synthetic pathways have been developed, but access to a bicyclo-[5.3.0]decane ring system via a two-carbon ring expansion of condensed electrophilic cyclobutenes has seldom been described.[1] In continuation of our interest in the synthesis and the reactivity of electrophilic cyclobutenes,[2] we report here the synthesis of polyfunctionalized bicyclo[5.3.0]-decane ring systems **C** via a two-carbon ring-enlargement reaction of cyclobutenes **B** prepared from diquinane derivatives **A** (Scheme 1).

Results and Discussion

Our first aim was to obtain electrophilic cyclobutenes condensed to a diquinane moiety and bearing at the ring junction either an amino group or a hydroxyl group. For that purpose, we started from the readily available bicyclo[3.3.0]octan-2-one **1**,[3] which was transformed into morpholino enamine **2**.[4] The enamine **2** reacted either with dimethyl acetylenedicarboxylate (DMAD) or with ethyl propynoate in dioxane, leading to the expected cyclobutene derivatives **3** and **4** in 80% and 77% yield, respectively (Scheme 2).[5]

SCHEME 1. Cyclobutene Pathway to a Hydroazulene Derivative



On the other hand, the trimethylsilyl enol ether **5** was prepared from diquinane **1** and was isolated as a mixture of the thermodynamic enol ether **5a** and the kinetic enol ether **5b** (ratio: 2/5).[6] A $ZrCl_4$-catalyzed [2 + 2] cycloaddition of the latter with ethyl propynoate led to three easily separable cyclobutene isomers **6**, **7**, and **8** isolated respectively in 24%, 42%, and 5% yield (Scheme 3).[2a] However, it should be noted that under the same conditions, the [2 + 2] cycloaddition with DMAD never led to

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(1) For a quite exhaustive review, see: Kantorowski, E. J.; Kurth, M. J. *Tetrahedron* **2000**, *56*, 4317−4353.

(2) (a) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett.* **1990**, *31*, 5027−5030. (b) Miesch, M.; Cotte, A.; Franck-Neumann, M. *Tetrahedron Lett.* **1994**, *35*, 7031−7032. (c) Miesch, M.; Mislin, G.; Franck-Neumann, M. *Synlett* **1996**, 385−386. (d) Miesch, M.; Mislin, G.; Franck-Neumann, M. *Tetrahedron Lett.* **1997**, *38*, 7551−7554. (e) Miesch, M.; Miesch-Gross, L.; Franck-Neumann, M. *Tetrahedron* **1997**, *53*, 2103-2110, (f) Mislin, G.; Miesch, M. *Eur. J. Org. Chem.* **2001**, 1753−1759. (g) Miesch, M.; Wendling, F. *Eur. J. Org. Chem.* **2000**, 3381−3392.

(3) Bicyclo[5.3.0]octan-2-one was prepared by transannular cyclization of commercially available cyclooctene oxide followed by an oxidation of the hydroxylated intermediate using Jones conditions. For the transcyclization reaction, see: Whitesell, J. K.; White, P. D. *Synthesis* **1975**, 602−603. For the Jones oxidation conditions, see: Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39−45.

(4) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkowicz, J.; Terrel, R. *J. Am. Chem. Soc.* **1963**, *85*, 207−222.

(5) (a) Brannock, K. C. Enamine Symposium. 140th National Meeting of the American Chemical Society; Chicago, IL, September 1961. (b) Huebner, C. F.; Donoghue, E. *J. Org. Chem.* **1963**, *28*, 1732. (c) Huebner, C. F.; Dorfman, L.; Robison, M. M.; Donoghue, E.; Pierson, W. G.; Strachan, P. *J. Org. Chem.* **1963**, *28*, 3134−3140. (d) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1464−1468. (e) Berchtold, G. A.; Uhlig, G.F. *J. Org. Chem.* **1963**, *28*, 1459−1462. (f) Brannock, K. C.; Burpitt, R. D.; Goodlett, V. W.; Thweatt, J. G. *J. Org. Chem.* **1964**, *29*, 818−823.

(6) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Götz, A.; West, W.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krägeloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 3−26.

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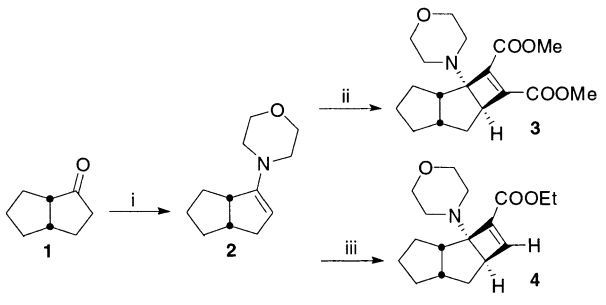
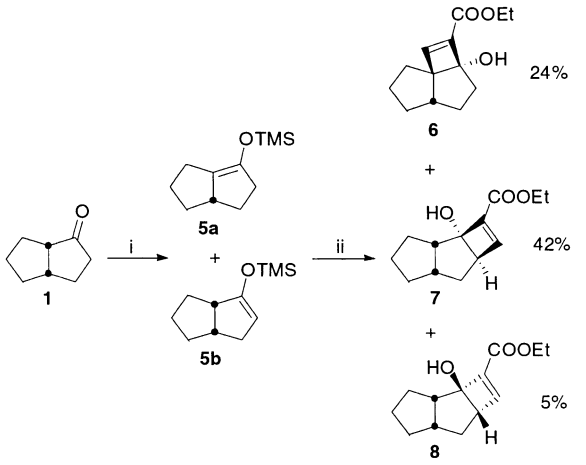
SCHEME 2. Synthesis of Cyclobutenes 3 and 4



i : morpholine, PTSA, Dean-Stark, toluene (yield : 82%).
ii : DMAD, dioxane reflux to 20°C (yield : 80%)
iii : ethyl propynoate, dioxane reflux to 20°C (yield : 77%).

SCHEME 3. Synthesis of Cyclobutenes 6−8



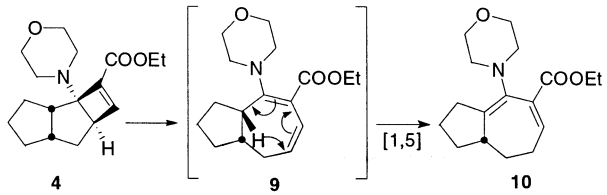
i : TMSOTf, NEt_3, CH_2Cl_2 reflux (yield : quant.)
ii : $ZrCl_4$, ethyl propynoate, CH_2Cl_2/Et_2O, 20°C (yield : 71%)

the desired cyclobutene adduct but only to a complex mixture of compounds.

Having these different cyclobutenes in hand, the behavior of the aminocyclobutene **4** was investigated under thermal conditions. Indeed, Brannock et al. reported that cyclobutene amino esters could undergo a thermally induced two-carbon ring-expansion reaction.[5] This methodology was successfully applied by Magnusson and Froborg for the total synthesis of velleral.[7]

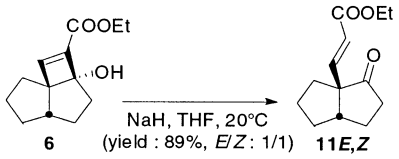
Unfortunately, in our hands, the cyclobutene **4**, heated in refluxing xylene, did not lead to the expected ring-enlargement product **9** but to the hydroazulene derivative **10** isolated in only 35% yield.[8] Compound **10** arose from a [1,5] sigmatropic proton-shift of the primary ring-expansion product **9** (Scheme 4). This result proved to be in agreement with those of Reinhoudt et al.[9] for related compounds. When the cyclobutene **3** was treated

SCHEME 4. Thermal Ring Enlargement of Cyclobutene 4

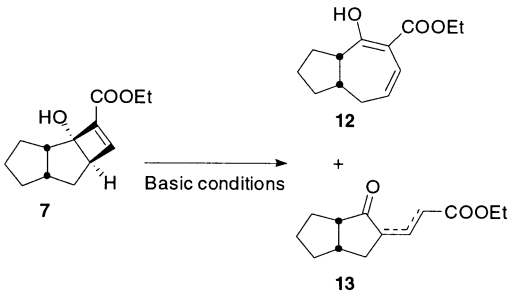


xylene reflux (yield : 35%)

SCHEME 5. Base-Induced Fragmentation of Cyclobutene 6



SCHEME 6. Base-Induced Ring Opening of Cyclobutene Hydroxy Ester 7



under the same thermal conditions, a complex mixture of compounds was obtained.

With this route being not very efficient for the synthesis of hydroazulene derivatives, we next turned our attention to the base-induced two-carbon ring expansion of cyclobutenes **6** and **7**.[10] When the hydroxy ester **6** was treated with NaH in THF, we did not observe the formation of a two-carbon ring-expansion product. Instead, product **11**, resulting from base-induced fragmentation, was isolated in 89% yield (Scheme 5).

However, when the hydroxy ester **7** was reacted with NaH in THF, the ring-expansion product **12** was isolated as a minor product along with the product **13** as major compound (complex mixture of isomers). If dimethoxyethane (DME) was used as solvent, the yield of compound **12** decreased.[10] When LiHMDS was used as a base, only the ring-expansion product **12** was isolated in 30% yield. On the contrary, product **13** (complex mixture of isomers) was isolated quantitatively when compound **7** was submitted to treatment with *t*-BuOK in *t*-BuOH (Scheme 6, Table 1). [11]

Thus, we observed that the thermal ring expansion of condensed cyclobutenes bearing an amino group at the ring junction as well as the base treatment of condensed cyclobutenes bearing a hydroxy group at the ring junction led only to the hydroazulene derivatives **10** and **12** in poor yields.

(7) (a) Fex., T.; Froborg, J.; Magnusson, G.; Thorèn, S. *J. Org. Chem.* **1976**, *41*, 3518−3520. (b) Froborg, J.; Magnusson, G. *J. Am. Chem. Soc.* **1978**, *100*, 6728−6733.

(8) Lakodey, A. Thèse de Doctorat de l'Université Louis Pasteur de Strasbourg, 1992. These results are in good accordance with those previously reported on related compounds by Dehmlow et al.: Dehmlow, E. V.; Heitkamp, T.; Sielemann, D. *Eur. J. Org. Chem.* **1999**, 3135−3138.

(9) (a) Reinhoudt, D. N.; Verboom, W.; Visser, G. W.; Trompenaars, W. P.; Harkema, S.; Van Hummel, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 1341−1350. (b) Vos, G. J. M.; Benders, P. H.; Reinhoudt, D. N.; Egberink, R. J. M.; Harkema, S.; Van Hummel, G. J. *J. Org. Chem.* **1986**, *51*, 2004−2011.

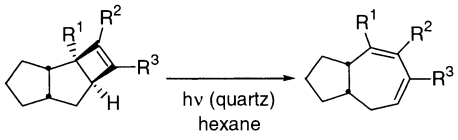
(10) (a) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 248−253. (b) Clark, R. D.; Untch, K. G. *J. Org. Chem.* **1979**, *44*, 253−255.

(11) Hydroxy ester **10** was formed in low yield and therefore was not submitted to the base-induced ring-enlargement reaction.

TABLE 1. Base Treatment of Hydroxy Ester 7

	% yield	
basic conditions	**12**	**13**
LiHMDS, THF, 78°C	30	
NaH, THF, 20°C	11	58
NaH, DME, 20°C	6	72
tBuOK/tBuOH, 30°C		100

SCHEME 7. Photoinduced Ring Enlargement of Cyclobutenes



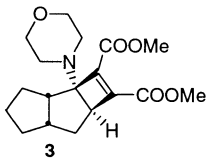
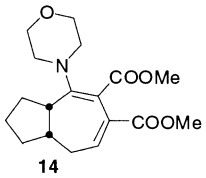
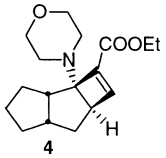
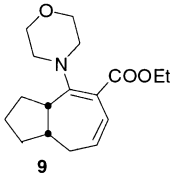
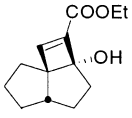
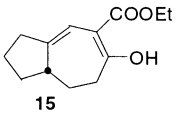
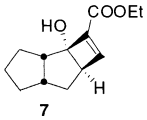
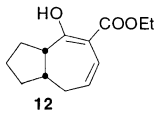
R^1 = morpholino-, hydroxy-, R^2 = COOMe, COOEt
R^3 = COOMe, H

These results and the fact that the photochemical ring opening of cyclobutenes is well-precedented[12] prompted us to explore the photolysis of the cyclobutenes **3**, **4**, **6**, and **7**. To the best of our knowledge, the photolytic ring opening of cyclobutenes condensed to the diquinane moiety has seldom been used as a synthetic approach to hydroazulene skeletons.[13] Our first experiments were performed in a Pyrex photoreactor with a medium-pressure Hg lamp (125 W). Under these conditions, neither the aminocyclobutenes **3** and **4** nor the hydroxycyclobutenes **6** and **7** led to the expected ring-enlargement products, even after long irradiation times: the starting materials were always recovered. The failure of this photolysis reaction could be explained as follows: the photoloysis of compound **3** through Pyrex produces a charge transfer excited state that simply undergoes rapid back-electron-transfer, regenerating the reactant and, consequently, no reaction was observed.[14] However, when the photolysis was carried out in a quartz apparatus using the same light source, cyclobutenes **3**, **4**, **6**, and **7** led to the expected ring-enlargement products **14**, **9**, **15**, and **12** isolated respectively in 90%, 90%, 90%, and 75% yield (Scheme 7, Table 2).

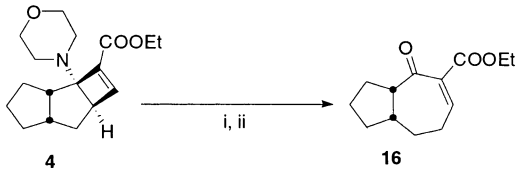
In the case of the photoinduced ring enlargement of hydroxycyclobutene **8**, the photolysis lamp was plugged to a power supply of 150 V. In fact, we observed that under these reaction conditions, the formation of side products could be reduced if a longer irradiation time was used. It should also be noted that the ring-enlargement product **9** is unstable and rapidly led to a complex mixture. To overcome this problem, the crude photolysis reaction mixture was immediately hydrolyzed (HCl 10%; THF) to give β-keto ester **16** isolated in 63% overall yield (Scheme 8).

Another possibility to promote a two-carbon ring-enlargement reaction is the reaction of an acetylenic ester (DMAD or ethyl propynoate) with enolates of cycloalkanones bearing an electron-withdrawing group on the β position. Examples were previously described in the literature with β-keto phosphonates,[15] β-keto sulfonium ylides,[16] or β-keto esters.[2c,17] For further synthetic convenience, we decided to investigate two-carbon ring-enlargement reactions of β-keto esters derived from

TABLE 2. Photolysis of Electrophilic Cyclobutenes 3, 4, 6, and 7

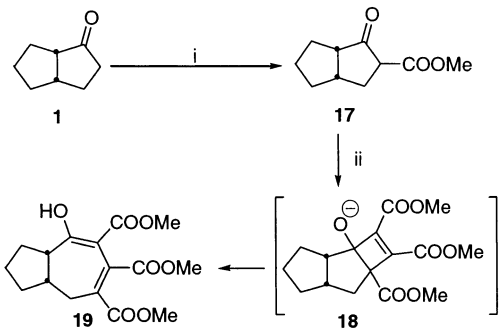
Starting material	λ_{max} (ε)	Photolysis time	Product	Yields (%)
 **3**	330 nm (1000) 220 nm (7000)	20 min	 **14**	90
 **4**	286 nm (1000) 218 nm (6400)	10 min	 **9**	90
 **6**	218 nm (6300)	5 min	 **15**	90
 **7**	213 nm (6400)	240 min	 **12**	75

SCHEME 8. Photolytic Cleavage of Cyclobutene 4 and Acidic Hydrolysis



i : hν (quartz), hexane, 20°C.
ii : HCl_{aq} 10%, THF, 20°C (overall yield : 63%)

SCHEME 9. Synthesis of Triester 19

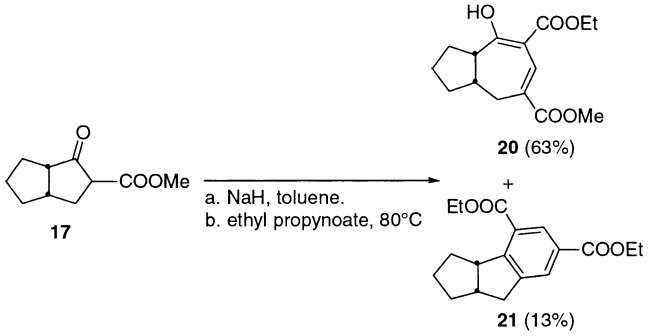


i : $CH_3OCOOCH_3$, NaH, MeOH cat., 60°C (yield : 91%).
ii : a. NaH, toluene. b. DMAD, 20°C (yield : 73%).

bicyclo[3.3.0]octan-2-one **1**. Thus, the β-keto ester **17** was prepared in 91% yield by heating ketone **1** with sodium hydride in neat dimethyl carbonate in the presence of a catalytic amount of methanol. Compound **17**, added to a suspension of NaH in toluene, generated the corresponding sodium enolate, which reacted at room temperature with DMAD, leading presumably to the cyclobutene intermediate **18**, which has never been isolated via a probable Michael-initiated ring-closure (MIRC) reaction.[18] The bridgehead electron-withdrawing group induced the fragmentation of the cyclobutene moiety to generate the corresponding two-carbon ring-enlargement compound. Thus, hydroazulene triester **19** was isolated in 73% yield (Scheme 9).

On the other hand, the sodium enolate of keto ester **17** reacted with ethyl propynoate, leading to the expected ring-enlargement compound **20** and more surprisingly to the aromatic diester **21**. The formation of the latter could be explained by a MiMiRC (Michael−Michael ring closure)[19] type reaction followed by an intramolecular lactonization. The decarboxylation of the resulting four-membered ring lactone led to the aromatic compound **21**. Modification of ethyl propynoate stoichiometry did not improve the **20**/**21** ratio, but surprisingly, we observed that an increase of the reaction temperature promoted the formation of ring-enlargement product **20**. Best results were obtained when ethyl propynoate was added to the sodium enolate of keto ester **17** at 80 °C. At this temperature, compounds **20** and **21** were isolated respectively in 63% and 13% yield. (Scheme 10). Along with ethyl propynoate and DMAD, other electrophilic acetylenes—ethynyl methyl ketone and ethyl phenyl propynoate—were tested, but in each case, the ring-enlargement reaction led only to complex mixtures.

SCHEME 10. Synthesis of Hydroazulene Diester 20



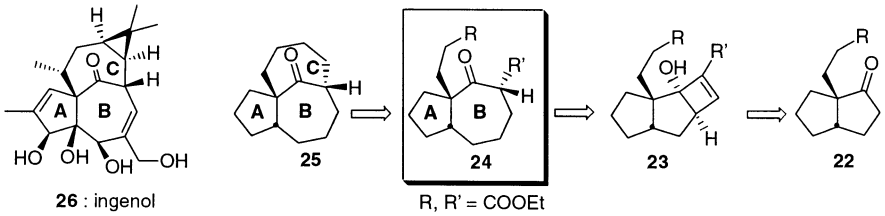
Thus, the "cyclobutene pathway" is an efficient and versatile set of complementary strategies, attending with good to high yields polyfunctionalized hydroazulene derivatives starting from a diquinane structure. To extend these results to other substrates, we wanted to use as starting material the diquinane **22** bearing at the ring junction a propionic ester side chain. Using our reaction sequence, we could obtain the hydroazulene derivative **24** via the cyclobutene **23**. Compound **24** could be considered as a potential precursor of the tricyclic derivative **25**, which possesses the ABC ring of ingenol **26** (Scheme 11).[20,21]

The diquinane **22** was prepared according to two different reaction pathways: either by catalytic hydrogenation of diquinane **11** (Scheme 12) or by addition of methyl acrylate to the pyrrolidino enamine **27** derived from bicyclo[3.3.0]octan-2-one **1** in 60% overall yield (Scheme 13).[22]

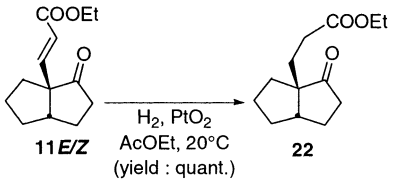
Keto ester **22** was transformed into silyl enol ether **28**,[6] which was added to ethyl propynoate in the presence of $ZrCl_4$ to afford the expected diester **29** isolated in 78% yield.[2a] The silylated hydroxyl function was then depro-

(12) (a) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*: Verlag Chemie: Weinheim, 1970. (b). Leigh, W. J. *Chem. Rev.* **1993**, *93*, 487−505.
(13) For significative references, see: (a) Doyle, T. W. *Can. J. Chem.* **1970**, *48*, 1629−1632. (b) Doyle, T. W. *Can. J. Chem.* **1970**, *48*, 1633−1638. (c) Leigh, W. J. *Can. J. Chem.* **1993**, *71*, 147−155 and references therein.
(14) This explanation was suggested by a referee. The authors fully agree with this remark and thank the referee.
(15) Ruder, S. M.; Kulkarni, V. R. *J. Org. Chem.* **1995**, *60*, 3084−3091.
(16) (a) Mukaiyama, T.; Higo, M. *Tetrahedron Lett.* **1970**, *11*, 5297−5300. (b) Higo, M.; Sakashita, T.; Toyoda, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 250−255.
(17) (a) Lennon, M.; McLean, A.; McWatt, I.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1828−1833. (b) Frew, A. J.; Proctor, G. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1245−1250. (c) Frew, A. J.; Proctor, G. R.; Silverton, J. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1251−1256.
(18) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609−2612.
(19) Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921−3926.
(20) Adlof, W.; Opferkuch, H. J.; Hecker, E. *Fette, Seifen Anstrichmittel* **1968**, *70*, 850.
(21) For a review of ingenol and analogues, see: Kim, S.; Winkler, J. D.*Chem. Soc. Rev.* **1997**, *26*, 387−399. For selected, more recent references, see: (a) Rigby, J. H.; Bazin, B.; Meyer, J. H.; Mohammadi, F. *Org. Lett.* **2002**, *4*, 799−801 (b) Tang, H.; Yusuff, N.; Wood, J. L. *Organic Lett.* **2001**, *3*, 1563−1566. (c) Kigoshi, H.; Suzuki, Y.; Aoki, K.; Uemura, D.; *Tetrahedron Lett.* **2000**, *41*, 3927−3930. (d) Winkler, J. D.; Kim, S.; Harrison, Sean; Lewin, N. E.; Blumberg, P. M. *J. Am. Chem. Soc.* **1999**, *121*, 296−300.
(22) For a similar reaction, see: Shono, T.; Kise, N.; Fujimoto, T.; Tominaga, N.; Morita, H. *J. Org. Chem.* **1992**, *57*, 7175−7187.

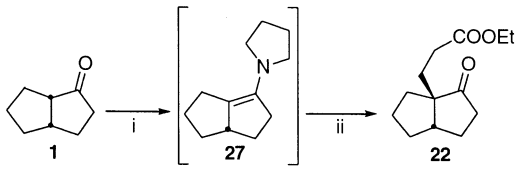
SCHEME 11. Retrosynthetic Approach to Ingenol Tricyclic Substructure



SCHEME 12. Catalytic Hydrogenation of Compound 11 Double Bond

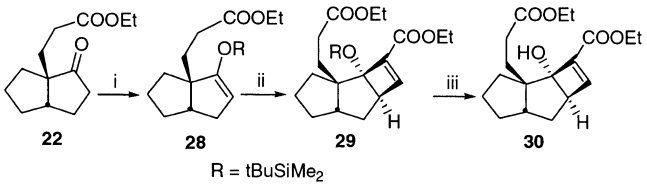


SCHEME 13. Access to Diquinane Derivative 22



i : pyrrolidine, Dean-Stark, benzene reflux.
ii : a. ethyl acrylate, dioxane reflux. b. H_2O
(overall yield : 60%)

SCHEME 14. Access to the Cyclobutene 30



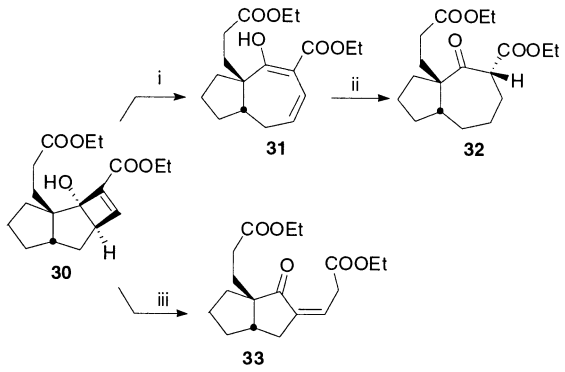
i : TBDMSOTf, NEt_3, CH_2Cl_2, 20°C (yield : quant.)
ii : $ZrCl_4$, ethyl propynoate, CH_2Cl_2/Et_2O, 20°C (yield : 70%)
iii : $HBF_4.H_2O$ 48%, EtOH, 50°C (yield : 75%)

tected with tetrafluoroboric acid in a hydroethanolic medium to generate the hydroxy ester **30** (Scheme 14).

The photolysis of the hydroxy ester **30** was conducted in hexane with a medium-pressure Hg lamp undersupplied at 150 V in a quartz photolysis apparatus. Thus, the desired hydroazulene derivative **31** was isolated in 98% yield. A catalytic hydrogenation of compound **31** yielded bicyclo[5.3.0]decane derivative **32** in 95% yield. It should be noted that this two-carbon ring-enlargement reaction could only be achieved photochemically. Indeed, we proved that the base treatment (NaH, THF, 20 °C) of cyclobutene hydroxy ester **30** led only to the undesired product **33** isolated from a complex crude mixture in 40% yield (Scheme 15).

The relative configuration of compound **32** was secured by an X-ray structure indicating the trans relationship between the ring junction chain and the ethyl ester group. The reactivity of the hydroazulenes derivatives **31** and **32** will be reported in due course.

SCHEME 15. Preparation of the Diester 32



i : hv, hexane, 20°C (yield : 98%). ii : H_2, PtO_2, AcOEt, 20°C (yield : 95%)
iii : NaH, THF, 20°C to 40°C (yield : 40%).

Conclusion

In conclusion, we have shown that hydroazulene derivatives could be obtained in high yields using photochemical, thermal, or base-induced ring cleavage of condensed electrophilic cyclobutenes. These strategies might be a promising tool for the total synthesis of natural compounds bearing a hydroazulene ring system as a main substructure. In this context, new approaches to ingenol and phorbol analogues are currently under investigation in our group.

Experimental Section

General Considerations. Reactions were carried out under argon with magnetic stirring and degassed solvents. Et_2O and THF were distilled from Na/benzophenone. Dioxane, benzene, and toluene were dried and distilled over CaH_2, and CH_2Cl_2 over P_2O_5. Thin layer chromatography (TLC) was carried out on silica gel plates, and the spots were visualized under UV lamp (254 or 365 nm) and/or sprayed with a solution of vanilin (25 g) in $EtOH/H_2SO_4$ (98/2; 1 L) followed by heating on a hot plate. For column chromatography, silica gel (40−60 μm) was used. Melting points (mp) were measured on a hot stage or a Kofler bench. IR spectra were recorded as CCl_4 solutions. UV−visible spectra were recorded in CH_3CN solution. ^1H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz using the signal of the residual nondeuterated solvent as internal reference. Significant ^1H NMR data are tabulated in the following order: chemical shift (δ) expressed in ppm, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constants in hertz, number of protons. Elemental analyses (C, H ± 0.3%) were performed by the Laboratoire de Microanalyses of the Université Louis Pasteur in Strasbourg.

4-(3,3a,4,5,6,6a-Hexahydropentalen-1-yl)morpholine (2). A solution of bicyclo[3.3.0]octan-2-one **1** (2.00 g, 16.13 mmol), morpholine (5.00 mL, 5.00 g, 57.39 mmol), and PTSA (5 mg) in toluene (60 mL) was refluxed 15 h in a Dean−Stark apparatus. The solvent was removed by distillation and the dark brown oily residue was purified by distillation under

reduced pressure, leading to the morpholinoenamine **2** (2.56 g, 13.23 mmol, 82% yield) as a colorless oil, bp 80−82 °C/0.1 mmHg.

2a-Morpholin-4-yl-2a,2b,3,4,5,5a,6,6a-octahydrocyclobuta[*a*]pentalen-1,2-dicarboxylic Acid Dimethyl Ester (3). To a solution of morpholino enamine **2** (1.26 g, 6.53 mmol) in dioxane (7 mL) was added dropwise neat DMAD (1.00 mL, 1.16 g, 8.14 mmol) over 30 min (exothermic reaction). After 15 h of stirring at room temperature (20 °C), the brown mixture was evaporated under reduced pressure (1 mmHg/35 °C). A mixture of THF (20 mL) and 10% aqueous H_2SO_4 solution (10 mL) was added to the oily residue. After 30 min of gentle stirring, the mixture was extracted with Et_2O and the aqueous layer was neutralized (pH = 7.0) with a saturated aqueous $NaHCO_3$ solution before extraction with CH_2Cl_2. The organic layers were collected and dried over $MgSO_4$, and after filtration, solvents were removed under reduced pressure (1 mmHg/25 °C), leading to the pure cyclobutene amino diester **3** (1.74 g, 5.17 mmol, 80% yield): red crystals; mp 85−86 °C; IR (CCl_4) 1721; UV (CH_3CN) 330 (1000), 220 (7000); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30−1.86 (m, 9H), 2.50−2.79 (m, 5H), 3.37 (d, J = 7.0 Hz, 1H), 3.65−3.72 (m, 4H), 3.76 (s, 3H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.5, 24.7, 27.1, 28.4, 43.5, 46.2, 50.1 (2C), 50.6, 51.8, 51.9, 67.2 (2C), 82.4, 139.5, 147.9, 163.8, 161.8. Anal. Calcd for $C_{18}H_{25}O_5N$: C, 65.44; H, 6.10. Found: C, 65.4; H, 6.3.

2a-Morpholin-4-yl-2a,2b,3,4,5,5a,6,6a-octahydrocyclobuta[*a*]pentalene-2-carboxylic Acid Ethyl Ester (4). Ethyl propynoate (3.00 mL, 2.90 g, 29.64 mmol) was added dropwise over 30 min (exothermic reaction) to a solution of morpholino enamine **2** (2.58 g, 13.37 mmol) in dioxane (12 mL). After stirring for 15 h at 20 °C, the brown-red mixture was evaporated under reduced pressure (1 mmHg/35 °C). The oily residue was dissolved in a 2/1 mixture of THF and 10% aqueous H_2SO_4 solution (30 mL). After 30 min of gentle stirring, the mixture was extracted with Et_2O and the aqueous layer was neutralized (pH = 7.0) with a saturated aqueous $NaHCO_3$ solution before extraction with CH_2Cl_2. The organic layers were collected and dried over $MgSO_4$, and after filtration, solvents were removed under reduced pressure (1 mmHg/25 °C), leading to the cyclobutene amino ester **4** (3.00 g, 10.31 mmol, 77% yield): yellow oil; IR (CCl_4) 1710; UV (CH_3CN) 218 (6400), 286 (1000); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 1.17−2.16 (m, 8H), 2.43−2.94 (m, 2H), 2.67 (t, J = 4.3 Hz, 4H), 3.17 (d, J = 7.4 Hz, 1H), 3.67 (q, J = 4.3 Hz, 4H), 4.16 (q, J = 7.1 Hz, 2H), 6.72 (d, J = 0.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 24.4, 24.6, 29.0, 30.3, 43.5, 46.2, 49.8, 50.3 (2C), 60.1, 67.4 (2C), 83.2, 142.4, 147.9, 162.8. Anal. Calcd for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65. Found: C, 70.2; H, 8.8.

(2,3,3a,4,5,6-Hexahydropentalen-1-yloxy)trimethylsilane (5a) and (3,3a,4,5,6,6a-Hexahydropentalen-1-yloxy)-trimethylsilane (5b). To a refluxing solution of bicyclo[3.3.0]-octan-2-one **1** (1.00 g, 8.06 mmol) and TMSOTf (1.60 mL, 1.97 g, 8.87 mmol) in CH_2Cl_2 (40 mL)was added NEt_3 (3.30 mL, 2.44 g, 24.24 mmol dropwise. After 1 h of reflux, the mixture was cooled to room temperature and hydrolyzed with a saturated aqueous $NaHCO_3$ solution (30 mL). After extraction with CH_2Cl_2, the organic layers were collected, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/35 °C). The crude product (3.00 g) was purified on a silica gel column (30 g SiO_2 neutralized with NEt_3, hexane), leading to a mixture of enol ethers **5a** and **5b** (1.58 g, 8.04 mmol, quantitative yield, **5a**/**5b**: 2/5) as a colorless oil.[23]

2a-Hydroxy-3,4,4a,5,6,7-hexahydro-2a*H*-cyclobuta[*c*]-pentalene-2-carboxylic Acid Ethyl Ester (6), 2a-Hydroxy-2a,2b,3,4,5,5a6,6a-octahydrocyclobuta[*a*]pentalene-2-carboxylic Acid Ethyl Ester (7), and 2a-Hydroxy-2a,2b,3,4,5,5a6,6a-octahydrocyclobuta[*a*]pentalene-2-carboxylic Acid Ethyl Ester (8). In a 50-mL three-necked flask, $ZrCl_4$ (1032 mg, 4.42 mmol) was suspended in CH_2Cl_2 (15 mL), and Et_2O (1.50 mL) was added. Ethyl propynoate (0.70 mL, 671 mg, 6.87 mmol) was then added dropwise, and after 15 min of stirring at 20 °C, the enol ethers **5a**/**5b** (790 mg, 4.02 mmol) were added dropwise at room temperature. The mixture then was hydrolyzed with a saturated aqueous $NaHCO_3$ solution (20 mL) before being extracted with Et_2O. The organic layers were collected, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/30 °C). The brown-red crude product (1031 mg) was purified on a silica gel column (30 g SiO_2, AcOEt/hexane: 5/95), leading to cycloadducts **6** (214 mg, 0.97 mmol, 24% yield), **7** (379 mg, 1.70 mmol, 42% yield), and **8** (42 mg, 0.19 mmol, 5% yield).

Data for **6**: colorless oil; IR (CCl_4) 1600, 1715, 3440, 3580; UV (CH_3CN) 218 (6300); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (t, J = 7.1 Hz, 3H), 1.57−1.94 (m, 9H), 2.00−2.17 (m, 2H), 2.11 (s, 1H), 4.23 (m, 2H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 25.6, 26.8, 28.5, 29.9, 30.3, 43.8, 60.2, 67.2, 87.0, 138.8, 152.3, 161.6. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.1; H, 8.0.

Data for **7**: colorless oil; IR (CCl_4) 1607, 1710, 3460, 3611; UV (CH_3CN) 213 (6400); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, J = 7.1 Hz, 3H), 1.37−2.17 (m, 8H), 2.26 (s, 1H), 2.39−2.56 (m, 2H), 3.00 (d, J = 7.6 Hz, 1H), 4.23 (dq, J = 1.9, 7.0 Hz, 2H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 24.9, 25.8, 30.3, 31.3, 44.1, 48.6, 54.9, 60.3, 88.1, 141.5, 148.3, 161.5. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.3; H, 8.2.

Data for **8**: colorless oil; IR (CCl_4) 1607, 1710, 3611, 3460; UV (CH_3CN) 213 (6400); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31 (t, J = 7.1 Hz, 3H), 1.37−2.17 (m, 8H), 2.51 (dt, J = 3.3, 8.9 Hz, 1H), 2.56−2.86 (m, 2H), 3.03 (d, J = 8.9 Hz, 1H), 4.23 (dq, J = 1.2, 7.1 Hz, 2H), 6.82 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 26.4, 27.7, 29.9, 32.6, 49.0, 52.8, 57.2, 60.3, 91.0, 142.0, 150.9, 162.0. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.1; H, 8.3.

4-Morpholin-4-yl-1,2,3,3a,8,8a-hexahydroazulen-5-carboxylic Acid Ethyl Ester (9). A solution of cyclobutene compound **4** (112 mg, 0.38 mmol) in hexane (150 mL) was irradiated for 10 min with a 125-W medium-pressure Hg lamp in a water-cooled quartz photolysis apparatus. The solvent was then removed under reduced pressure (15 mmHg/35 °C), leading to the pure hydroazulene derivative **9** (100 mg, 0.34 mmol, 90% yield): colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17−1.56 (m, 3H), 1.21 (t, J = 7.0 Hz, 3H), 1.60−1.91 (m, 4H), 2.21−2.30 (m, 1H), 2.67−2.89 (m, 2H), 3.11 (dt, J = 4.7, 18.2 Hz, 2H), 3.39 (dt, J = 4.7, 18.2 Hz, 2H), 3.70 (t, J = 4.6 Hz, 4H), 4.15 (q, J = 7.0 Hz, 2H), 5.85 (ddd, J = 6.3, 7.7, 10.4 Hz, 1H), 7.02 (dd, J = 2.0, 10.4 Hz, 1H).

4-Morpholin-4-yl-1,2,3,7,8,8a-hexahydroazulene-5-carboxylic Acid Ethyl Ester (10). The cyclobutene amino ester **4** (500 mg, 1.72 mmol) dissolved in xylene (15 mL) was refluxed for 12 h. The mixture was then cooled to room temperature and xylene was removed under reduced pressure (0.1 mmHg/35 °C). The crude product (650 mg) was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 7/93), affording the hydroazulene amino ester **10** (165 mg, 0.57 mmol, 32% yield): colorless oil; IR (CCl_4) 1721; UV (CH_3CN) 214 (8700); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.17−1.91 (m, 7H), 1.27 (t, J = 7.1 Hz, 3H), 2.17−2.90 (m, 8H), 3.32 (dt, J = 7.2, 10.7 Hz, 2H), 3.65 (t, J = 4.5 Hz, 2H), 3.72 (q, J = 7.1 Hz, 2H), 7.26 (t, J = 4.3 Hz, 1H); ^{13}C NMR (C_6D_6, 50 MHz) δ 14.5, 25.7, 26.4, 31.5, 32.8, 40.4, 44.2, 50.0 (2C), 60.4, 68.0 (2C), 135.8, 136.9, 138.3, 145.0, 166.9. Anal. Calcd for $C_{17}H_{25}O_3N$: C, 70.07; H, 8.65. Found: C, 70.0; H, 8.9.

***E*-3-(3-Oxohexahydropentalen-3a-yl)-2-propenoic Acid Ethyl Ester (11E) and *Z*-3-(3-Oxohexahydropentalen-3a-yl)-2-propenoic Acid Ethyl Ester (11Z).** A solution of cyclobutene hydroxy ester **6** (416 mg, 1.87 mmol) in THF (2 mL) was added dropwise to a suspension of NaH (54 mg, 2.25 mmol) in THF (20 mL). Evolution of the reaction was followed

(23) Spectral data consistent with those described previously: Gross, L. Thèse de Doctorat de l'Université Louis Pasteur de Strasbourg, 1991.

by TLC, and when all starting material was consumed, the mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (30 mL). After extraction with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered before solvents were removed under reduced pressure (1 mmHg/30 °C). The crude product (450 mg) was purified by column chromatography (15 g SiO_2, AcOEt/hexane: 7/93), leading to keto ester **11** (370 mg, 1.66 mmol, 89% yield, **11*E***/**11*Z***: 1/1).

Data for **11*E***: colorless oil; IR (CCl_4) 1721, 1739; UV (CH_3CN) 208 (8100); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.22 (t, J = 7.1 Hz, 3H), 1.40−1.78 (m, 3H), 1.88−2.22 (m, 5H), 2.31 (t, J = 8.0 Hz, 2H), 2.61−2.73 (m, 1H), 4.12 (q, J = 7.1 Hz, 2H), 5.74 (d, J = 15.9 Hz, 1H), 6.88 (d, J = 15.9 Hz, 1H);^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 25.1, 25.4, 33.0, 36.8, 37.3, 46.9, 60.4, 63.3, 120.2, 148.7, 166.3, 219.1.

Data for **11*Z***: colorless oil; IR (CCl_4) 1721, 1739; UV (CH_3CN) 208 (8100); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.25 (t, J = 7.1 Hz, 3H), 1.49−2.12 (m, 5H), 2.31−2.80 (m, 2H), 2.37 (t, J = 7.9 Hz, 2H), 2.80−3.00 (1H, m), 4.15 (q, J = 7.1 Hz, 2H), 5.85 (1H, d, J = 11.7 Hz), 6.12 (d, J = 11.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 25.3, 27.7, 33.7, 38.4, 39.0, 51.6, 60.1, 62.9, 121.0, 152.3, 165.7, 218.0. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.3; H, 8.4.

4-Hydroxy-1,2,3,3a,8,8a-hexahydroazulen-5-carboxylic Acid Ethyl Ester (12). A solution of cyclobutene **7** (420 mg, 1.89 mmol) in hexane (150 mL) was irradiated for 4 h with a 125 W medium-pressure Hg lamp undersupplied at 150 V in a water-cooled quartz photolysis apparatus. The solvent was removed under reduced pressure (15 mmHg/35 °C). The crude product (451 mg) was purified on a silica gel column (20 g SiO_2, AcOEt/hexane: 3/97), leading to the cyclobutene **7** (70 mg, 0.30 mmol, yield: 16%) along with **12** (330 mg, 1.48 mmol, 78% yield, conversion ratio: 94%): colorless oil; IR (CCl_4) 1644, 1712; UV (CH_3CN) 209 (12 000), 222 (9500), 284 (6000); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, J = 7.1 Hz, 3H), 1.24−1.57 (m, 2H), 1.68−1.99 (m, 6H), 2.17 (ddd, J = 4.0, 7.0, 13.2 Hz, 1H), 2.69−2.92 (m, 2H), 4.23 (q, J = 7.1 Hz, 2H), 5.98 (dt, J = 6.8, 10.5 Hz, 1H), 6.17 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 25.1, 30.0, 30.8, 32.1, 48.4, 53.8, 60.7, 99.6, 124.4, 129.3, 172.5, 182.1. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.3; H, 8.1.

Complex Mixture of Isomers (13). To a solution of compound **7** (100 mg, 0.45 mmol) in *t*-BuOH (15 mL) was added *t*-BuOK (53 mg, 0.47 mmol) at room temperature. After 1 h of gentle stirring, the mixture was acidified with AcOH and hydrolyzed with water (20 mL). After extraction with Et_2O, the combined organic layers were dried over $MgSO_4$ and filtered, and the solvents were removed under reduced pressure. Purification by column chromatography (15 g SiO_2, AcOEt/hexane: 2/98) gave **13** as a mixture of isomers (99 mg, 0.45 mmol, quantitative yield): colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18−3.00 (m, 15H), 3.15 (dd, J = 6.0, 2.0 Hz, 2H), 5.80 (d, J = 15.0 Hz, 1H), 5.80 (d, J = 16.0 Hz, 1H), 5.90 (d, J = 11.0 Hz, 1H), 6.15 (d, J = 11.0 Hz, 1H), 6.66 (ddt, J = 2.0, 3.0, 6.0 Hz, 1H), 6.94 (d, J = 15.0 Hz, 1H), 6.94 (d, J = 16.0 Hz, 1H).

4-Morpholin-4-yl-1,2,3,3a,8,8a-hexahydroazulene-5,6-dicarboxylic Acid Dimethyl Ester (14). A solution of cyclobutene **3** (200 mg, 0.60 mmol) in a mixture of hexane (150 mL) and ether (2 mL) was irradiated for 20 min with a 125 W medium-pressure Hg lamp in a water-cooled quartz photolysis apparatus. The white solid that formed during the reaction was collected by filtration. The filtrate was evaporated to dryness under reduced pressure (1 mmHg/30 °C). The residual solid was washed with ice-cold Et_2O (20 mL) and added to the white solid. Residual solvents were removed under reduced pressure (0.1 mmHg/20 °C), leading to the hydroazulene diester **14** (179 mg, 0.54 mmol, 90% yield): white powder; mp 154−156 °C; IR (CCl_4) 1725; UV (CH_3CN) 202 (11 800), 292 (4400), 337 (7800); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30−1.55 (m, 1H), 1.56−1.87 (m, 5H), 2.00 (ddd, J = 2.6, 8.0, 10.7 Hz, 1H), 2.32 (ddd, J = 4.7, 7.0, 12.3 Hz, 1H), 2.78 (qb, J = 10.2 Hz, 1H), 3.22 (dt, J = 4.7, 13.2 Hz, 2H), 3.28 (m, 1H), 3.42 (dt, J = 4.7, 13.2 Hz, 2H), 3.65 (s, 3H), 3.72 (s, 3H), 3.72 (t, J = 4.7 Hz, 4H), 7.02 (t, J = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 26.3, 30.3, 31.8, 32.4, 48.4, 51.4, 51.8 (2C), 59.5, 67.4 (2C), 104.0, 134.5, 140.5, 167.8, 168.2, 169.1. Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51. Found: C, 64.2; H, 7.3.

6-Hydroxy-1,2,3,7,8,8a-hexahydroazulen-5-carboxylic Acid Ethyl Ester (15). A solution of cyclobutene compound **6** (132 mg, 0.59 mmol) in hexane (150 mL) was irradiated for 15 min with a Philips HPK 125 lamp in a water-cooled quartz photolysis apparatus. The solvent was removed under reduced pressure (1 mmHg/35 °C) and the crude product (202 mg) was purified on a silica gel column (5 g SiO_2, hexane), leading to the ring-enlargement product **15** (118 mg, 0.53 mmol, 90% yield): colorless oil; IR (CCl_4) 1644, 1728; UV (CH_3CN) 208 (11 000), 229 (9300), 292 (4200); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.32 (t, J = 7.1 Hz, 3H), 1.41−1.96 (m, 4H), 2.23−2.62 (m, 7H), 4.23 (dq, J = 2.0, 7.1 Hz, 2H), 6.04 (q, J = 2.0 Hz, 1H), 12.95 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 25.4, 33.8, 34.4, 34.6, 36.0, 41.7, 60.6, 100.8, 112.9, 147.0, 172.4, 177.8.

4-Oxo-1,2,3,3a,4,7,8,8a-octahydroazulen-5-carboxylic Acid Ethyl Ester (16). The amino ester **9** (100 mg, 0.34 mmol) was dissolved in a mixture of THF (10 mL) and 10% aqueous HCl solution (2.50 mL). After 15 min of gentle stirring at room temperature, the mixture was neutralized by addition of a saturated aqueous $NaHCO_3$ solution (50 mL) and extracted with Et_2O. The organic layers were combined, dried over $MgSO_4$, and filtered, and solvents were removed under reduced pressure (1 mmHg/30 °C). The crude product (100 mg) was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 15/85), affording to the β-keto ester **16** (53 mg, 0.24 mmol, 63% overall yield starting from **4**): colorless oil; IR (CCl_4) 1712, 1725; UV (CCl_4) 219 (7400); ^{1}H NMR (C_6D_6, 200 MHz) δ 0.97 (t, J = 7.1 Hz, 3H), 0.97−1.31 (m, 3H), 1.32−1.97 (m, 7H), 2.40 (m, 1H), 2.98 (ddd, J = 6.9, 7.9, 10.6, 1H), 3.72 (dq, J = 1.6, 7.0 Hz, 2H), 7.05 (dd, J = 3.2, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 25.7, 26.8, 30.1, 30.8, 34.0, 43.1, 57.8, 61.1, 136.0, 147.1, 165.0, 202.6. Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.0; H, 8.3.

1-Oxooctahydropentalen-2-carboxylic Acid Methyl Ester (17). In a three-necked 100-mL flask, the bicyclo[3.3.0]-octan-2-one **1** (1.00 g, 8.06 mmol) was added rapidly to a suspension of NaH (482 mg, 20.15 mmol) in dry methyl carbonate (25 mL) preheated to 50 °C. The reaction was initiated by addition of MeOH (5 drops). When the hydrogen evolution stopped, the mixture was cooled to 0 °C and hydrolyzed with a saturated aqueous NH_4Cl solution (75 mL). After extraction with Et_2O, the organic layers were collected, washed with brine, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/30 °C then 0.2 mmHg/25 °C). The crude product (2.24 g) was purified on a silica gel column (30 g SiO_2, AcOEt/hexane: 3/97), leading to the β-keto ester **17** (1.33 g, 7.33 mmol, 91% yield): colorless oil; IR (CCl_4) 1731, 1755; UV (CH_3CN) 253 (1100); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10−2.42 (m, 7H), 2.52−2.71 (m, 3H), 3.13−3.32 (m, 1H), 3.58 (s, 3H).

8-Hydroxy-1,2,3,3a,4,8a-hexahydroazulene-5,6,7-tricarboxylic Acid Trimethyl Ester (19). At room temperature (20 °C), the neat β-keto ester **17** (329 mg, 1.80 mmol) was added dropwise to a suspension of NaH (52 mg, 2.16 mmol) in dry toluene (15 mL). When hydrogen evolution stopped, neat DMAD (0.23 mL, 255 mg, 1.80 mmol) was added dropwise. After 45 min of gentle stirring at 20 °C, the reaction mixture was hydrolyzed with a saturated aqueous NH_4Cl solution (20 mL) and then extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered before the solvents were removed under reduced pressure (15 mmHg/30 °C). The crude product was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 5/95), affording the hydroazulene compound **19** (434 mg, 1.34 mmol, 73% yield): colorless oil; IR (CCl_4) 1650, 1726; UV (CH_3CN) 258 (7000),

260 (8500); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.31−1.92 (m, 6H), 2.08−2.19 (m, 1H), 2.61 (dd, 1H, J = 4.7, 12.7 Hz), 2.82−3.01 (m, 2H), 3.73 (s, 6H), 3.78 (s, 3H), 13.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 24.8, 31.3, 34.0 (2C), 46.6, 51.9, 52.1, 52.2, 55.0, 97.6, 133.0, 139.5, 167.4, 169.1, 171.4, 184.1. Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.3; H, 6.4.

8-Hydroxy-1,2,3,3a,4,8a-hexahydroazulen-5,7-dicarboxylic Acid 7-Ethyl-5-Methyl Ester (20) and 1,2,3,3a,8,8a-Hexahydrocyclopenta[*a*]indene-4,6-dicarboxylic Acid Diethyl Ester (21). The β-keto ester **17** (250 mg, 1.37 mmol) was added dropwise to a NaH suspension (40 mg, 1.65 mmol) in dry toluene (8 mL) preheated to 80 °C. When hydrogen evolution stopped, ethyl propynoate (0.14 mL, 135 mg, 1.37 mmol) was added dropwise. Immediatly after the addition, the mixture was cooled to room temperature and hydrolyzed with a saturated aqueous NH_4Cl solution (15 mL). After dilution with water (15 mL) and extraction with Et_2O, organic layers were collected, washed with brine, dried over $MgSO_4$, and filtered, and solvents were removed under reduced pressure (15 mmHg/30 °C). The crude product (633 mg) was purified on a silica gel column (30 g SiO_2, AcOEt/hexane: 3/97), leading to ring-enlargement product **20** (242 mg, 0.86 mmol, 63% yield) along with aromatic compound **21** (49 mg, 0.17 mmol, 13% yield).

Data for **20**: IR (CCl_4) 1644, 1712; UV (CH_3CN) 214 (6500), 264 (9400), 294 (7900); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.34 (t, J = 7.1 Hz, 3H), 1.41−1.94 (m, 6H), 2.20 (dd, J = 8.6, 13.3 Hz, 1H), 2.59 (dd, J = 3.6, 13.5 Hz, 1H), 2.83−2.89 (m, 2H), 3.78 (s, 3H), 4.28 (q, J = 7.1 Hz, 2H), 7.48 (s, 1H), 13.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.3, 25.0, 30.1, 30.7, 32.1, 48.8, 51.9, 52.7, 61.2, 99.6, 130.0, 134.6, 168.3, 172.1, 186.1. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.5; H, 7.1.

Data for **21**: colorless oil; IR (CCl_4) 1728; UV (CH_3CN) 209 (4900), 238 (21 100); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.42−2.12 (m, 6H), δ_a = 2.72, δ_b = 3.26 (ABX, $\Delta\nu$ = 107.6 Hz, J_{AB} = 17.1 Hz, J_{AX} = 9.1 Hz, J_{BX} = 2.9 Hz, 2H), 2.89−2.97 (m, 1H), 3.66 (dt, J = 3.2, 8.6 Hz, 1H), 4.34 (q, J = 7.2 Hz, 2H), 4.35 (q, J = 7.2 Hz, 2H), 7.48 (s, 1H), 7.51 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2 (2C), 26.0, 34.0, 34.8, 39.4, 42.3, 50.2, 61.4 (2C), 124.9, 125.1, 130.9, 131.1, 147.2, 151.5, 168.1, 168.2. Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.5; H, 7.34. Found: C, 71.5; H, 7.2.

3-(3-Oxohexahydropentalen-3a-yl)propionic Acid Ethyl Ester (22). A degassed mixture of unsaturated keto ester **11** (255 mg, 1.15 mmol) in AcOEt (10 mL) and PtO_2 (5 mg) was hydrogenated at room temperature for 3 h. The crude product was degassed with an argon stream before filtration over Celite. Removal of AcOEt under reduced pressure (1 mmHg/30 °C) afforded keto ester **22** (256 mg, 1.15 mmol, quantitative yield) colorless oil; IR (CCl_4) 1732, 1740; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.24 (t, J = 7.1 Hz, 3H), 1.49−1.65 (m, 5H), 1.78−1.92 (m, 4H), 2.00−2.15 (m, 1H), 2.22−2.48 (m, 5H), 4.09 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 24.8, 25.2, 30.2, 31.9, 33.3, 35.8, 37.3, 46.1, 59.0, 60.1, 173.1, 223.0.

3-[4-(*tert*-Butyldimethylsilanyloxy)-2,3,6,6a-tetrahydro-1*H*-pentalen-3a-yl]propionic Acid Ethyl Ester (28). To a solution of keto ester **22** (1.00 g, 4.46 mmol) and TBDMSOTf (1.30 mL, 1.52 g, 4.91 mmol) in CH_2Cl_2 (60 mL) was added dropwise NEt_3 (2.00 mL, 1.45 g, 14.38 mmol). After 1 h of stirring at room temperature, the mixture was hydrolyzed with a saturated aqueous $NaHCO_3$ solution (30 mL). After extraction with CH_2Cl_2, the organic layers were collected, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/35 °C). The crude product was purified on a silica gel column (30 g SiO_2, AcOEt/hexane: 4/96), leading to the enol ether **28** (1.52 g, 4.46 mmol, quantitative yield): colorless oil; IR (CCl_4) 1646, 1737; UV (CH_3CN) 208 (3000); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.85 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H), 1.32−1.87 (m, 8H), 2.09−2.22 (m, 4H), 2.37 (ddd, J = 2.1, 8.9, 15.3 Hz, 1H), 4.02 (q, J = 7.1 Hz, 2H), 4.36 (t, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −5.2, −4.8, 14.2, 18.0, 25.2, 25.6 (3C), 30.9, 32.9, 35.2, 36.5, 42.9, 58.8, 60.0, 99.8, 155.4, 174.3.

2a-(*tert*-Butyldimethylsilanyloxy)-2b-(2-Ethoxycarbonylethyl)-2a-hydroxy-2a,2b,3,4,5,5a,6,6a-octahydrocyclobuta[a]pentalene-2-carboxylic Acid Ethyl Ester (29). In a three-necked flask, $ZrCl_4$ (1447 mg, 6.21 mmol) was suspended in CH_2Cl_2 (25 mL), then Et_2O (1.50 mL) and ethyl propynoate (1.00 mL, 963 mg, 9.60 mmol) were successively added. At room temperature, neat enol ether **28** (1915 mg, 5.65 mmol) was added dropwise (1 drop/5 s). After completion of the addition, the mixture was neutralized with a saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with Et_2O. Organic layers were collected, washed with brine, and dried over $MgSO_4$, and then solvents were removed under reduced pressure (15 mmHg/30 °C). The crude product was purified on a silica gel column (40 g SiO_2, AcOEt/hexane: 4/96), leading to diester **29** (1915 mg, 4.38 mmol, 78% yield): colorless crystals; mp 54−56 °C; IR (CCl_4) 1615, 1725, 1730; UV (CH_3CN) 213 (5400); ^{1}H NMR ($CDCl_3$, 200 MHz) δ −0.05 (s, 3H), 0.00 (s, 3H), 0.83 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H), 1.21 (t, J = 7.1 Hz, 3H), 1.10−1.88 (m, 11H), 2.37 (ddd, J = 4.9, 11.1, 16.5 Hz, 1H), 2.96 (bd, J = 6.2 Hz, 1H), 3.03 (ddd, J = 5.2, 11.6, 16.5 Hz, 1H), 4.10 (dq, J = 1.3, 7.1 Hz, 2H), δ_a = 4.14, δ_b = 4.21 (ABX$_3$, J_{AX} = 7.1 Hz, J_{BX} = 7.1 Hz, J_{AB} = 10.8 Hz, $\Delta\nu$ = 13.7 Hz, 2H), 6.85 (d, J = 1.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ −3.7, −3.2, 14.1, 14.2, 18.2, 22.2, 25.7 (3C), 28.7, 29.2, 30.4, 31.0, 48.8, 53.5, 57.2, 59.9, 60.2, 93.4, 142.7, 149.3, 161.9, 174.3. Anal. Calcd for $C_{24}H_{40}O_5Si$: C, 66.02; H, 9.23. Found: C, 66.0; H, 9.1.

2b-(2-Ethoxycarbonylethyl)-2a-hydroxy-2a,2b,3,4,5,-5a,6,6a-octahydrocyclobuta[*a*]pentalene-2-carboxylic Acid Ethyl Ester (30). To a solution of compound **29** (1440 mg, 3.29 mmol) in EtOH (50 mL) was added a 48% HBF_4 aqueous solution (50 mL). The medium was gently stirred at 50 °C for 3 h and then cooled to room temperature, diluted with water (100 mL), and extracted with CH_2Cl_2. The combined organic layers were washed successively with a saturated aqueous $NaHCO_3$ solution and brine, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/30 °C). The crude product was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 10/90), leading to cyclobutene **30** (790 mg, 2.45 mmol, 75% yield): colorless oil; IR (CCl_4) 1607, 1720, 1732, 2942, 3606; UV (CH_3CN) 211 (4300); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.21 (t, J = 7.2 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 1.12−1.86 (m, 10H), 1.93−2.05 (m, 1H), 2.31 (s, 1H), 2.38 (ddd, J = 5.1, 12.3, 16.7 Hz, 1H), 2.86 (ddd, J = 5.1, 12.3, 16.7 Hz, 1H), 2.86 (d, J = 9.0 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), δ_a = 4.12, δ_b = 4.20 (ABX$_3$, J_{AX} = 7.1 Hz, J_{BX} = 7.1 Hz, J_{AB} = 10.8 Hz, $\Delta\nu$ = 13.7 Hz, 2H), 6.90 (d, J = 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.1, 14.3, 22.6, 27.3, 28.2, 29.2, 30.5, 30.7, 50.0, 54.6, 55.9, 60.1, 60.5, 92.2, 140.9, 149.9, 162.0, 174.6. Anal. Calcd for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 67.2; H, 8.2.

3a-(2-Ethoxycarbonylethyl)-4-hydroxy-1,2,3,3a,8,8a-hexahydroazulene-5-carboxylic Acid Ethyl Ester (31). A solution of cyclobutene **30** (84 mg, 0.26 mmol) in hexane (150 mL) was irradiated for 45 min in a water-cooled quartz photolysis apparatus with a 125 W medium-pressure Hg lamp undersupplied at 150 V. The solvent was removed under reduced pressure (15 mmHg/30 °C). The resulting oil was purified on a silica gel column (20 g SiO_2, AcOEt/hexane: 3/97) to afford the hydroazulene compound **31** (82 mg, 0.25 mmol, 98% yield): colorless oil; IR (CCl_4) 1579, 1639, 1733, 1739; UV (CH_3CN) 211 (11 000), 221 (8200), 291 (5600); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.19−1.46 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.51−1.80 (m, 4H), 1.89−2.08 (m, 4H), 2.11−2.37 (m, 4H), 4.02 (q, J = 7.1 Hz, 2H), 4.22 (q, J = 7.1 Hz, 2H), 5.89 (dt, J = 7.0, 10.4 Hz, 1H), 6.17 (d, J = 10.3 Hz, 1H), 13.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 14.2, 22.5, 30.8, 32.3, 35.1, 35.9, 56.0, 57.3, 60.3, 61.0, 100.0, 123.4, 127.6, 173.1, 173.8, 182.8.

3a-(2-Ethoxycarbonylethyl)-4-oxodecahydroazulene-5-carboxylic Acid Ethyl Ester (32). A degassed mixture of alkene **31** (79 mg, 0.25 mmol) in AcOEt (20 mL) and PtO_2 (5 mg). was hydrogenated at room temperature for 2 h. The medium was degassed for 15 min by bubbling an argon stream through the mixture and then filtered over Celite. The solvents were removed under reduced pressure (15 mmHg/30 °C). The crude mixture was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 5/95), leading to diester **32** (75 mg, 0.23 mmol, 95% yield): colorless crystals suitable for an X-ray analysis were obtained from a pentane−Et_2O mixture; mp 58−60 °C; IR (CCl_4)1705, 1739, 1747; UV (CH_3CN) 206 (700); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.15 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H), 1.22−1.57 (m, 8H), 1.77−2.25 (m, 9H), 3.80 (dd, J = 2.7, 12.0 Hz, 1H), 4.07 (q, J = 7.1 Hz, 2H), δ_a = 4.03, δ_b = 4.14 (ABX_3, J_{AX} = 7.2 Hz, J_{BX} = 7.2 Hz, J_{AB} = 10.9 Hz, $\Delta\nu$ = 22.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 13.9, 14.2, 22.4, 28.0, 28.4, 29.5, 30.1, 32.6 33.7, 35.3, 48.2, 54.9, 60.4, 60.9, 64.1, 169.8, 173.3, 210.0. Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.59; H, 8.74. Found: C, 66.6; H, 8.7.

3-[2-(2-Ethoxycarbonylethylidene)-3-oxohexahydropentalen-3a-yl]propionic Acid Ethyl Ester (33). A solution of hydroxy ester **30** (50 mg, 0.16 mmol) in THF (5 mL) was added dropwise to a suspension of NaH (5 mg, 0.21 mmol) in THF (2 mL) at room temperature. After the end of the addition, the medium was heated at 40 °C for 20 min and then cooled to room temperature and hydrolyzed with a saturated aqueous NH_4Cl solution (10 mL). The mixture was then extracted with Et_2O, the organic layers were collected, dried over $MgSO_4$, and filtered, and the solvents were removed under reduced pressure (15 mmHg/30 °C). The resulting dark oil was purified on a silica gel column (15 g SiO_2, AcOEt/hexane: 7/93) to afford keto diester **33** (21 mg, 0.06 mmol, 40% yield): colorless oil; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.18 (t, J = 7.1 Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H), 1.46−1.67 (m, 7H), 1.75−1.93 (m, 5H), 2.60−2.70 (m, 1H), 3.11 (dt, J = 1.5, 7.4 Hz, 2H), 4.06 (q, J = 7.1 Hz, 2H), 4.10 (q, J = 7.1 Hz, 2H), 6.65 (tt, J = 2.5, 7.4 Hz, 1H).

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Supporting Information Available: X-ray structural information for compound **32** (CCDC 185900). This material is available free of charge via the Internet at http://pubs.acs.org.

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