Synthesis of the Right-Hand Substructure of Solanoeclepin A

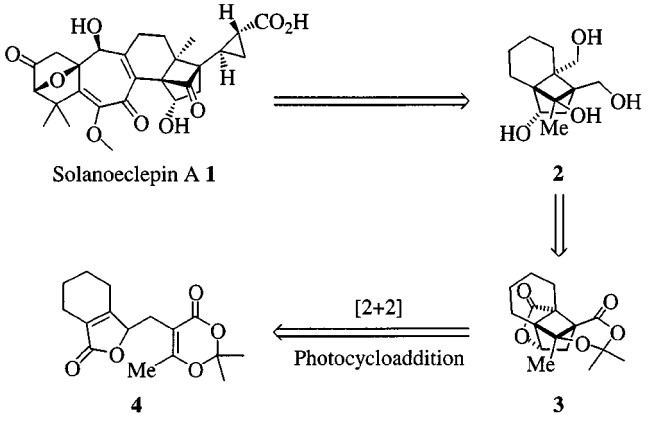
Jean-François Brière,[a] Richard H. Blaauw,[a] Jorg C. J. Benningshof,[a] Angeline E. van Ginkel,[a] Jan H. van Maarseveen,[a] and Henk Hiemstra*[a]

Keywords: Photochemistry / Natural products / Cycloaddition / Cyclization

A synthesis of the right-hand substructure **7** of solanoeclepin A (**1**), the most active natural hatching agent of potatocyst nematodes, was approached by an intramolecular [2+2] photocycloaddition. The construction of the strained bicyclo[2.1.1]hexane skeleton was achieved in five steps from dioxenone **9**. A Simmons–Smith cyclopropanation enabled the installation of the required cyclopropane. Finally, a TPAP oxidation allowed the smooth formation of the strained cyclobutanone moiety.

Introduction

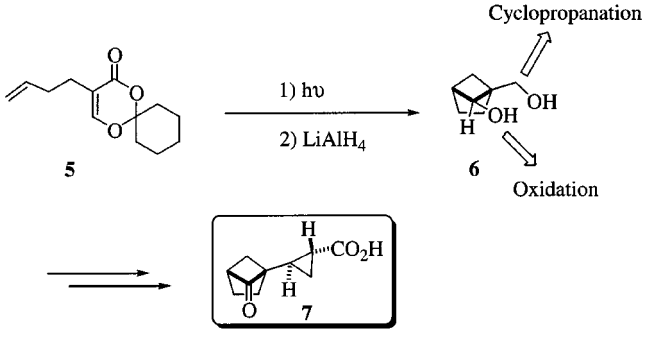
Solanoeclepin A (**1**, Scheme 1), excreted in minute quantities by the potato root, is the most active natural hatching agent of the potatocyst nematode,[1] an organism that causes severe crop losses in potato production. The fascinating architecture of this novel molecule[2] contains all ring sizes ranging from three to seven, including a highly strained bicyclo[2.1.1]hexanone unit, which, to the best of our knowledge, is an unprecedented structural feature in naturally occurring products.



Scheme 1. Retrosynthetic approach

During our research effort towards the construction of this challenging target,[3] we have recently described the successful diastereoselective formation of the highly substituted cyclobutane ring **2**.[3a,3c] The key step of this synthesis was based on a [2+2] photocycloaddition reaction of the lactone dioxenone precursor **4**, followed by the reduction of the obtained adduct (**3** → **2**). This tetraol (**2**) contains the appropriate substitution pattern and stereochemistry for further elaboration towards the right-hand substructure of solanoeclepin A (**1**). This study was initially carried out with a methyl substituent at the dioxenone C-6 position, which greatly facilitates the synthesis of the photocycloaddition precursors.[3a,3c] However, the removal of this extra carbon to obtain the cyclobutanone was expected to be difficult.

In order to circumvent this problem, we undertook the investigation of intramolecular photochemical [2+2] cycloadditions of a new alkene-dioxenone **5** (Scheme 2), lacking the extra methyl group at C-6. We wish to describe in this article the synthesis of diol **6** which served as a key building block in the synthesis of the right-hand substructure **7** of solanoeclepin A. This small fragment of ten carbon atoms already contains three different ring sizes ranging from three to five, together with four stereogenic centres. This model study should allow us to probe both the formation of the strained bicylo[2.1.1]hexanone unit and the introduction of the cyclopropane ring next to this sterically crowded and labile moiety. Finally, this study is meant to provide insight into the structure-activity relationship of solanoeclepin A so as to eventually examine its potential role in the search for an environmentally benign method to combat the nematode.



Scheme 2. Approach towards the right-hand substructure of solanoeclepin A

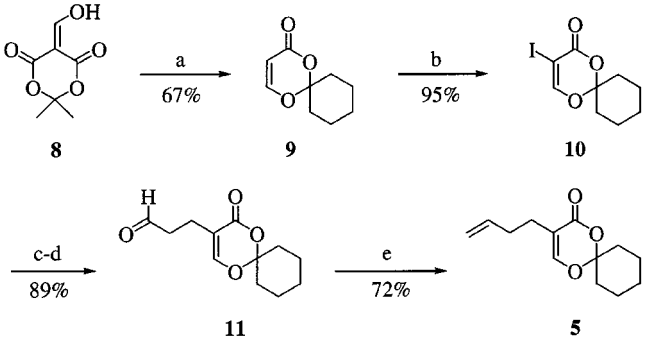
Results and Discussion

Sato et al. have reported a straightforward synthesis of the 5,6-unsubstituted dioxenone **9** starting from Meldrum's

[a] Institute of Molecular Chemistry, Laboratory of Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, 1018 WS Amsterdam, The Netherlands

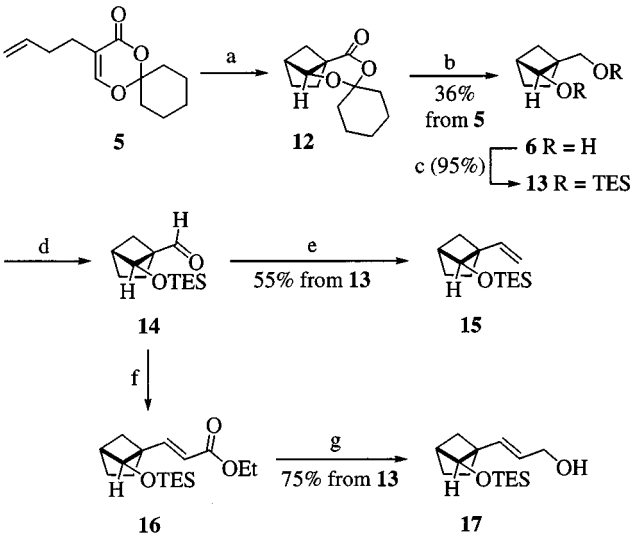
  1434–193X/01/0612–2371 $ 17.50+.50/0

acid **8** (Scheme 3).[4] The iododioxenone **10** was then formed in 67% yield in two steps: i) iodo-acetoxylation by means of *N*-iodosuccinimide in acetic acid, followed by ii) elimination of the β-acetate with Et_3N.[5] In the course our work, we found that treatment of **9** with iodine in pyridine/CCl_4 led directly to the iodo derivative **10** with an improved yield of 95%. In order to introduce the required pendant alkene for the envisaged photocycloaddition reaction, we attempted an iodide-lithium exchange with *t*BuLi at −90 °C in THF. Unfortunately, the dioxenone underwent addition of the lithium base instead of iodide-lithium exchange. Nevertheless, by means of isopropylmagnesium chloride[6] a smooth magnesium-iodide exchange was observed leading quantitatively to the protonated product **9** after workup. Our first attempt to introduce the required alkene chain involved alkylation of the in-situ-prepared Grignard reagent with 1-iodo-3-butene. However, the magnesium intermediate proved to be unreactive towards this alkylating agent and addition of copper salts did not remedy this problem. Acrolein, on the other hand, proved to be an excellent electrophile in this reaction if the magnesium intermediate was pretreated with copper(I) and HMPA,[7] and a smooth 1,4-addition took place to afford the aldehyde **11** in high yield. Subsequent Wittig olefination with KHMDS as a base[8] provided 3-butenyldioxenone **5**, setting the stage for the [2+2] photocycloaddition reaction.



Scheme 3. (a) cyclohexanone, xylene, reflux; (b) I_2, pyridine/CCl_4 (1:1, v/v), room temp.; (c) *i*PrMgCl, THF, −78 °C; (d) acrolein, CuBr·Me_2S (cat.), HMPA, TMSCl, THF, −78 °C to room temp.; (e) Ph_3PCH_3Br, KHMDS, toluene/THF, −78 °C to room temp.

Upon irradiation of dioxenone **5** at 300 nm (acetonitrile/acetone, 9:1 v/v, room temp.) complete conversion of the starting material was observed after 2 h (^1H NMR) and the expected crossed adduct **12** was formed (Scheme 4). This mode of closure was also observed with the analogous 6-methyldioxenones[3] and is in accordance with the so-called empirical rule of five.[9] This cycloadduct appeared to be unstable, decomposing slowly under the reaction conditions and during the subsequent workup. Therefore, dioxanone **12** was immediately reduced to diol **6**. The modest yield of this two-step reaction sequence is due to partial polymerisation of the terminal alkene precursor during the cycloaddition. However, we have shown that more highly functionalised tethered alkenes, which will eventually be used in the total synthesis of solanoeclepin A, usually give photoadducts in good yields.[3] The obtained diol **6** was disilylated by treatment with TESCl to afford **13**. The primary silyl ether was then oxidised selectively under Swern conditions to afford the aldehyde **14**.[10] This two-step sequence allowed the facile differentiation of the primary and secondary hydroxyl groups.



Scheme 4. (a) hν, MeCN/acetone (9:1, v/v), room temp.; (b) $LiAlH_4$, THF, room temp.; (c) TESCl, imidazole, DMF, room temp.; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to room temp. (e) Ph_3PCH_3Br, *n*BuLi, Et_2O, 0 °C to room temp.; (f) $EtOC(O)CH_2P(O)(OEt)_2$, NaH, THF, 0 °C to room temp.; (g) DIBAL−H, CH_2Cl_2, −78 °C to room temp.

A Wittig olefination of aldehyde **14** resulted in the formation of the terminal alkene **15**, which was envisaged to be a good starting material for the introduction of the cyclopropane carboxylic acid moiety. Unfortunately, this alkene proved to be very volatile and difficult to handle. Therefore, a new strategy was probed involving allylic alcohol **17** as the cyclopropane precursor. Thus, aldehyde **14** was subjected to a Horner−Wadsworth−Emmons reaction, affording the unsaturated ester **16** as a single double bond isomer. Subsequent reduction with DIBAL-H led to the desired allylic alcohol **17** in 75% overall yield from silyl ether **13**. This (*E*)-alkene was expected to be a good precursor for a Simmons−Smith cyclopropanation,[11] which should lead to the *trans*-substituted cyclopropane of the target molecule **7** (Scheme 2). Employing Charette's reagent[12] on alcohol **17** (Scheme 5), a smooth three-membered-ring formation occurred to give the desired *trans* cyclopropane **18** in 88% yield as a 3:2 diastereoisomeric mixture. After cleavage of the silyl ether with TBAF, both isomers of diol **19** could be easily separated by silica gel column chromatography. The minor isomer **19b** was crystalline and proved suitable for a crystal structure determination (Figure 1),[13] thereby providing unequivocal proof of our tricyclic structure.

Indeed, this isomer featured the correct relative stereochemistry for further elaboration towards **7**. Attempts to improve the diastereoselectivity of this reaction by using enantiopure auxiliaries such as Charette's ligand[14] or tartaric-ester-derived additives[15] failed. In both cases, smooth cyclopropanation took place but no improved stereoselect-

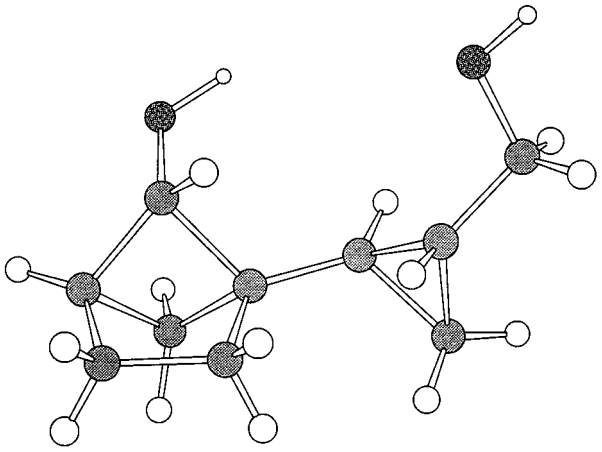
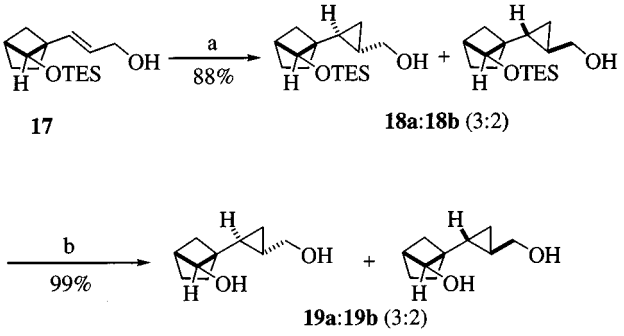


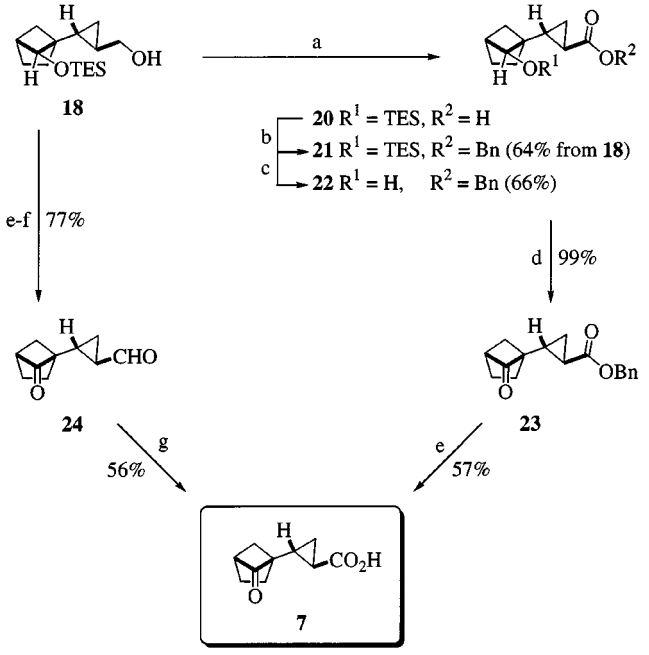
Figure 1. Crystal structure of compound **19b**



Scheme 5. (a) $Zn(CH_2I)_2$·DME, CH_2Cl_2, room temp.; (b) TBAF, THF, 0 °C

ivity was observed. It could be that the steric bulk on one side of the alkene prevents the correct approach of the ligand-metal complex.

Disappointed by the diastereoselectivity of the cyclopropanations with the allylic alcohol, we turned our attention to diazo-ester carbenoid chemistry with alkene **15**.[16] However, no reaction was observed in the presence of bis-oxazoline ligands[17] and the starting material was fully recovered. Assuming that this outcome was due to the bulkiness of our substrate, we paid attention to Haddad's work[18] on the formation of enantiomerically enriched cyclopropane rings from sterically hindered alkenes with chiral diazoester derivatives. Unfortunately, following this approach a complex mixture of products was obtained in which no cyclopropanated product could be detected. Finally, a palladium-catalysed reaction with diazomethane was attempted on the α,β-unsaturated ester **16**. But, once again, the starting material was completely consumed and no three-membered-ring formation could be observed in the ^1H NMR spectrum of the crude mixture. These results indicate the instability of bicyclo[2.1.1]hexanols **15** and **16** towards carbenoid species, which probably engage in ring-opening reactions under the cyclopropanation conditions. Nevertheless, with alcohol **18** in hand, albeit as a 3:2 mixture of diastereoisomers, we decided to probe the follow-up chemistry of our structure and especially to investigate the formation of the bicyclo[2.1.1]-hexanone subunit of solanoeclepin A (Scheme 6), which was expected to be rather unstable. The carboxylic acid moiety was first introduced by oxidation of **18** with $RuCl_3$/$NaIO_4$ to afford **20**, and subsequently transformed into its benzyl ester **21**. Removal of the TES group with TBAF afforded the secondary alcohol **22**, the precursor for the strained cyclobutanone. As far as we know, the only reported oxidation of a bicyclo[2.1.1]hexanol into its cyclobutanone counterpart involves rather harsh chromium(VI)-mediated strongly acidic conditions.[19] So, more subtle conditions which should be compatible with the sensitive substrate during the last stage of the synthesis of our target molecule were sought. We were very pleased to find that a smooth oxidation reaction occurred with TPAP and NMO at 0 °C giving rise to bicyclo[2.1.1]hexanone **23** in nearly quantitative yield. Finally, hydrogenolysis of the benzyl ester led to the target molecule **7**.



Scheme 6. All compounds refer to a mixture of diastereoisomers in a ratio of 3:2 as indicated in Scheme 5; the minor isomer is drawn: (a) $RuCl_3$·xH_2O (cat.), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, 0 °C; (b) BnBr, Cs_2CO_3, CH_3CN, room temp.; (c) TBAF, THF, 0 °C; (d) TPAP (cat.), NMO, acetone, 0 °C; (e) H_2, $Pd(OH)_2$, MeOH, room temp.; (f) TPAP (cat.), NMO, acetone, 0 °C; (g) $RuCl_3$·xH_2O (cat.), $NaIO_4$, $CH_3CN/CCl_4/H_2O$, 0 °C

With these oxidation conditions in hand, a shorter pathway towards **7** was investigated. After deprotection of the TES group of **18**, a one-pot TPAP bis-oxidation of the obtained diol afforded the keto-aldehyde **24** in good yield. A rapid ruthenium oxidation (30 min.) of carboxaldehyde **24** provided the target molecule **7** in only three steps from **18**. This compound proved to be sufficiently stable to be isolated and purified. However, slow decomposition of the bicyclo[2.1.1]hexanone was observed by ^1H NMR spectroscopy when **7** was treated with an excess of MeOH in $CDCl_3$. It is believed that the instability of the strained cyclobutanone, probably due to the reactivity of the ketone towards nucleophilic attack, could in part be at the origin

of the activity and instability of the natural product **1**. Unfortunately, the isomeric mixture of **7** showed no hatching activity for potato-cyst nematodes and therefore more elaborate structures are currently under investigation.

Conclusions

In conclusion, we have described a straightforward approach towards the right-hand substructure **7** of solanoeclepin A (**1**). The intramolecular [2+2] photocycloaddition of alkene-dioxenone **5**, followed by exhaustive reduction, furnished the bicyclo[2.1.1]hexanol unit **6**. A diastereoselective cyclopropanation using the classical methods failed, due both to the instability and the steric hindrance of this dense bicyclic structure. However, a Simmons−Smith-type reaction of the allylic alcohol **17** afforded a diastereoisomeric mixture of *trans* cyclopropanes **18**. Finally, TPAP oxidation allowed the smooth formation of the strained cyclobutanone. Unfortunately, the target molecule showed no hatching activity for potatocyst nematodes.

Experimental Section

General: All reactions were carried out under an inert atmosphere of dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for the transfer of air-sensitive reagents and dry solvents. IR spectra were obtained from $CHCl_3$ solutions, using a Bruker IFS 28 FT-spectrophotometer and wavelengths are reported in cm^{-1}. ^1H and ^{13}C NMR spectra were determined in $CDCl_3$ using a Bruker ARX 400 (400 MHz and 100 MHz, respectively) unless indicated otherwise. Chemical shifts are given in ppm downfield from tetramethylsilane. HRMS measurements were carried out using a JEOL JMS-SX/SX 102 A Tandem mass spectrometer. Chromatographic purification refers to flash chromatography[20] using the indicated solvent (mixture) and Acros silica gel (0.030−0.075 mm). R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel F_{254}) with the solvent (mixture) mentioned before unless noted otherwise. Melting points are uncorrected. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over MS 4Å under a dry nitrogen atmosphere. Triethylamine was dried and distilled from KOH pellets. All commercially available reagents were used as received, unless indicated otherwise.

3-Iodo-1,5-dioxa-spiro[5.5]undec-3-en-2-one[5] **(10):** To a solution of dioxenone **9** (5.00 g, 29.7 mmol) in CCl_4/pyridine (100 mL, 1:1 v/v) was added in one portion I_2 (22.8 g, 90 mmol). The reaction mixture was stirred at room temperature for 16 h. The mixture was then diluted with ether (100 mL), aqueous $Na_2S_2O_3$ (1 M, 50 mL) was added and the resulting mixture was stirred for 30 min. The layers were separated and the aqueous layer was extracted with ether (3 × 50 mL). The combined organic layers were washed with aqueous $Na_2S_2O_3$ (50 mL), a saturated aqueous solution of $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:4) afforded **10** (8.30 g, 95%) as a slightly yellow solid. R_f = 0.21. − ^1H NMR: δ = 7.45 (s, 1 H), 2.07−1.95 (m, 4 H), 1.76−1.44 (m, 6 H).

3-(4-Oxo-1,5-dioxa-spiro[5.5]undec-2-en-3-yl)propionaldehyde (11): To a solution of isopropylmagnesium chloride (2 M in THF, 11 mL, 22 mmol) in THF (16 mL) at −78 °C was added dropwise a solution of iododioxenone **10** (5.89 g, 20.0 mmol) in THF (80 mL) over 4 h. Copper(I)bromide-dimethyl sulfide complex (412 mg, 2.0 mmol) was added in one portion, followed by hexamethylphosphoric triamide (10.4 mL, 57 mmol). Then, a solution of acrolein (2.8 mL, 42 mmol), and trimethylsilyl chloride (7.6 mL, 60 mmol) in 10 mL of THF was added dropwise over 30 min. The mixture was stirred for 5 h at −78 °C, allowed to warm to room temperature and stirred for 12 h. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl (40 mL) and most of the THF was evaporated. The aqueous phase was extracted with EtOAc (4 × 40 mL). The combined organic layers were washed with water (2 × 16 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:4) afforded **11** (3.99 g, 89%) as a colourless oil. The product showed some degradation after being stored at −20 °C for a week. R_f = 0.21. − ^1H NMR: δ = 9.78 (s, 1 H), 7.04 (s, 1 H), 2.73 (t, J = 6.9 Hz, 2 H), 2.47 (t, J = 6.9 Hz, 1 H), 2.00−1.91 (m, 1 H), 1.70−1.57 (m, 3 H), 1.48−1.44 (m, 2 H). − ^{13}C NMR: δ = 201.1, 161.4, 154.3, 107.6, 107.4, 42.6, 33.7, 24.5, 22.1, 18.9. − IR: ṽ = 2710, 1727, 1640, 1187.

3-But-3-enyl-1,5-dioxa-spiro[5.5]undec-3-en-2-one (5): To a solution of methyltriphenylphosphonium bromide (10.4 g, 29 mmol) in THF (18 mL) at 0 °C was added dropwise KHMDS (0.5 M in toluene, 57 mL, 29 mmol). The resulting mixture was stirred for 30 min. at 0 °C and cooled to −78 °C. Then, a solution of aldehyde **11** (5.80 g, 26 mmol) in toluene (10 mL) was added dropwise. The solution was stirred for 30 min. at −78 °C, 30 min. at 0 °C and allowed to warm to room temperature over 3 h. The reaction mixture was treated with a saturated aqueous solution of NH_4Cl (30 mL). The layers were separated and the aqueous phase was extracted with ether (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:9) afforded **5** (4.15 g, 72%) as a colourless oil. R_f = 0.33. − ^1H NMR: δ = 6.90 (s, 1 H), 5.83−5.70 (m, 1 H), 5.05−4.99 (m, 2 H), 2.25 (br s, 4 H), 2.01−1.94 (m, 5 H), 1.75−1.55 (m, 3 H), 1.48−1.45 (m, 2 H). − ^{13}C NMR: δ = 161.5, 153.0, 137.5, 115.7, 108.8, 107.0, 34.0, 32.7, 25.5, 25.0, 22.0. − IR: ṽ = 1730, 1639, 1186. − HRMS ($C_{13}H_{19}O_3$ [MH^+]; FAB): calcd. 223.1334; found 223.1333.

Cycloadduct 12: The photoreaction was carried out in a Pyrex glass vessel with a Rayonet RPR 3000 Å at room temperature. A solution of dioxenone-alkene **5** (351 mg, 1.6 mmol) in acetonitrile/acetone (40 mL, 9:1 v/v) was degassed by bubbling argon through it for 30 min. The solution was kept under argon and irradiated for 2 h. The reaction was followed by monitoring the UV absorption of the starting material on TLC. The solvent was removed in vacuo to give the adduct **12** (351 mg) as a colourless oil. The crude product was used immediately in the next reaction without further purification. − ^1H NMR: δ = 3.90 (d, J = 6.1 Hz, 1 H), 2.80−2.77 (m, 1 H), 2.60−2.58 (m, 1 H), 2.10−1.43 (m, 15 H). − IR: ṽ = 1712, 1638.

1-Hydroxymethylbicyclo[2.1.1]hexan-5-ol (6): To a solution of $LiAlH_4$ (1 M in THF, 28 mL, 28 mmol) was added dropwise at room temperature a solution of crude cycloadduct **12** (1.76 g, 7.9 mmol) in THF (15 mL). The reaction mixture was stirred for 10 min. Then, the reaction was carefully quenched by addition of EtOAc and saturated aqueous Na_2SO_4 (3 mL) was added. The resulting mixture was stirred for 1 h. After the addition of solid Na_2SO_4, the mixture was filtered through Celite and concentrated in vacuo.

Purification by chromatography (EtOAc) afforded **6** (364 mg, 36% from **12**) as a white powder. Colourless crystals. R_f = 0.23. m.p. 66−68 °C. − ^{1}H NMR: δ = 3.91 (d, *J* = 6.5 Hz, 1 H), 3.86 (d, *J* = 11.6 Hz, 1 H), 3.79 (d, *J* = 11.6 Hz, 1 H), 2.80 (br s, 1 H, OH), 2.65−2.63 (m, 1 H), 2.31 (br, 1 H), 2.14 (br s, 1 H, OH), 1.64−1.61 (m, 2 H), 1.48−1.45 (m, 2 H), 1.22 (dd, *J* = 6.9−6.7 Hz, 1 H). − ^{13}C NMR: δ = 82.6, 63.8, 53.6, 42.6, 35.0, 26.4, 24.2. − IR: ṽ = 3334 (br). − HRMS ($C_7H_{12}O_2$; EI): calcd. 128.0837; found 128.0822.

5-Triethylsilanyloxy-1-triethylsilanyloxymethyl-bicyclo[2.1.1]hexane (13): To a solution of alcohol **6** (175 mg, 1.4 mmol) and imidazole (377 mg, 5.5 mmol) in DMF (5 mL) at 0 °C was added TESCl (0.7 mL, 4.1 mmol). The mixture was stirred at room temperature for 1 h. The resulting mixture was diluted with water (6 mL) and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were washed with water (2 × 3 mL), a saturated aqueous solution of $NaHCO_3$ (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:9) afforded **13** (464 mg, 95%) as a colourless oil. R_f = 0.7. − ^{1}H NMR: δ = 3.75 (d, *J* = 10.5 Hz, 1 H), 3.67 (d, *J* = 6.5 Hz, 1 H), 3.55 (d, *J* = 10.5 Hz, 1 H), 2.22−2.19 (m, 2 H), 1.55−1.52 (m, 4 H), 1.13 (dd, *J* = 6.4, 6.3 Hz, 1 H), 0.95 (t, *J* = 7.8 Hz, 9 H), 0.94 (t, *J* = 7.8 Hz, 9 H), 0.57 (br q, *J* = 7.8 Hz, 12 H). − ^{13}C NMR: δ = 80.3, 61.1, 55.2, 43.4, 35.6, 25.9, 24.0, 6.8, 4.9, 4.5. − HRMS ($C_{19}H_{41}O_2Si_2$ [MH^+]; FAB): calcd. 357.2645; found 357.2645.

5-Triethylsilanyloxybicyclo[2.1.1]hexane-1-carbaldehyde (14): To a solution of oxalyl chloride (198 μL, 2.3 mmol) in CH_2Cl_2 (6 mL) was added dropwise DMSO (341 μL, 4.8 mmol) at −60 °C, then, after 5 min., a solution of silyl ether **13** (381 mg, 1.1 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 40 min. at −40 °C. Finally, triethylamine (2.3 mL, 17 mmol) was added at −78 °C and the solution was allowed to warm to room temperature over 30 min. Water (7.5 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with water (2 × 3 mL), a saturated aqueous solution of $NaHCO_3$ (3 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was used immediately in the next reaction without further purification. An analytically pure sample was obtained after chromatography (EtOAc/PE, 1:9) to afford **14** as a colourless oil. R_f = 0.41. − ^{1}H NMR: δ = 9.75 (s, 1 H), 4.08 (d, *J* = 6.4 Hz, 1 H), 2.98−2.96 (m, 1 H), 2.31 (br s, 1 H), 1.81−1.65 (m, 4 H), 1.40 (dd, *J* = 6.8, 6.7 Hz, 1 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.57 (q, *J* = 7.9 Hz, 6 H). − ^{13}C NMR: δ = 202.9, 83.9, 62.7, 44.4, 35.2, 24.5, 23.7, 6.6, 4.6. − IR: 2800, 2725, 1713.

Triethyl-(1-vinylbicyclo[2.1.1]hex-5-yloxy)silane (15): To a solution of methyltriphenylphosphonium bromide (123 mg, 0.34 mmol) in ether (3 mL) at 0 °C was added dropwise *n*BuLi (1.6 M in hexane, 221 μL, 0.35 mmol). The resulting mixture was stirred for 1 h at 0 °C. Then, a solution of aldehyde **14** (81 mg, 0.28 mmol) in ether (2 mL) was added dropwise. The solution was stirred for 1 h at 0 °C and then allowed to warm to room temperature. The reaction mixture was quenched with acetone (2 mL) and filtered through a short pad of silica gel. The solvent was carefully evaporated to afford the volatile alkene **15** (45 mg, 55% from **13**) as a colourless liquid. − ^{1}H NMR: δ = 5.99 (dd, *J* = 15.7, 10.7 Hz, 1 H), 5.04 (m, 2 H), 3.70 (d, 1 H), 2.55−2.53 (m, 1 H), 2.18 (br s, 1 H), 1.61−1.64 (m, 2 H), 1.30−1.21 (m, 2 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.56 (q, *J* = 7.9 Hz, 6 H).

Ethyl 3-(5-Triethylsilanyloxybicyclo[2.1.1]hex-1-yl)acrylate (16): To a dispersion of sodium hydride (60% dispersion in mineral oil, 47 mg, 1.2 mmol) in THF (3 mL) at 0 °C was added dropwise a solution of triethyl phosphonoacetate (244 μL, 1.2 mmol). The resulting mixture was stirred for 1 h at 0 °C and a solution of crude aldehyde **14** (260 mg, ca. 1.1 mmol) in THF (3 mL) was added dropwise. The solution was stirred for 30 min. at 0 °C and allowed to warm to room temperature. A saturated aqueous solution of NH_4Cl (10 mL) was added and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with ether (3 × 7 mL). The combined organic layers were washed with water (5 mL), dried over $MgSO_4$ and concentrated in vacuo. The crude product was used in the next reaction without further purification. An analytically pure sample was obtained after chromatography (EtOAc/PE, 1:9) to afford **16** as a colourless oil. R_f = 0.55. − ^{1}H NMR: δ = 7.05 (d, *J* = 15.9 Hz, 1 H), 5.79 (d, *J* = 15.9 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.78 (d, *J* = 6.4 Hz, 1 H), 2.64−2.62 (m, 1 H), 2.25−2.24 (m, 1 H), 1.69−1.59 (m, 4 H), 1.31−1.25 (m, 1 H), 1.28 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.9 Hz, 9 H), 0.56 (q, *J* = 7.9 Hz, 6 H). − ^{13}C NMR: δ = 166.8, 147.4, 121.3, 83.7, 60.0, 55.7, 44.0, 37.7, 28.0, 24.1, 14.2, 6.8, 4.7. − IR: ṽ = 1722. − HRMS ($C_{17}H_{31}O_3Si$ [MH^+]; FAB): calcd. 311.2042; found 311.2045.

3-(5-Triethylsilanyloxybicyclo[2.1.1]hex-1-yl)-prop-2-en-1-ol (17): To a solution of crude ester **16** (340 mg, ca. 1.1 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added dropwise a solution of DIBAL-H (1.5 M in toluene, 1.7 mL, 2.5 mmol). The resulting mixture was stirred for 1 h at −78 °C and allowed to warm to room temperature. Then, the reaction was carefully quenched by addition of EtOAc, and a saturated aqueous solution of Na_2SO_4 (10 drops) was added. The resulting mixture was stirred for 1 h. After the addition of solid Na_2SO_4 the mixture was filtered through Celite and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:6) afforded **17** (216 mg, 75% from **13**) as a colourless oil. R_f = 0.30. − ^{1}H NMR: δ = 5.85 (d, *J* = 15.7 Hz, 1 H), 5.66 (dt, *J* = 15.7, 5.9 Hz, 1 H), 4.13 (m, 2 H), 3.69 (d, *J* = 6.4 Hz, 1 H), 2.54−2.52 (m, 1 H), 2.20−2.18 (m, 1 H), 1.65−1.52 (m, 4H + OH), 1.23 (dd, *J* = 6.6, 6.4 Hz, 1 H), 0.94 (t, *J* = 7.9 Hz, 9 H), 0.56 (q, *J* = 7.9 Hz, 6 H). − ^{13}C NMR: δ = 131.7, 129.5, 83.5, 63.9, 55.1, 43.5, 37.9, 28.1, 24.2, 6.7, 4.7. − IR: 3297 (br).

{2-(5-Triethylsilanyloxybicyclo[2.1.1]hex-1-yl)cyclopropyl}methanol (18): To a solution of DME (150 μL, 1.4 mmol) and Et_2Zn (1 M in hexane, 1.4 mL, 1.4 mmol) in freshly distilled CH_2Cl_2 (3 mL) at −10 °C was added dropwise CH_2I_2 (225 μL, 2.8 mmol). The resulting solution was stirred for 30 min. at −10 °C.

To a solution of allylic alcohol **17** (49 mg, 0.18 mmol) in freshly distilled CH_2Cl_2 (2 mL) at 0 °C was added dropwise the previously prepared $Zn(CH_2I)_2$·DME reagent (2 mL, 0.3 M, 0.6 mmol). The mixture was allowed to warm to room temperature and stirred for 6 h. A saturated aqueous solution of NH_4Cl (4 mL) was added at 0 °C and the resulting mixture was stirred for 15 min. The layers were separated and the aqueous phase was extracted with ether (3 × 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:7) afforded a 3:2 mixture of diastereoisomers of **18** (45 mg, 88%) as a colourless oil. R_f = 0.25. − ^{1}H NMR: δ = 3.67 (d, *J* = 6.5 Hz, 1 H^a), 3.63 (d, *J* = 6.5 Hz, 1 H^b), 3.57 (dd, *J* = 10.7, 6.5 Hz, 1 H^a), 3.45 (dd, *J* = 11.0, 7.0 Hz, 1 H^b), 3.38 (dd, *J* = 11.0, 7.3 Hz, 1 H^b), 3.29 (dd, *J* = 10.7, 7.9 Hz, 1 H^a), 2.22 (br, 1 H^b), 2.14 (br, 2 H^a + 1 H^b), 1.59 (br, 2 H^{a+b}, OH), 1.54−1.50 (m, 4 $H^{a/b}$), 1.37−1.20 (m, 4 $H^{a/b}$), 1.05 (dd, *J* = 6.5, 6.3 Hz, 1 $H^{a/b}$), 1.01−0.96 (m, 1 $H^{a/b}$), 0.96 (br t, 9 H), 0.89−0.83 (m, 1 $H^{a/b}$), 0.80−0.75 (m, 1 $H^{a/b}$), 0.71−0.61 (m, 3 $H^{a/b}$), 0.42−0.35 (m, 2 H^{a+b}), 0.27−0.23 (m, 1 $H^{a/b}$). − IR: ṽ = 3334 (br). − HRMS ($C_{16}H_{28}OSi$ [M^+ − H_2O]; EI): calcd. 264.1909; found 264.1910.

1-(2-Hydroxymethylcyclopropyl)bicyclo[2.1.1]hexan-5-ol (19): To a solution of alcohol **18** (39 mg, 0.14 mmol) in 4 mL of THF at 0 °C was added dropwise TBAF (1 M in THF, 280 μL, 0.28 mmol). The resulting mixture was stirred for 15 min. at 0 °C. A saturated aqueous solution of NH_4Cl (5 mL) was then added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with ether (3 × 5 mL). The combined organic layers were washed with water (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc) afforded a 3:2 mixture of two diastereomers **19a** and **19b** (18 mg, 99%) as a colourless oil. Both isomers were obtained pure after repeated chromatography.
19a: colourless oil. $R_f = 0.31$. − ^{1}H NMR: δ = 3.89 (dd, J = 10.6, 5.4 Hz, 1 H), 3.77 (d, J = 6.4 Hz, 1 H), 3.07 (dd, J = 10.6, 9.3 Hz, 1 H), 2.75 (br s, 1 H, OH), 2.23 (q, J = 1.5 Hz, 1 H), 2.14 (br s, 1 H, OH), 2.10−2.07 (m, 1 H), 1.61−1.38 (m, 4 H), 1.25−1.16 (m, 1 H), 0.97 (t, J = 6.6 Hz, 1 H), 0.67−0.63 (m, 1 H), 0.35−0.26 (m, 2 H). − ^{13}C NMR: δ = 82.8, 67.0, 53.7, 41.0, 34.2, 29.0, 24.3, 18.6, 16.9, 3.9. − IR: $\tilde{\nu}$ = 3300 (br).
19b: Single crystals suitable for an X-ray structure determination were obtained after recrystallisation from EtOAc/pentane. R_f = 0.24; m.p. 92−93 °C. − ^{1}H NMR: δ = 3.71 (d, J = 6.4 Hz, 1 H), 3.66 (dd, J = 11.0, 6.2 Hz, 1 H), 3.25 (dd, J = 11.0, 8.0 Hz, 1 H), 2.28 (br s, 1 H, OH), 2.22−2.19 (m, 2 H), 1.67 (br s, 1 H, OH), 1.59−1.53 (m, 2 H), 1.41−1.37 (m, 1 H), 1.32−1.27 (m, 1 H), 1.11 (dd, J = 6.7, 6.4 Hz, 1 H), 0.93−0.87 (m, 1 H), 0.65 (ddd, J = 8.3, 5.5, 4.6 Hz, 1 H), 0.44 (dt, J = 9.6, 4.8 Hz, 1 H). − ^{13}C NMR: δ = 82.4, 66.1, 53.1, 41.5, 36.2, 29.7, 27.1, 24.2, 16.2, 7.4. − IR: $\tilde{\nu}$ = 3300 (br).

2-(5-Triethylsilanyloxybicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylic Acid (20): To a solution of alcohol **18** (21 mg, 0.073 mmol), $NaIO_4$ (62 mg, 0.29 mmol) and $NaHCO_3$ (12 mg, 0.15 mmol) in CH_3CN/CCl_4/H_2O (1.8 mL, 1:1:1.5 v/v) at 0 °C was added $RuCl_3{\cdot}xH_2O$ (tip of a spatula). The resulting solution was stirred for 3 h at 0 °C and then filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated in vacuo (bath temperature: 30 °C) to afford acid **20** (17 mg) as a yellow oil. The crude product was used immediately in the next reaction without further purification. − ^{1}H NMR: δ = 11.52 (br s, 1 H^{a+b}), 3.68 (d, J = 6.4 Hz, 1 H^b), 3.67 (d, J = 6.5 Hz, 1 H^a), 2.24 (br s, 1 H^{a+b}), 2.13 (br s, 1 H^{a+b}), 1.70−1.66 (m, 1 H^b), 1.61−1.45 (m, 2 H^{a+b} + 1 H^a), 1.43−1.33 (m, 2 H^{a+b}), 1.22−1.19 (m, 1 H^{a+b}), 1.08−1.00 (m, 2 H^{a+b}), 0.94 (t, J = 7.9 Hz, 9 H^{a+b}), 0.90−0.85 (m, 1 H^{a+b}), 0.58 (q, J = 7.9 Hz, 6 H^a), 0.57 (q, J = 7.9 Hz, 6 H^b). − IR: $\tilde{\nu}$ = 2955 (br), 1699.

Benzyl 2-(5-Triethylsilanyloxybicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylate (21): To a solution of the crude acid **20** (17 mg, 0.057 mmol) in 2 mL of CH_3CN at room temperature was added in one portion Cs_2CO_3 (20 mg, 0.061 mmol). The solution was stirred for 15 min. and benzyl bromide was added dropwise (8 μL, 0.07 mmol). The resulting mixture was stirred for 16 h at room temperature. A saturated aqueous solution of NH_4Cl (5 mL) was added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with ether (3 × 4 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 1:7) afforded **21** (18 mg, 64% from **18**) as a 3:2 mixture of diastereoisomers as a colourless oil. $R_f = 0.55$. − ^{1}H NMR: δ = 7.36−7.31 (m, 5 H^{a+b}), 5.14 (d, J = 12.4 Hz, 1 H^a), 5.12 (d, J = 12.4 Hz, 1 H^b), 5.06 (d, J = 12.4 Hz, 1 H^b), 5.05 (d, J = 12.4 Hz, 1 H^a), 3.66 (d, J = 6.4 Hz, 1 H^{a+b}), 2.28 (br, 1 H^b), 2.22 (br s, 1 H^a), 2.11 (br s, 1 H^{a+b}), 1.78−1.74 (m, 1 H^a), 1.60−1.54 (m, 3 H^{a+b}), 1.41−1.33 (m, 2 H^{a+b}), 1.20−1.15 (m, 1 H^b), 1.04−0.99 (m, 2 H^{a+b}), 0.95−0.89 (m, 1 H^b), 0.93−0.89 (m, 9 H^{a+b}), 0.79 (ddd, J = 8.2, 6.7, 3.9 Hz, 1 H^a), 0.59−0.51 (m, 6 H^{a+b}). − ^{13}C NMR: δ = 174.7^a, 174.7^b, 136.2^b, 136.2^a, 128.5^b, 128.5^a, 128.2^{a+b}, 128.1^b, 128.1^a, 82.5^a, 82.4^b, 66.2^a, 66.1^b, 53.2^b, 53.14^a, 42.6^b, 42.6^a, 35.6^b, 35.6^a, 27.7^a, 27.4^b, 23.9^b, 23.7^a, 22.8^b, 22.6^a, 17.2^a, 15.8^b, 12.8^b, 11.1^a, 6.7^b, 6.7^a, 4.8^b, 4.7^a. − IR: $\tilde{\nu}$ = 1728.

Benzyl 2-(5-Hydroxybicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylate (22): To a solution of ester **21** (18 mg, 0.047 mmol) in THF (2 mL) at 0 °C was added dropwise TBAF (1 M in THF, 67 μL, 0.067 mmol). The solution was stirred for 1 h at 0 °C. Then, a saturated aqueous solution of NH_4Cl (5 mL) was added and the resulting mixture was stirred for 15 min. The aqueous phase was extracted with ether (3 × 4 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$ and concentrated in vacuo. Purification by chromatography (EtOAc/PE, 2:5) afforded a 3:2 mixture of diastereoisomers of **22** (8 mg, 66%) as a colourless oil. $R_f = 0.21$. − ^{1}H NMR: δ = 7.39−7.30 (m, 5 H^{a+b}), 5.14 (d, J = 12.4 Hz, 1 H^a), 5.13 (d, J = 12.4 Hz, 1 H^b), 5.09 (d, J = 12.4 Hz, 1 H^b), 5.08 (d, J = 12.4 Hz, 1 H^a), 3.79 (d, J = 6.4 Hz, 1 H^b), 3.77 (d, J = 6.5 Hz, 1 H^a), 2.22 (br s, 2 H^{a+b}), 1.84 (br s, 1 H^{a+b}, OH), 1.80−1.76 (m, 1 H^{a+b}), 1.59−1.35 (m, 5 H^{a+b}), 1.25−1.21 (m, 1 H^a), 1.11−1.02 (m, 2 H^{a+b}), 0.79 (ddd, J = 8.2, 6.7, 4.0 Hz, 1 H^a). − IR: $\tilde{\nu}$ = 3444 (br), 1724.

Benzyl 2-(5-Oxobicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylate (23): To a solution of alcohol **22** (8 mg, 0.03 mmol) and NMO (11 mg, 0.09 mmol) in acetone (2 mL) at 0 °C was added TPAP (0.5 mg, 0.002 mmol) in one portion. The resulting solution was stirred for 45 min. at 0 °C, concentrated in vacuo to 1 mL (bath temperature: 30 °C) and filtered through a short pad of silica gel. Purification by chromatography (EtOAc/PE, 2:5) afforded a 3:2 mixture of two diastereoisomers of **23** (8 mg, 99%) as a colourless oil. $R_f = 0.40$. − ^{1}H NMR: δ = 7.37−7.32 (m, 5 H^{a+b}), 5.14 (d, J = 12.4 Hz, 1 H^{a+b}), 5.08 (d, J = 12.4 Hz, 1 H^{a+b}), 2.79 (br s, 1 H^{a+b}), 1.90−1.66 (m, 5 H^{a+b}), 1.60−1.56 (m, 1 H^{a+b}), 1.44 (d, J = 7.2 Hz, 1 H^a), 1.39 (d, J = 7.2 Hz, 1 H^b) 1.26−1.20 (m, 2 H^{a+b}), 1.13−1.09 (m, 1 H^b), 1.08 (ddd, J = 8.4, 6.7, 4.3 Hz, 1 H^a). − ^{13}C NMR: δ = 199.7^b, 199.6^b, 173.7^a, 173.7^b, 138.0^b, 137.8^a, 128.5^{a+b}, 128.2^b, 128.2^a, 128.1^a, 128.1^a, 66.4^{a+b}, 64.5^b, 66.4^a, 52.4^b, 52.2^a, 31.4^a, 30.9^b, 25.4^b, 25.0^a, 21.8^a, 21.7^b, 19.9^{a+b}, 17.3^a, 17.1^b, 12.8^b, 12.2^a. − IR: $\tilde{\nu}$ = 1776, 1725.

2-(5-Oxobicyclo[2.1.1]hex-1-yl)cyclopropanecarbaldehyde (24): To a solution of diol **18** (17 mg, 0.10 mmol) and NMO (37 mg, 0.31 mmol) in acetone (3 mL) at 0 °C was added TPAP (2 mg, 0.005 mmol) in one portion. The resulting solution was stirred for 2 h at 0 °C, concentrated in vacuo to 1 mL (bath temperature: 30 °C) and filtered through a short pad of silica gel. Purification by chromatography (EtOAc/PE, 2:3) afforded a 3:2 mixture of diastereoisomers of **24** (17 mg, 77%) as a colourless oil. $R_f = 0.38$. − ^{1}H NMR: δ = 9.15 (d, J = 4.9 Hz, 1 H^a), 9.12 (d, J = 5.0 Hz, 1 H^b), 2.83 (m, 1 H^{a+b}), 2.09 (m, 1 H^a), 2.02 (m, 1 H^b), 1.91−1.66 (m 4 H^{a+b}), 1.62−1.56 (m, 1 H^{a+b}), 1.47 (d, J = 7.2 Hz, 1 H^a), 1.42 (d, J = 7.2 Hz, 1 H^b), 1.37−1.24 (m, 3 H^a + 2 H^b), 0.97−0.85 (m, 1 H^b). − ^{13}C NMR: δ = 200.6^b, 200.5^b, 199.6^a, 199.5^b, 64.4^b, 64.2^a, 52.7^a, 52.6^b, 31.8^a, 31.2^b, 27.0^a, 26.9^b, 25.7^b, 25.2^a, 22.0^a, 21.9^b, 20.2^a, 19.9^b, 12.4^a, 12.0^a. − IR: $\tilde{\nu}$ = 1773, 1705.

2-(5-Oxobicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylic Acid (7 from 23): To a solution of ester **23** (8 mg, 0.03 mmol) in MeOH (2 mL) at room temperature was added a small portion of $Pd(OH)_2$. The solution was vigorously stirred while hydrogen was bubbled through for 5 min. Finally, the solution was stirred for 30 min. under a hydrogen atmosphere. The mixture was filtered through Celite and concentrated in vacuo (bath temperature: 30 °C). Purification

by chromatography (EtOAc/PE, 3:4 + 1% acetic acid) afforded a 3:2 mixture of diastereoisomers of **7** (3 mg, 57%) as a white solid.

2-(5-Oxobicyclo[2.1.1]hex-1-yl)cyclopropanecarboxylic Acid (7 from 24): To a solution of keto-aldehyde **24** (8 mg, 0.05 mmol) and $NaIO_4$ (43 mg, 0.20 mmol) in $CH_3CN/CCl_4/H_2O$ (1.8 mL, 1:1:1.5 v/v) at 0 °C was added $RuCl_3{\cdot}xH_2O$ (tip of a spatula). The resulting solution was stirred for 30 min. at 0 °C and then filtered through Celite. The filtrate was dried over $MgSO_4$ and concentrated in vacuo (bath temperature: 30 °C). Purification by chromatography (EtOAc/PE, 3:4 + 1% acetic acid) afforded a 3:2 mixture of diastereoisomers of **7** (5 mg, 56%) as a white solid. $R_f \approx 0.21$. – ^{1}H NMR: δ = 11.0 (br s, 1 H^{a+b}), 2.81 (br s, 1 H^{a+b}), 1.89–1.68 (m, 5 H^{a+b}), 1.61–1.57 (m, 1 H^{a+b}), 1.45 (d, J = 7.2 Hz, 1 H^a), 1.40 (d, J = 7.2 Hz, 1 H^b), 1.30–1.23 (m, 2 H^{a+b}), 1.18–1.12 (m, 1 H^{a+b}). – ^{13}C NMR: δ = 199.6^b, 199.4^b, 179.7^{a+b}, 64.4^b, 64.2^a, 52.4^a, 52.3^b, 31.4^a, 30.9^b, 25.4^a, 25.0^b, 21.8^b, 21.7^a, 20.7^a, 20.7^b, 17.1^a, 16.8^b, 13.3^a, 12.7^a. – IR: $\tilde{\nu}$ = 1776, 1695.

Acknowledgments

The HLB Agricultural Research Centre, Assen, The Netherlands is kindly acknowledged for performing the hatching activity tests. Jan Fraanje and Kees Goubitz from the Laboratory of Crystallography, University of Amsterdam, The Netherlands are kindly acknowledged for the X-ray crystal structure determination. These investigations are supported (in part) by the Netherlands Research Council for Chemical Sciences (CW) with financial aid from the Netherlands Technology Foundation (STW).

[1] J. G. Mulder, P. Diepenhorst, P. Plieger, I. E. M. Brüggemann-Rotgans, PCT Int. Appl. WO 93/02,083; *Chem Abstr.* **1993**, *118*, 185844z.
[2] H. Schenk, R. A. J. Driessen, R. De Gelder, K. Goubitz, H. Nieboer, I. E. M. Brüggemann-Rotgans, P. Diepenhorst, *Croat. Chem. Acta* **1999**, *72*, 593–606.
[3] [3a] R. H. Blaauw, J.-F. Brière, R. de Jong, J. C. J. Benningshof, A. E. van Ginkel, F. P. J. T. Rutjes, J. Fraanje, K. Goubitz, H. Schenk, H. Hiemstra, *Chem. Commun.* **2000**, 1463–1464. – [3b] J. C. J. Benningshof, R. H. Blaauw, A. E. van Ginkel, F. P. J. T. Rutjes, J. Fraanje, K. Goubitz, H. Schenk, H. Hiemstra, *Chem. Commun.* **2000**, 1465–1466. – [3c] R. H. Blaauw, J-F. Brière, R. de Jong, J. C. J. Benningshof, A. E. van Ginkel, F. P. J. T. Rutjes, J. Fraanje, K. Goubitz, H. Schenk, H. Hiemstra, *J. Org. Chem.* **2001**, *66*, 233–242.
[4] M. Sato, K. Sekiguchi, H. Ogasawara, C. Kaneko, *Synthesis* **1985**, *2*, 224–226.
[5] M. Sato, N. Yoneda, C. Kaneko, *Chem. Pharm. Bull.* **1986**, *34*, 4577–4584.
[6] M. Abarbri, P. Knochel, *Synlett* **1999**, 1577–1578.
[7] Y. Horiguchi, S. Matsuzawa, E. Nakamura, I. Kuwajima, *Tetrahedron Lett.* **1986**, *27*, 4025–4028.
[8] The reaction performed with lithium bases led to a complex mixture of products. We assume that the dioxenone moiety undergoes an attack of the generated oxoanion leading to ring opening side-reactions.
[9] [9a] R. Srinivasan, K. H. Carlough, *J. Am. Chem. Soc.* **1967**, *89*, 4932–4936. – [9b] R. S. H. Liu, G. S. Hammond, *J. Am. Chem. Soc.* **1967**, *89*, 4936–4944.
[10] A. Rodriguez, M. Nomen, B. W. Spur, J. J. Godfroid, *Tetrahedron Lett.* **1999**, *40*, 5161–5164.
[11] J. Balsells, P. J. Walsh, *J. Org. Chem.* **2000**, *65*, 5005–5008 and references cited therein.
[12] A. B. Charette, S. Prescott, C. Brochu, *J. Org. Chem.* **1995**, *60*, 1081–1083.
[13] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155465. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
[14] A. B. Charette, H. Juteau, H. Lebel, C. Molinaro, *J. Am. Chem. Soc.* **1998**, *120*, 11943–11952.
[15] S. Harada, H. Kiyono, R. Nishio, Y. Hanzawa, *J. Org. Chem.* **1997**, *62*, 3994–4001.
[16] [16a] M. P. Doyle, in *Comprehensive Organometallic Chemistry II* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon: Oxford, **1995**, Vol. 12, pp 387–420. – [16b] T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091–1160.
[17] D. A. Evans, K. A. Woerpel, M. M. Hinman, M. F. Margaret, *J. Am. Chem. Soc.* **1991**, *113*, 726–728.
[18] N. Haddad, N. Galili, *Tetrahedron: Asymmetry* **1997**, *8*, 3367–3370.
[19] [19a] J. Meinwald, A. Lewis, P. G. Gassman, *J. Am. Chem. Soc.* **1962**, *84*, 977–983. – [19b] P. Müller, J. Blanc, D. Lenoir, *Helv. Chim. Acta* **1982**, *65*, 1212–1220.
[20] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923–2925.

Received January 10, 2001
[O01010]