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Synthesis of the sex pheromone of the Oleander scale (*Aspidiotus nerii*).

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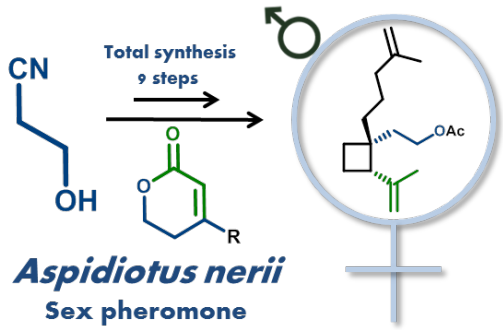

ABSTRACT

A total synthesis of the Oleander scale (Aspidiotus nerii (Bouche)) sex pheromone, the unique sesquiterpenoid containing a cyclobutane moiety of this class of compounds, has been developed. In order to implement this sex pheromone as a new enviromental-friendly tool to manage this pest, a more cost-effective, multigram synthesis was required. This new synthetic route, having a Blaise reaction, an iron catalyzed carbon-carbon coupling and a [2+2] photocycloaddition reactions as key steps, provides a general access to 4-alkyl lactones as well as a robust access to the target sex pheromone. Starting from readily available compounds as 3-hydroxypropane nitrile, ethyl bromoacetate and 2-acetyl butyro lactone, the synthetic sequence afforded the A. nerii sex pheromone with minimum intermediate purification and good overall yield, in 9 linear steps.

INTRODUCTION

Oleander scale (*Aspidiotus nerii* (Bouche)) is a polyphagous pest affecting more than 100 plant species.[1] Among these, damages caused to ornamental species, such as *Nerium oleander* L., and those caused by this pest to lemon and olives trees are of particular and economical importance in the Mediterranean area. Sessile females are sap-suckling, causing general weakness of the affected plant, defoliation and reducing dramatically the quality of the fruit for commercialization purposes.[2] Conventional treatment of this pest with traditional pesticides could be poorly effective due to its cryptic behavior, [3] together with the decreasing number of chemical principles available under the increasingly restrictive new environmental laws.[4] Moreover, the limit of pesticides residues admitted in fruit is continuously decreasing, being particularly low

or unacceptable when an integrated or ecological production is chosen. The use of sex pheromones *via* mating disruption to control insect pests is a well-stablished technique mainly in Lepidoptera species,[5] whereas only two commercial examples are known within the Coccoidea family, the vineyard mealybug *Planococcus ficus* Signoret (Checkmate VMB; Suterra LLC, Bend, OR),[6a] and the related citrus scale *Aonidiella aurantii* Maskell (Rescalure; Ecología y Protección Agrícola SL, Valencia, Spain).[6b-d] As in the latter, *A. nerii* males have a very short life cycle, thus, the use of the sex pheromone emitted by females **1** (Figure 1) to control this pest could be an environmentally respectful and valuable option. Based on the experience of our research group with related species,[6a-d] we sought its implementation in the field by using appropriated techniques such as mating disruption or attract-and-kill. Despite needing the later lower doses of sex pheromone per hectare, its price is still nowadays a key point for practical purposes, thus, a more cost-effective synthesis in a multigram scale of this sex pheromone is undoubtedly required. In regards to this, following the pattern behaviour of related species, an enantioselective synthesis is not required due to the non-inhibitory effect of the rest of the stereoisomers. [7]

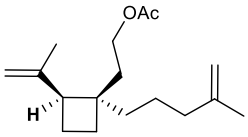

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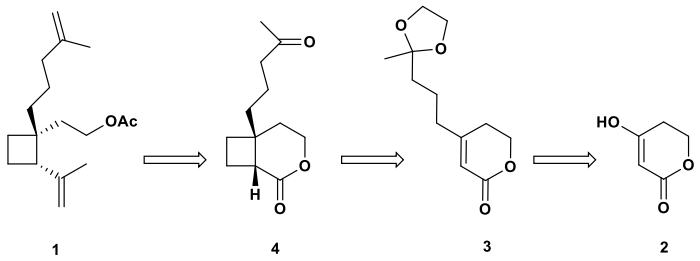
Figure 1. Sex pheromone of *Aspidiotus nerii*.

Several sex and aggregation pheromones containing a cyclobutane ring are known. Some of them are emitted by mealybugs or scale insects, and its structures have being classified in two main groups, planoccociol-type (1,1,2 substitution pattern), isolated from the species *Antonomous grandi*,[8a] *Pissodes strobi*,[8b] *Curculio caryae*,[8c] *Conotrachelus nenuphar,*[8d] *Conotrachelus psidii,*[8e] or maconelliol-type (1,2,2,3

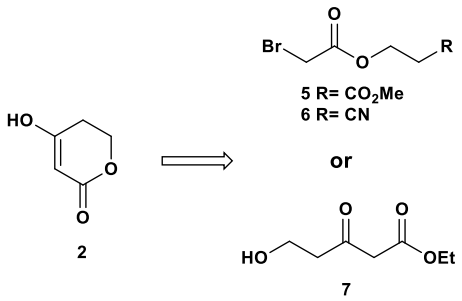
substitution pattern), isolated from the species *Maconellicoccus hirsutus*,[9a] *Acutaspis albopicta*[9b] *Phenacoccus solenopsis,*[9c] *Planocccocus citri*,[9d] *Pseudococcus criptus*.[9e] The oleander scale sex pheromone **1** belongs to the planoccociol series, being the only sesquiterpenoid of this family identified so far. Since its isolation in 1998 by Einhorn *et al*.,[10] one stereoselective synthesis starting from carvone[11a,b] and one racemic synthesis have been developed.[12] Having both an intramolecular cyclization as key step for the cyclobutane ring formation, the two synthetic approaches implied more than fifteen synthetic steps and overall yields below 1 %, being non suitable for multigram synthetic purposes. Inspired by previous synthetic works of structurally related cyclobutane-containing pheromones such as grandisol,[13] we sought a total synthesis of the *A. nerii* pheromone using a 2+2 photocycloaddition reaction as a key step for the cyclobutane ring construction. We envisaged a synthetic route in which an enol phosphate or tosylate derivative of keto-lactone **2** (Scheme 1) could be transformed via metal catalyzed coupling reaction with the appropriate organometallic reagent to afford 4-alkyl-α,β insaturated lactone **3**. Subsequently, a cycloaddition reaction could provide the cyclobutane lactone intermediate **4**. This intermediate could be easily transformed in the target sex pheromone of *A. nerii*. **1** after lactone opening, by using a minimum number of chemical transformations.



Scheme 1. Retrosynthetic analysis of **1**. All compounds are racemic but only one enantiomer is shown for simplicity.

RESULTS AND DISCUSSION

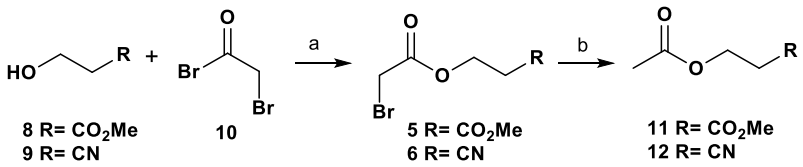
4-alkyl lactones are an important class of moieties in natural products showing diverse biological activities. Several synthetic approaches- thoroughly revised by Campagne *et al*.[14] had been previously developed. Unfortunately, the vast majority of these methods were not flexible enough for the substitution pattern required in our target lactone **3**. We envisaged two different intramolecular cyclizations to give access to its precursor lactone **2**. The first one, based on an intramolecular Blaise-type reaction,[15a] uses bromides **5** or **6** (Scheme 2) as starting materials, whereas the second one relies on the cyclization of hydroxy ketoester **7.**



Scheme 2. Retrosynthetic analysis of **2**.

Firstly, we decide to attempt the synthesis of **2** [16a,b] *via* cyclization of a bromide ester synthesized from methyl 3- hydroxypropanonate **8** or 3-hydroxypropanonitrile **9** (Scheme 3). Reaction of alcohols **8** or **9** in toluene using Et_3N as base with bromoacetyl bromide **10** afforded ketobromides **5** or **6,** respectively, in a similar yield (ca. 70 %). Attempts to cyclize esters **5** or **6** *via* formation of the corresponding zincate in THF under reflux did not provide lactone **2**. Only dehalogenated products **11** and **12,** coming

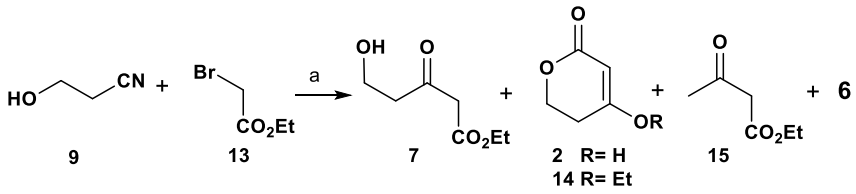
from **5** and **6** respectively, were obtained as main products in low yields (from 20 to 30 % estimated by GC-MS) together with some unreacted starting material. The use of different methods to activate zinc metal (HCl, TMSCl, or sonication), as well as different solvents (DCM or Toluene) or temperatures, did not make any substantial change to the previous result.[15b]



Scheme 3. Attempts of synthesis of **2** *via* intramolecular Blaise reaction. Reagents and conditions: a) Et_3N, DMAP, PhMe, 70 % in both cases; b) Zn, THF, reflux.

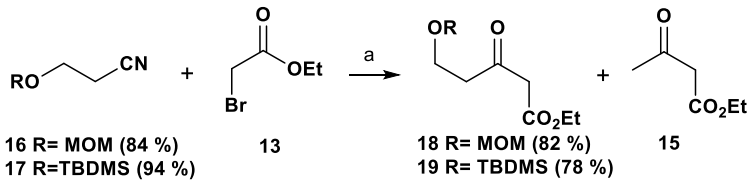
Thus, we decided to change our synthetic route to lactone **2** by using an intramolecular cyclization of hydroxyl-ester **7** (scheme 4), which in turn, could be easily synthesized *via* intermolecular Blaise reaction from readily available 3-hydroxypropane nitrile **9** and ethyl bromoacetate **13**. In our hands, keto-ester **7** was not identified in the crude mixture following the conditions described by Uang, B.J. *et al.*[17a] (Zn activation under sonication), or using different Zn activators such as $MeSO_3H$ [17b] or TMSCl (chlorotrimethylsilane).[17c] Only bromo-ester **6,** together with ethyl acetoacetate **15** (coming from the autocondensation of **13**), were identified in the reaction mixture. Finally, using the methodology described by Prasak *et al.,*[18a] (Zn activation with TMSCl, followed by a combined addition of alcohol **9** and bromide **13** under reflux), the reaction afforded a scanty 32 % yield of hydroxyester **7.** Variable amounts of starting material, lactone **2** and its corresponding ethyl enol ether **14** were also detected

by GC-MS analysis of the crude reactions, formed by the reaction of the *in situ* generated ethanol.[18b]



Scheme 4. Synthesis of **2** *via* intermolecular Blaise reaction. Reagents and conditions: a) Zn, THF, TMSCl, reflux, 6 h, 32% yield.

With these results in hand, we decided to protect the hydroxyl group present in **9,** which was probably involved in promoting undesired side reactions. A series of oxygen and silicon protecting groups were assayed (scheme 5).[19a] Based on the afforded yield, we selected MOM (methoxymethyl ether) and TBDMS (tert-butyldimethylsilyl ether) derivatives **16** and **17** respectively, as candidates for the synthesis of target lactone **2** (yields of protected alcohols and the corresponding keto-esters after chromatography column are given in round brackets in scheme 5).



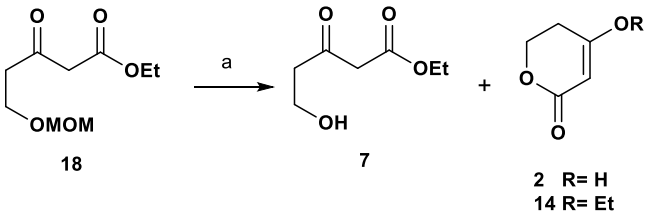
Scheme 5. Synthesis of protected ketoesters **18** and **19** *via* intramolecular Blaise reaction**.** Reagents and conditions: a) Zn, THF, TMSCl, reflux 30 min., slow addition of **13** and corresponding cyanide, then, reflux for 6h.

Both groups provided moderate to good yields of the desired ketoesters **18** or **19**, however, ethyl acetoacetate **15** was invariably obtained in the crude materials in

amounts ranging from 9 to 15 % (determined by GC-MS analysis of the crude mixtures). In order to optimize the reaction conditions and improve the yield, we proceeded to tune some parameters thereof. We found that using 3 eq. Zn metal and reducing the amount of solvent employed by a third, the yield was not diminished. Additionally, a tight control of the internal temperature of the mixture between 60 to 65 ºC during the addition of the reagents until the end of the reaction (aprox. 7 h), allowed us to improve the yield for **18** up to 98%. We estimated a purity of the crude material of 95 % based on the ^{1}H, ^{13}C NMR and GC-MS spectra, paving the way to the use of this crude material for the next step without further purification. These new developed conditions were also very successful when applied to the synthesis of silyl keto-ester **19**, giving a 94 % yield of the aforementioned ester after purification by chromatography column.

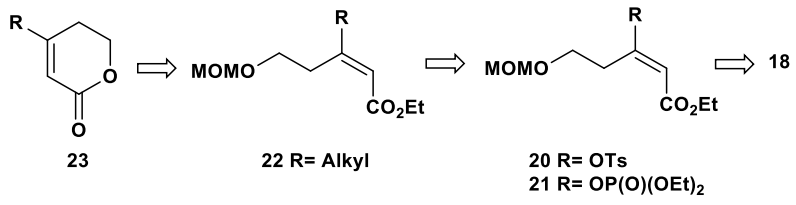
Following our initial synthetic retro analysis scheme, the next step of the synthesis involved a cyclization of keto-ester **7** to lactone **2** (scheme 2)**,** preceded by deprotection of MOM group present in compound **18** (scheme 5). Unfortunately, the use of catalytic amounts of p-TsOH[20a] or HCl[20b] in a protic medium (scheme 6), afforded keto-ester **7** in low yield varying from 20 to 50 %, accompanied by different amounts of keto lactone **2,** and its corresponding ethyl enol-ether **14** (determined by GC-MS analysis of the crude materials). The use of $ZnBr_2$ as a Lewis acid and n-PrSH[20c] as a nucleophile, did not improve the yield of **7,** whereas the use of an aprotic solvent like THF in the presence of a catalytic amount of HCl left the starting material unaffected. Finally, a low yield of 55 % of lactone **2** was obtained by the use of H_2SiF_6[21] as an acid at 45 ºC in acetonitrile.[22a,b] Although a total conversion of keto-ester **18** was achieved in the last

mentioned conditions (determined by GC-MS analysis of the crude material), the instability of lactone **2** was complicating its isolation.[16]



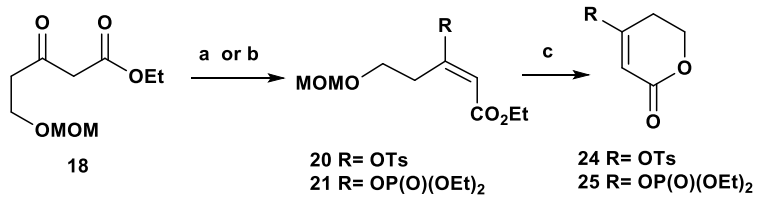
Scheme 6. Synthesis of lactone **2** *via* intramolecular cyclization reaction**.** Reagents and conditions: a) Different conditions: i) MeOH or EtOH and HCl or *p*-TsOH (20 to 50 % of **7**); ii) $ZnBr_2$, n-PrSH, DCM, rt, 50 % of **7;** iii) H_2SiF_6, CH_3CN, 45 ºC, 55 % of **2**.

In order to improve the yield of the deprotection-lactonization reaction, we decided to transform keto ester **18** in its corresponding enol tosylate **20** and enol phosphate **21** derivatives (scheme 7). According to the literature, both enol derivatives are good candidates to introduce a suitable alkyl chain by the use of an organometallic reagent *via* metal catalyzed carbon-carbon coupling reaction.[23] These 3-alkyl esters **22** would afford a more robust 4-alkyl pyran-2-one **23** after the deprotection-cyclization reaction sequence.



Scheme 7. Retrosynthesis of 4-alkyl pyran-2-one **23**

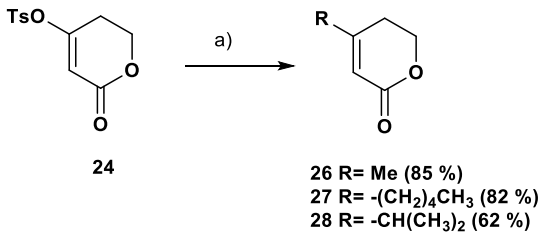
The synthesis of keto enol tosylate **20** (scheme 8) was achieved with 90 % yield after column chromatography using Et_3N and NMI (1-methylimidazole) as bases and TsCl under the conditions reaction developed by Nakatsuji *et al*.[24a] Enol phosphate **21** was synthesized in a 70 % yield after column chromatography using HMDSLi (lithium bis(trimethylsilyl)amide) as a base in the presence of $ClP(O)(OEt)_2$.[24b] To our delight, subsequent deprotection of the MOM group employing the previously assayed conditions for keto-enol **18** using H_2SiF_6 acid in acetonitrile, directly afforded phosphate enol lactone **25** with a moderate 65 % after column chromatography as an oil. When these conditions were applied to keto enol **20,**[25]an excellent 85 % yield of enol lactone **24** was obtained after crystallization of the crude residue from ethyl acetate. This result prompted us to select tosyl group to continue with our synthetic strategy.



Scheme 8. Synthesis of enol lactones **24** and **25.** Reagents and conditions: a) Et_3N, NMI, TsCl, THF, 90 %; b) HMDSLi, $ClP(O)(OEt)_2$, Et_2O, 70 %; c) H_2SiF_6, CH_3CN, 45 ºC, (65 % for **25**, 85 % for **24** after EtOAc crystallization).

The next step involved the insertion of an appropriate alkyl chain in position 4 of enol lactone **24** *via* metal catalyzed carbon-carbon coupling. We choose the coupling conditions developed by Cahiez, G. *et al.*, using a mixture of NMP/THF as solvents and cheap $Fe(acac)_3$ as metal catalyst.[26 a -c] Methyl magnesium chloride, pentyl magnesium bromide and isopropyl magnesium chloride, were used as carbon chain models to see the scope of the coupling and also to optimize the reaction conditions (scheme 9). The

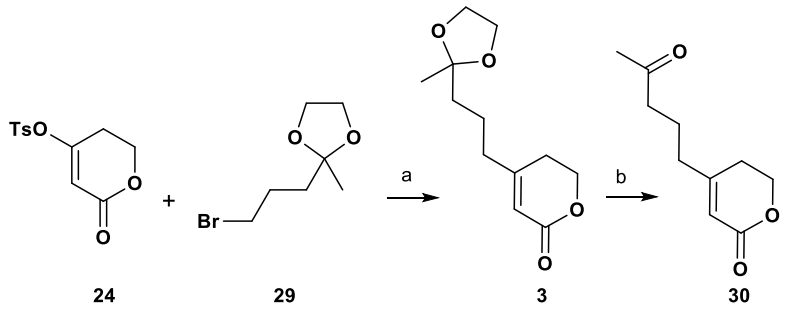
best results were consistently obtained by using 0.03 eq. of $Fe(acac)_3$ as catalyst, in the presence of 3 equiv. of NMP. Higher amounts of NMP did not improve the yield, whereas lower amounts of metal catalyst or absence of NMP as a co-solvent systematically lowered the yield of the coupling reaction. Moreover, a more reproducible yield in a multigram scale was obtained when a portion of the catalyst dissolved in THF (0.02 equiv.) was continuously added to the reaction medium during the Grignard reagent addition. Finally, a slightly better yield for the coupling above 80 % after column chromatography was obtained when a primary alkyl halide was employed (85 % for methyl lactone **26** [27a] and 82 % for n-pentyl lactone **27**), compared to 62 % yield for **28,** [27b] when isopropyl magnesium chloride was used as a coupling partner.



Scheme 9. Synthesis of model alkyl lactones **26, 27** and **28.** Reagents and conditions**:** a) Grignard reagent, $Fe(acac)_3$ (0.03 eq.), THF, NMP (3 eq), 0 ºC. (85 % for **26**, 85 % for **27**, 62 % for **28**).

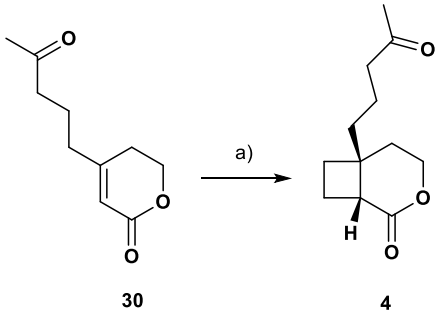
Synthesis of alkyl lactone **3** (scheme 10) was achieved applying the previously carbon-carbon coupling developed conditions to tosyl enolate **24,** using a Grignard derivative of bromide **29**. The former was synthesized in two steps starting from readily available 2-acetyl butyrolactone after HBr treatment, followed by ketal formation under standard conditions.[28] The iron catalyzed coupling reaction delivered alkyl lactone **3** in an

acceptable 70 % yield after column cromatography. Ketal deprotection of **3** using acetone and a catalytic amount of *p*-TsOH afforded compound **30** in 80 % yield.[29]



Scheme 10. Synthesis of alkyl lactone **30.** Reagents and conditions: a) Mg, $Fe(acac)_3$ (0.03 $eq_{)}$, THF, NMP (3 eq), 0 ºC; b) Acetone, *p*-TsOH cat.

Having developed an efficient route to achieve alkyl lactone **3** in a multigram scale, the construction of the 1,1,2 substituted cyclobutane moiety present in the target sex pheromone, as well as in the related aggregation pheromone Grandisol,[8a] was the next step in our synthetic strategy. Its synthesis has being attempted by the use of a nucleophilic substitution reaction.[30] However, the use of a photochemical [2 + 2] cycloaddition using ethylene[31] as a partner is, by far, the most preferred method.[32] Thus, we decided to set up the photoreaction parameters by irradiating a solution of alkyl lactone **30** in DCM, CH_3CN or Me_2CO as solvents, using a quartz photo reactor system equipped with a medium pressure immersion Hg lamp, a cooling system and a gas inlet. We founded that using a mixture 85:15 DMC:Me_2CO as solvent and photoinitiator respectively, compound **4** (scheme 11) was obtained from α,β-unsaturated lactone **30** with a moderate 63 % yield after chromatography column.



Scheme 11. Synthesis of bicyclic lactone **4.** Reagents and conditions: a) DCM:Acetone 85:15, ethylene (1.5 atm), hv (Hg lamp, 254 nm), 8h.

As previously described in the literature for related photocycloaddition reactions, *cis* stereochemistry was obtained for cyclobutane **4** (figure 2). This stereochemistry was confirmed with a detailed analyis of the ^{1}H NMR , COSY and NOESY spectra of this compound. Particularly, the NOESY spectra shows a clear NOE effect between H-1 and H-8a and H-1'a, confirming the *cis* orientation of substituents placed at bridgehead carbons C-1 and C-6 of bicyclic compound **4**.

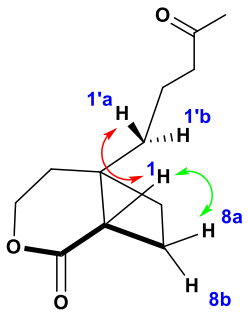
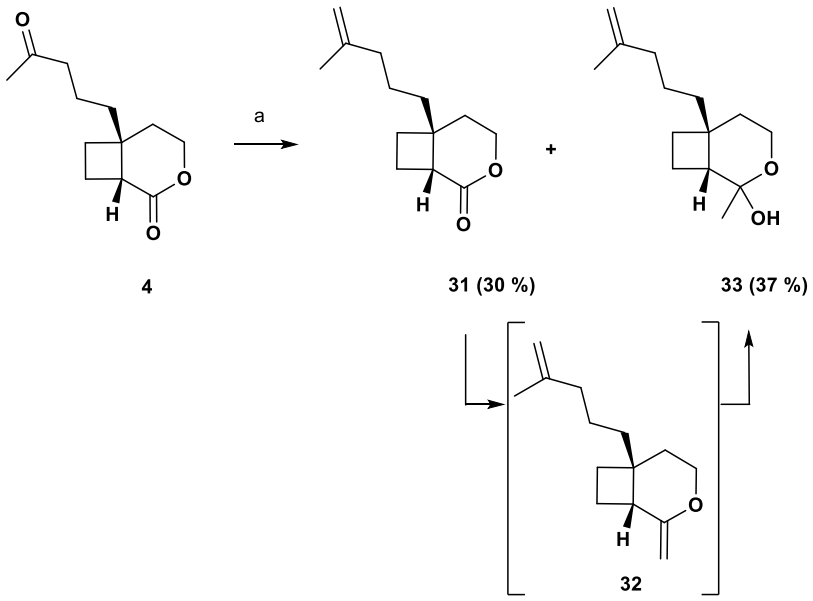


Figure 2. NOE effect observed in compound **4**.

Prior to continue with the lactone opening reaction with MeLi, a methylenation of carbonyl in compound **4** was mandatory. The first attempts to carry out this reaction under standard Wittig conditions reaction using 5 eq. of the ylide and 0 ºC, unexpectedly afforded an approximately 1:1 mixture of the desired product **31** and

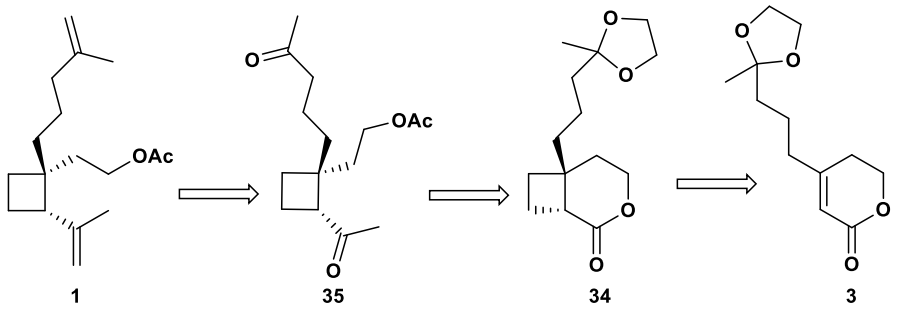
hemiketal **33** (scheme 12).[33a-c] The formation of product **33** could be rationalized by a double methylenation of **4** followed by a hydrolysis of the intermediate enol ether **32** and concomitant intramolecular ketal formation during the work-up process. [34]



Scheme 12. Methylenation of keto lactone **4.** Reagents and conditions: a) $Ph_3P^+CH_3Br^-$ **,** BuLi, THF, 0 ºC.

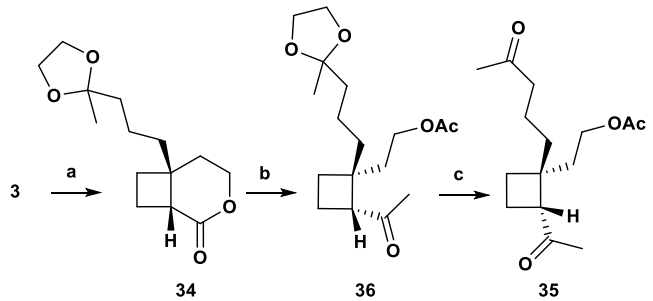
When the amount of the ylide was reduced to 1.25 eq and the reaction was carried out at -78 ºC, we were able to avoid the formation of ketal **33**, but a poor 40 % yield was obtained for lactone **31**.[35]

These last results led us to reconsider the original synthetic sequence by introducing the cyclobutane ring moiety in lactone **3,** prior to ketal deprotection (scheme 13). Thus, opening of the lactone moiety with Meli, followed by acetylation of the alcohol would afford diketo acetate **35** which in turn, after double methylenation would give access to sex pheromone **1**.



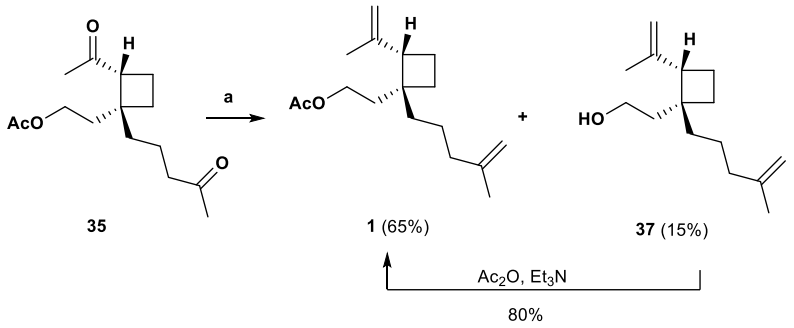
Scheme 13. Retrosynthetic strategy of **1** starting from **3**

The photoreaction conditions developed for compound **4** using ethylene as a [2+2] partner where applied to ketal lactone **3** (scheme 14). The reaction afforded ketal cyclobutane **34** with a moderate 62 % yield after column chromatography.[36] Treatment of compound **34** with an equimolecular amount of MeLi at -78 ºC and subsequent treatment of the crude material with Ac_2O and Et_3N in DCM afforded acetate **36** in 85 % yield after column chromatography.[37] Finally, simple deprotection of the ketal moiety in acetone produced compound **35** with 95 % yield. When the last two steps were reproduced in the lab into a multigram scale without purifiying any of the intermediate crude materials,[38] diketo acetate **35** was obtained in a 62 % overall yield.



Scheme 14. Synthesis of diketo cyclobutane **35.** Reagents and conditions: a) DCM:Acetone 85:15, ethylene (1.5 atm), hv (Hg lamp, 254 nm), 8h; b) MeLi, THF, -78 ºC; then Ac_2O, Et_3N, DCM; c) Acetone, HCl (1M) cat., r.t.

Double Lombardo methylenation of compound **35** (scheme 15) was initially attempted,[39] but a low 40 % yield of **1** was achieved, recovering about 10 % of starting material. Finally, double methylenation of compound **35** employing 1.75 eq of the corresponding ylide per carbonyl group in THF, using n-BuLi as base and THF as solvent, afforded compound **1** in a moderate 65 % yield together with a 15 % amount of alcohol **37**. The last alcohol could be easily re-acetylated to achieve *A. nerii* sex pheromone **1** in a 80 % yield overall from di keto compound **35**.



Scheme 15. Synthesis of *A. nerii* sex pheromone **1.** Reagents and conditions: a) $Ph_3P^+CH_3Br^-$ (3.5 eq), BuLi, THF, 0 ºC.

CONCLUSIONS

In conclusion, we have accomplished a multigram-scale total synthesis of *A. Nerii* sex pheromone **1**. The synthesis, featuring a Blaise reaction and a carbon-carbon iron catalyzed coupling of a diketo ester, also provides a general and robust access to 4-alkyl α,β-unsaturated esters or lactones starting with inexpensive and available materials in

five linear synthetic steps with virtually no purification steps in a 45 % overall yield. Finally, the access to the sex pheromone has been accomplished in nine steps using a [2+2] photocycloaddition reaction to introduce the cyclobutane moiety, opening of the lactone ring and minimum functional group manipulation. A multigram synthesis scaled up in our lab afforded **1** in a 10 % overall yield, allowing us to have enough material to further check the biological activity of this pheromone in real field conditions.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under a nitrogen atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Solvents were dried under standard procedures. All purchased chemicals were used without further purification. Organometallics reagent solutions were titrated before using with an appropiate method (for organomagnesium reagents see: Krasovskiy, A., Knochel, P. *Synthesis*, **2006**, 0890-0891; for organolithium reagents see: Kofron, W. G., & Baclawski, L. M. *J. Org. Chem*., **1976**, *41*, 1879-1880). Silica gel 60 F254 TLC plates were used for analytical thin layer chromatography technique. Plates were visualized by using a UV lamp or using an appropriate stainer (p-anisaldehyde in ethanol/aqueous H_2SO_4/CH_3CO_2H or 10 % solution of phosphomolibdic acid in ethanol and heat as developing agents). Chemical shifts were reported as parts per million (δ) relative to the signal of $CHCl_3$ at 7.26 ppm for ^{1}H NMR, and center line signal of the $CDCl_3$ triplet at 77 ppm for ^{13}C {1H} NMR. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded at 300 MHz at 75 MHz respectively. Chemical shifts are reported in parts per million using the following peak pattern abbreviations: br, broad; s, singlet; d, doublet; dd, double doublet; ddd, doublet of doublet of doublets; t, triplet; dt, double triplet; q,

quartet; pent, pentet; sext, sextet; m, multiplet. High resolution mass spectra (ESI-HRMS) were measured on a Waters Xevo Q-TOF spectrometer (Waters Corp., Milford, MA, USA) coupled with an Acquity UPLC-PDA system (Waters) using ionization by electrospray (ESI). The ESI source operated in positive ionization mode using leucine-enkephalin as the reference mass ($[M+H]^+$ ion m/z 556.2771).

4-Hydroxy-5,6-dihydro-2H-pyran-2-one, 2: Hexafluorosilicic acid (0.35 mL, 35%, 1.4 mmol) was added using a plastic syringe to a solution of keto-ester **18** (900 mg, 4.4 mmol) in CH_3CN (10 mL) placed in a polypropylene plastic tube. The reaction mixture was stirred at 45 °C for 3 h and cooled to room temperature, and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 50% AcOEt/hexane) to give 275 mg of **2** (55%) as a colorless liquid. Spectroscopical data are in full agreement with those previously reported. [16b]

4-(3-(2-Methyl-1,3-dioxolan-2-yl)propyl)-5,6-dihydro-2*H*-pyran-2-one 3. To a vigorously stirred suspension of magnesium turnings (1 g, 42 mmol) and of Iodine (30 mg, 0.12 mmol) in anhydrous THF (18 mL), a solution of bromide **29 (**1 M, 29 mL, 29 mmol) in THF was dropwise added over a period of 2h, during which the internal temperature of the mixture was kept at 45 ºC. After this time, the reaction was cooled down to room temperature and an aliquot was titrated with iodine. The resultant solution was dropwise added in parallel with a solution of $Fe(acac)_3$ in THF (0,2 M, 149 mg, 0.38 mmol) to a mixture of enol tosylate **24** (5 g, 18.5 mmol), $Fe(acac)_3$ (74.5 mg, 0.19 mmol) and anhydrous NMP (5.6 ml, 57 mmol) in anhydrous THF (10 mL) at 0 ºC. The reaction was stirred at this temperature for 60 min, quenched with saturated aqueous NH_4Cl (20 mL), poured over H_2O (20 ml) and extracted with EtOAc (3 x 60

mL). The combined organic layers were washed with brine (3 X 15ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 50% EtOAc/hexane) afforded **3** (3 g, 70%) as a yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.82 (s, 1H), 4.37 (t, *J* = 6.2 Hz, 2H), 3.99–3.87 (m, 4H), 2.37 (t, *J*= 6.2 Hz, 2H), 2.27 (t, *J*= 6.3 Hz, 2H), 1.71–1.53 (m, 4H), 1.31 (s, 3H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 164.8, 161.3, 116.1, 109.7, 66.1, 64.9 (2C), 38.6, 36.7, 28.0, 23.9, 20.9. **MS (EI)** m/z (%): 211 (M^+-15, 5), 99 (15), 87 (100), 55 (12), 43 (47). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{12}H_{19}O_4$ 227.1278; found 227.1278.

6-(4-Oxopentyl)-2-oxo-3-oxabicyclo[4.2.0]octane 4. A solution of lactone **30** (910 mg, 5 mmol) in 15% Acetone/CH_2Cl_2 (100 mL) was placed in a quartz container connected to an inlet of ethylene and this mixture was purged with ethylene for 15 min at -20 °C. The reaction mixture was internally irradiated (254 nm) at room temperature using a 125 W medium pressure Hg lamp as the light source (a constant pressure of ethylene of 1.2 atm was kept along the irradiation period). The reaction was monitored by TLC on silica gel and GC-MS. After the solvent mixture was evaporated under reduced pressure, the residue was purified by flash column chromatography (silica gel, 50 EtOAc/hexane) to give photoadduct **4** (651 mg, 62 %) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.57 (ddd, *J*= 11.7, 9.1, 3.6 Hz, 1H), 4.40 (ddd, *J*= 11.7, 4.8, 4.2 Hz, 1H), 2.91-2.79 (m, 1H), 2.48-2.36 (m, 3H), 2.12 (s, 3H), 2.09-1.95 (m, 2H), 1.92-1.80 (m, 1H), 1.78-1.62 (m, 2H), 1.54-1.42 (m, 4H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 208.4, 173.9, 66.3, 43.6, 41.7, 40.8, 39.7, 32.4, 30.2, 28.4, 19.7, 16.7. **MS (EI)** m/z (%): 210 (M^+, 3), 182 (3), 125 (56), 95 (20), 79 (31), 55 (48), 43 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{12}H_{19}O_3$ 211.1329; found 211.1324.

Methyl 3-(2-bromoacetoxy)propanoate 5: Et_3N (1.5 mL, 10.6 mmol) and imidazole (0.72 g, 10.6 mmol) were added to a solution of hydroxy ester **8** (1 g, 9.6 mmol) in anhydrous CH_2Cl_2 (30 mL). The solution was cooled to 0ºC and bromoacetyl bromide **10** (0.85 mL, 9.6 mmol) was added dropwise. The reaction was warmed up to room temperature and stirred for 5h. After this period the reaction was diluted with CH_2Cl_2 (15 mL) and washed with 0.5 N HCl solution (2 x 15 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 30% EtOAc/hexane) to give 1.5 g of **5** (70%) as a light-yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.43 (t, *J*= 6.3 Hz, 2H), 3.81 (s, 2H), 3.70 (s, 3H), 2.68 (t, *J*= 6.3 Hz, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 170.8, 167.1, 61.6, 52.1, 33.5, 25.6. **MS (EI)** m/z (%):194 (M^+-29, 4), 123 (17), 121 (17), 103 (19), 93 (13), 87 (59), 59 (62), 55 (100), 42 (54). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_6H_{10}BrO_4$ 224.9757; found 224.9748

2-Cyanoethyl 2-bromoacetate 6: Et_3N (1.6 mL, 11.8 mmol) was added to a solution of bromoacetyl bromide **10** (2.4 g, 1 mL, 11.8 mmol) in toluene (9.5 mL) and then, 3-hydroxypropanenitrile (0.7 mL, 9.9 mmol) was slowly added with stirring. The reaction mixture was heated to reflux for 2 h. After this period, the reaction mixture was cooled down to room temperature, diluted with EtOAc (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 x 15 mL), water (15 mL) and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 20% EtOAc/hexane) gave bromo ester **6** (1.9 g, 72%) as a yellow liquid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 4.37 (t, *J*= 6.3 Hz, 2H), 3.87 (s, 2H), 2.74 (t, *J*= 6.3 Hz, 2H). **^{13}C{1H} NMR** (75 MHz, $CDCl_3$) δ: 166.9, 116.4, 60.3, 25.1, 17.9. **MS (EI)** m/z (%): 175 (M^+-

15, 1), 173 (1), 153 (4), 151 (4), 123 (33), 121 (33), 95 (29), 93 (31), 68 (16), 54 (100), 42 (48), 41 (38). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_5H_7BrNO_2$ 191.9655; found 191.9661

Ethyl 5-hydroxy-3-oxopentanoate 7. TMSCl (0.13 mL, 0.4 mmol) dissolved in anhydrous THF (0.3 mL) was added to a suspension of zinc dust (4.6 g, 70.4 mmol) in anhydrous THF (22 mL), and the resulting mixture was refluxed for 25 min. To this refluxing slurry of activated zinc, 3-hydroxypropanenitrile **9** (1 g, 14.1 mmol) in 5 mL THF and ethyl bromoacetate **13** (3 mL g, 27.8 mmol) in 5 mL THF were added in parallel. The color of the reaction mixture changed from colorless to dark green, which turned finally to brown with time progression. The reaction mixture was stirred at reflux for 6h and after this period was allowed to cool at room temperature. The organic layer was filtered, and the pH was adjusted to 4 using 20% aqueous citric acid. THF was removed under reduced pressure and the resulting mixture was diluted with 80 mL CH_2Cl_2 and washed with water (2 x 20 mL) and with brine (2 x 20 mL). The resultant organic layer was dried over $MgSO_4$, filtered and the solvent was rotary evaporated to get the crude product which was purified by flash column chromatography using 50% EtOAc/hexane to give 722 mg of **7** (32%) as a yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 Hz) δ: 4.2 (q, 2H), 3.87 (brs, 2H), 3.48 (s, 2H), 2.81 (t, *J*=5.4 Hz, 2H), 1.28 (t, *J*= 7.1 Hz, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 203.5, 167.1, 61.7, 57.7, 49.8, 45.1, 14.2. **MS (IE)** m/z (%): 160 (M^+, 1), 159 (8), 143 (6), 115 (8), 113 (7), 98 (6), 87 (10), 71 (5), 69 (5), 55 (23), 45 (100). **HRMS (ESI-TOF)** m/z: $[M-H]^-$ Calcd for $C_7H_{11}O_4$ 159.0657; found 159.0656.

3-(Methoxymethoxy)propanenitrile 16: LiBr (12 g, 0.14 mol) and *p*-toluensulfonic acid (*p*-TsOH) (11.7 g, 0.07 mol) were added to a solution of hydroxy nitrile **9** (70 g, 0.7 mol) in dimethoxymethane (735 mL, 8.3 mol) at 35 ºC. After continous stirring for 12 h at the same temperature, the reaction was quenched with brine (500 mL) and extracted with EtOAc (2 X 350 mL). The organic layer was successively washed with sat. $NaHCO_3$ (2 X 150 ml), brine (150 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 86 g of **16** (85%) as a colorless liquid. **^{1}H-NMR** ($CDCl_3$, 300 MHz) δ: 4.67 (s, 2H), 3.75 (t, *J*= 7.6 Hz, 2H), 3.39 (s, 3H), 2.63 (t, *J*= 7.6 Hz, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 117.7, 96.5, 62.3, 55.6, 19.1. **MS** (IE) m/z (%): 115 (M+, 1), 85 (14), 75 (7), 61 (20), 54 (98), 45 (100). Spectroscopical data are in full agreement with those previously reported.[19 b]

3-((*tert*-Butyldimethylsilyl)oxy)propanenitrile 17. Alcohol **9** (2.5 g, 35.2 mmol) and imidazole (4.8 g, 70.4 mmol) were dissolved in anhydrous CH_2Cl_2 (80 mL) and TBDMSCl (6.4 g, 42.2 mmol) in CH_2Cl_2 (20 mL) was slowly added. The reaction mixture was stirred at room temperature overnight, quenched with saturated aqueous NH_4Cl (10 mL) and diluted with CH_2Cl_2 (25 mL). The organic layer was successively washed with HCl (1M, 2 x 25 ml), $NaHCO_3$ sat. (2 x 25ml), brine (20 ml), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5% EtOAc/hexane) to give 6.1 g of **17** (94%) as a colorless oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 3.84 (t, *J*=6.3 Hz, 2H), 2.54 (t, *J*=6.3 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H). **MS (EI)** m/z (%): 185 (M^+, 1), 170 (9), 143 (8), 128 (84), 98 (100), 89 (15), 73 (46), 58 (40), 43 (43), 41 (55). Spectroscopical data are in full agreement with those previously reported. [19 c]

Ethyl 5-(methoxymethoxy)-3-oxopentanoate 18. TMSCl (1.7 mL, 5.2 mmol) was added to a suspension of zinc dust (76.1 g, 1.1 mol) in anhydrous THF (320 mL). The resulting mixture was refluxed for 25 min and then allowed to cool down up to 60 °C. A solution of MOM protected 3-(methoxymethoxy)propanenitrile **16** (45 g, 0.39 mol) and ethyl bromoacetate **13** (86 mL g, 0.78 mol) in anhydrous THF (80 mL) was added to this suspension over a period of 3 h, using an addition funnel. During this period, the internal reaction temperature was kept between 60-65 °C, and the color of the reaction mixture changed first to dark green, and finally turned to brown by the end of the addition. After stirring at 65 °C for 6 h, the reaction mixture was allowed to cool at room temperature, filtered, and the pH was adjusted to 4 using 20% m/m aqueous citric acid. THF was removed under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (3 x 150 mL). The combined organic phases were successively washed with brine (2 X 150 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure, to give β-ketoester **18** (78 g, 98%) as a yellow liquid, which was used in the next reaction without further purification. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.60 (s, 2H), 4.19 (c, *J*= 7.1 Hz, 2H), 3.81 (t, *J*= 6.1 Hz, 2H), 3.49 (s, 2H), 3.35 (s, 3H), 2.82 (t, *J*= 6.1 Hz, 2H), 1.27 (t, *J*= 7.1 Hz, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 201.2, 167.0, 96.7, 62.5, 61.5, 55.4, 49.9, 43, 14.2. **MS (EI)** m/z (%):204 (M^+, 1), 188 (1), 172 (2), 158 (4), 143 (28), 128 (15), 114 (9), 96 (35), 83 (8), 69 (38), 54 (19), 435 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_9H_{17}O_5$ 205.1071; found 205.1062.

Ethyl 5-((*tert*-butyldimethylsilyl)oxy)-3-oxopentanoate 19. TMSCl (0.15 mL, 0.48 mmol) was added to a suspension of zinc dust (6.9 g, 0.1 mol) in anhydrous THF (30 mL). The resulting mixture was refluxed for 25 min and then allowed to cool down up to 60 °C. A solution of TBDMS protected 3-hydroxypropanenitrile **17** (6.6 g, 0.04 mol)

and ethyl bromoacetate **13** (7.8 mL g, 0.09 mol) in anhydrous THF (8 mL) was added to this suspension over a period of 3 h, using a syringe pump. During this period, the internal reaction temperature was kept between 60-65 °C. Along the addition, the color of the reaction mixture changed first to dark green, and finally turned to brown. After stirring at 65 °C for 6 h, the reaction mixture was allowed to cool at room temperature, filtered, and the pH was adjusted to 4 with a 20% m/m aqueous citric acid solution. THF was removed under reduced pressure and the resulting mixture was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic phases were successively washed with brine (2 X 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20% EtOAc/hexane) to give to give β-ketoester **19** (9.3 g, 94%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.19 (c, *J*= 7.1 Hz, 2H), 3.90 (t, *J*= 6.2 Hz, 2H), 3.49 (s, 2H), 2.72 (t, *J*= 6.2 Hz, 2H), 1.28 (t, *J*= 7.1 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 6H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 202.1, 167.2, 61.4, 58.8, 50.3, 45.9, 25.9 (3C), 18.3, 14.2, –5.40. **MS (EI)** m/z (%): 274 (M+, 1), 228 (12), 216 (65), 188 (12), 170 (98), 128 (16), 96 (33), 75 (100), 57 (17), 41 (32). Spectroscopical data are in full agreement with those previously reported.[19 d]

Ethyl (*E*)-5-(methoxymethoxy)-3-(tosyloxy)pent-2-enoate 20. Et_3N (73.5 mL, 0.51 mol) and NMI (42 mL, 0.51 mol) were added to a solution of β-ketoester **18** (70 g, 0.34 mol) in anhydrous THF (980 mL). The resultant solution was stirred at room temperature for 30 min and *p*-toluenesulfonyl chloride (TsCl) (98 g, 0.51 mol) was added in portions. After 5 h, one third of the solvent was removed under reduced pressure and water (500 mL) was added. The resulting mixture was extracted with EtOAc (3 x 400 mL). The combined organic layers were successively washed with 1 M

HCl solution (200 mL), brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to give 125 g of crude material. 4 g of this crude material was purified by flash column chromatography (silica gel, 30% EtOAc/hexane) to give 3.5 g of **20** (90%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 7.82 (d, *J*= 8.1 Hz, 2H), 7.36 (d, *J*= 8.1 Hz, 2H), 5.84 (s, 1H), 4.53 (s, 2H), 4.14 (c, *J*= 7.1 Hz, 2H), 3.63 (t, *J*= 6.5 Hz, 2H), 3.29 (s, 3H), 3.02 (t, *J*= 6.5 Hz, 2H), 2.46 (s, 3H), 1.25 (t, *J*= 7.1 Hz, 3H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 165.2, 162.6, 145.9, 133.0, 130.1 (2C), 128.4 (2C), 111.8, 96.3, 63.7, 60.7, 55.3, 32.2, 21.8, 14.2. **MS (EI)** m/z (%): 341 (M^+-17, 1), 327 (7), 313 (1), 173 (8), 155 (21), 142 (9), 115 (7), 91 (58), 65 (16), 55 (13), 45 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{16}H_{23}O_7S$ 359.1159; found 359.1156.

Ethyl (*Z*)-3-((diethoxyphosphoryl)oxy)-5-(methoxymethoxy)pent-2-enoate 21. A solution of 1 M LiHMDS in THF (11.3 mL, 11.3 mmol) was added to an ice-cooled solution of β-ketoester **18** (2 g, 9.8 mmol) in anhydrous THF (25 mL). After 20 min, $(EtO)_2POCl$ (2 mL, 14 mmol) was slowly added and the resulting solution was stirred at room temperature for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL), poured in water (30 ml) and extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (35 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/hexane) to give 2.3 g of **21** (70%) as a yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.93 (d, *J*= 3.0 Hz, 1H), 4.61 (s, 2H), 4.22–4.14 (m, 6H), 3.75 (t, *J*= 6.7 Hz, 2H), 3.35 (s, 3H), 3.13 (t, *J*= 6.7 Hz, 2H), 1.37 (m, 6H), 1.26 (t, *J*= 7.1 Hz, 3H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 165.9, 163.3 (d, $^2J_{P,C}$= 9.2 Hz), 106.9 (d, $^3J_{P,C}$= 3.0 Hz), 96.2, 64.9 (d, $^2J_{P,C}$= 6.2 Hz, 2C), 64.1 (2C), 60.2, 55.2, 32.3 (d, $^3J_{P,C}$= 6.0 Hz), 16.1 (d, $^3J_{P,C}$= 6.8Hz, 2C), 14.2. **MS (EI)** m/z (%): 310 (M^+-30,

3), 295 (10), 278 (11), 249 (13), 206 (10), 155 (65), 141 (18), 127 (51), 113 (25), 99 (67), 81 (31), 69 (19), 55 (17), 45 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{13}H_{26}O_8P$ 341.1360; found 341.1357.

6-Oxo-3,6-dihydro-2*H*-pyran-4-yl 4-methylbenzenesulfonate 24. Hexafluorosilicic acid (8 mL, 35%, 34 mmol) was added using a plastic syringe to a solution of crude ester **20** (40 g, 112 mmol) in CH_3CN (225 mL) placed in a polypropylene plastic bottle. The reaction mixture was stirred at 45 °C for 3 h and cooled to room temperature, and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue (41 g) was recrystallized from hot AcOEt (45 ml) to afford lactone **24** (25.5 g, 85%) as light brown crystals (m.p.: 69-70 °C). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 7.82 (d, *J*= 8.3 Hz, 2H), 7.39 (d, *J*= 8.2 Hz, 2H), 5.75 (s, 1H), 4.34 (t, *J*= 6.3 Hz, 2H), 2.59 (t, *J*= 6.3 Hz, 2H), 2.46 (s, 3H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 164.2, 162.9, 146.8, 131.9, 130.4 (2C), 128.4 (2C), 106.7, 64.7, 27.4, 21.9. **MS (EI)** m/z (%): 268 (M^+, 1), 155 (46), 91 (100), 65 (28), 41 (9). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{12}H_{13}O_5S$ 269.0478; found 269.0479.

Diethyl (6-oxo-3,6-dihydro-2*H*-pyran-4-yl) phosphate 25. Hexafluorosilicic acid (0.4 mL, 35%, 2 mmol) was added using a plastic syringe to a solution of ester **25** (2 g, 7.3 mmol) in CH_3CN (25 mL) placed in a polypropylene plastic tube. The reaction mixture was stirred at 45 °C for 3 h and then cooled to room temperature, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified by flash column chromatography (silica gel, 50% AcOEt/hexane) to give 960 mg of **2** (65%) as a liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.83 (d, *J*= 0.9 Hz, 1H), 4.41 (t, *J*= 6.4 Hz, 2H), 4.30-4.17 (m, 4H), 2.70 (t, *J*= 6.4 Hz, 2H), 1.39 (td, *J*= 7.1, 1.0 Hz, 6H).

^{13}C{1H} NMR ($CDCl_3$, 75 MHz) δ: 165.1, 164, 103.7 (d, $^3J_{P,C}$= 9.2 Hz), 65.5 (d, $^2J_{P,C}$= 6.1 Hz, 2C), 64.4, 27.6 (d, $^3J_{P,C}$= 6.0 Hz), 16.2 (d, $^3J_{P,C}$= 6.5 Hz, 2C). **MS (EI)** m/z (%): 250 (M^+, 12), 204 (22), 176 (38), 155 (45), 127 (52), 99 (100), 81 (52), 66 (47), 52 (26), 42 (22). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_9H_{16}O_6P$ 251.0679; found 251.0670.

General procedure for preparation of 4-alkyl-pyran-2-ones 26, 27 and 28: $Fe(acac)_3$ dissolved in anhydrous THF and anhydrous NMP were added to a solution of enol tosylate **24** in anhydrous THF. The reaction mixture was cooled down to 0 °C with vigorous stirring and a solution of Grignard reagent was added dropwise. The mixture was stirred at this temperature for 30-60 min, quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 20-50% EtOAc/hexane).

4-methyl-5,6-dihydro-2*H*-pyran-2-one 26. Lactone **26** was prepared according to the above general procedure using tosylate **24** (1 g, 3.7 mmol), THF (4 mL), 3 M methylmagnesium chloride solution in THF (1.2 mL), $Fe(acac)_3$ (39.2 mg, 0.1 mmol), NMP (1.1 mL, 11.1 mmol), NH_4Cl (4 mL), EtOAc (3 X 15 mL), brine (2 X 10 mL). Purification of the crude residue by flash column chromatography (silica gel, 20% EtOAc/hexane) gave 354 mg of **26** (85% yield) as a light-yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.82 (s, 1H), 4.37 (t, *J*= 6.3 Hz, 2H), 2.37 (t, *J*= 6.3 Hz, 2H), 2.0 (s, 3H). **MS (EI)** m/z (%): 112 (M^+, 41), 82 (100), 67 (14), 54 (53), 44 (28), 41 (20). Spectroscopical data are in full agreement with those previously reported.[13]

4-pentyl-5,6-dihydro-2*H*-pyran-2-one 27. This lactone was prepared from according to the above general procedure: using tosylate **24** (1 g, 3.7 mmol), THF (3.8 mL), freshly prepared 0.7 M pentylmagnesium bromide solution in THF (5.3 mL), $Fe(acac)_3$ (39.2 mg, 0.1 mmol), NMP (1.1 mL, 11.1 mmol), NH_4Cl (4 mL), EtOAc (3 X 15 mL), brine (2 X 10 mL).. Purification of both residues by flash column chromatography (silica gel, 30-40% EtOAc/hexane) gave 514 mg (82% yield) of lactone **28** as a light-yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.79 (t, *J*= 1.4 Hz, 1H), 4.36 (t, *J*= 6.2 Hz, 2H), 2.36 (t, *J*= 6.3 Hz, 2H), 2.24 (t, *J*= 7.6 Hz, 2H), 1.60-1.43 (m, 2H), 1.39-1.25 (m, 4H), 0.9 (t, *J*= 6.6 Hz, 3H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 164.7, 160.6, 117.1, 66.0, 43.7, 32.53, 29.9, 28.0, 22.5, 14. **MS (EI)** m/z (%): 153 (M^+-15, 7), 140 (10), 125 (4), 110 (3), 95 (6), 82 (17), 67 (8), 55 (10), 45 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{10}H_{17}O_2$ 169.1223; found 169.1221.

4-isopropyl-5,6-dihydro-2*H*-pyran-2-one 28. This lactone was prepared according to the above general procedure using tosylate **24** (1 g, 3.7 mmol), THF (4 mmol) 2 M isopropylmagnesium chloride solution in THF (1.9 mL), $Fe(acac)_3$ (39.2 mg, 0.1 mmol), NMP (1.1 mL, 11.1 mmol), NH_4Cl (4 mL), EtOAc (3 X 15 mL), brine (2 X 10 mL). Purification of the crude residue by flash column chromatography (silica gel, 30% EtOAc/hexane) gave 323 mg (62% yield) of lactone **28** as a colorless liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.8 (s, 1H), 4.35 (t, *J*= 6.5 Hz, 2H), 2.45 (m, 1H), 2.38 (t, *J*= 6.5 Hz, 2H), 1.10 (d, *J*= 6 Hz, 6H). **MS (EI)** m/z (%):140 (M^+, 10), 125 (5), 110 (12), 95 (83), 81 (100), 67 (85), 53 (28), 41 (78). Spectroscopical data are in full agreement with those previously reported.[27 b]

4-(4-oxopentyl)-5,6-dihydro-2*H*-pyran-2-one 30. A 1 N HCl solution (3 mL) was added to a solution of lactone **3** (1 g, 4.4 mmol) in acetone (7 mL) and the resultant

solution was stirred at room temperature for 1 h. The reaction was neutralized to pH=8 with saturated aqueous $NaHCO_3$ solution, and the mixture was extracted with EtOAc (20 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 50% EtOAc/hexane) to give 640 mg of **30** (80%) as a yellow oil. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 5.79 (s, 1H), 4.36 (t, *J*= 6.2 Hz, 2H), 2.48 (t, *J* = 6.2 Hz, 2H), 2.37 (t, *J*= 6.0 Hz, 2H), 2.24 (t, *J*= 6.0 Hz, 2H), 2.14 (s, 3H), 1.79 (m, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 207.8, 164.6, 161.0, 115.7, 65.9, 42.2, 35.6, 29.9, 27.6, 19.9. **MS (EI)** m/z (%): 182 (M^+, 3), 164 (3), 125 (70), 112 (14), 79 (20), 58 (24), 43 (100). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{10}H_{15}O_3$ ($[M+H]^+$) 183.1016; found 183.1011.

6-(4-Methylpent-4-en-1-yl)-3-oxabicyclo[4.2.0]octan-2-one 31 and **2-methyl-6-(4-methylpent-4-en-1-yl)-3-oxabicyclo[4.2.0]octan-2-ol 33.** *n*-Butyllithium in hexane (2.5 M, 6.8 mL) was slowly added over a suspension of methyltriphenylphosphonium bromide (6.0 g, 17 mmol) in anhydrous THF (30 mL) at -78 °C. The resultant mixture was stirred for 30 min and the temperature was raised up to - 20 ºC. The solution was cooled again to -78°C and a solution of lactone **4** (693 mg, 3.3 mmol) in anhydrous THF (10 mL) was slowly added, and the resultant mixture was allowed to warm to room temperature and stirred for additional 30 min. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with ethyl acetate (2 x 35 mL). The combined organic layers were washed with saturated brine (2 X 20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, 5-25% EtOAc/hexane) to give 206 mg (30 %) of lactone **31** as a yellow oil along with 199 mg (37 %) of hemiketal **33** as a

faint yellow oil. **Spectroscopical data for 31**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.71 (dt, *J*= 3.1, 1.5 Hz, 1H), 4.66 (dq, *J*= 2.2, 1.1 Hz, 1H), 4.58 (ddd, *J*= 11.6, 8.5, 4.3 Hz, 1H), 4.42 (dt, *J*= 11.6, 4.4 Hz, 1H), 2.92 – 2.82 (m, 1H), 2.52 – 2.34 (m, 1H), 2.16 – 1.97 (m, 4H), 1.96 – 1.81 (m, 1 H), 1.75 – 1.68 (m, 2 H), 1.70 (s, 3 H), 1.57 – 1.45 (m, 2 H), 1.43 – 1.31 (m, 2 H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 174.10, 145.39, 110.43, 66.35, 41.72, 41.04, 39.65, 38.02, 32.56, 28.56, 22.43, 21.60, 19.70. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{13}H_{21}O_2$ 209.1536; found 209.1534. **Spectroscopical data for 33**: **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.73 – 4.63 (m, 2H), 3.89 (ddd, *J*= 12.3, 11.5, 2.5 Hz, 1H), 3.56 (ddd, *J*= 11.5, 4.7, 2.7 Hz, 1H), 2.06 – 1.94 (m, 3H), 1.90 – 1.73 (m, 2H), 1.71 (t, *J*= 1.1 Hz, 3H), 1.68 – 1.48 (m, 4H), 1.47 – 1.32 (m, 4H), 1.23 (s, 3H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ: 146.20, 109.91, 96.28, 57.46, 45.29, 39.83, 38.64, 38.33, 31.02, 29.93, 26.67, 22.55, 22.18, 19.08. **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{14}H_{25}O_2$ 225.1849; found 225.1850.

6-(3-(2-Methyl-1,3-dioxolan-2-yl)propyl)-2-oxo-3-oxabicyclo[4.2.0]octane 34. A solution of the corresponding lactone **3** (2 g, 8.9 mmol) in 15% Acetone/CH_2Cl_2 (180 mL) was placed in a quartz container connected to a gas inlet and purged with ethylene for 15 min at -20 °C. The reaction mixture was internally irradiated (254 nm) at 0 ºC using an immersion 125 W medium-pressure Hg lamp as light source (the internal pressure of ethylene was kept at 1.2 atm during the irradiation period). The reaction was monitored by TLC on silica gel and GC-MS. After 9h of irradiation, the reaction was purged with nitrogen and the solvent mixture rotary evaporated under reduced pressure. Purification of the crude residue using flash column chromatography (silica gel, 50% EtOAc/hexane) gave **34** (1.4 g, 62%) as yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.57 (ddd, *J*= 12.7, 8.1, 4.6 Hz, 1H), 4.40 (ddd, *J*= 14, 10.1, 5.3 Hz, 1H), 3.98-3.84 (m,

4H), 2.93-2.82 (m, 1H), 2.49-2.37 (m, 1H), 2.14-1.97 (m, 2H), 1.93-1.83 (m, 1H), 1.74-1.70 (m, 2H), 1.67-1.61 (m, 2H), 1.56-1.49 (m, 2H), 1.30 (s, 3H), 1.39-1.23 (m, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 174.1, 109.9, 66.4, 64.8 (2C), 41.8, 41.7, 39.8, 39.6, 32.6, 28.6, 23.9, 19.8, 18.3. **MS (EI)** m/z (%): 239 (M^+-15, 4), 195 (3), 125 (3), 99 (10), 87 (100), 55 (29), 43 (58). **HRMS (ESI-TOF)** m/z: $[M+H]^+$ Calcd for $C_{14}H_{23}O_4$ 255.1591; found 255.1586.

2-(-2-Acetyl-1-(4-oxopentyl)cyclobutyl)ethyl acetate 35. Methyllithium in hexane (1.6 M, 15 mL) was added dropwise under inert atmosphere over a solution of bicyclic compound **34** (5 g, 20 mmol) in anhydrous THF (100 mL) at -78 °C. After 3 h of continuous stirring, the reaction was quenched with saturated aqueous NH_4Cl (15 mL), poured over water (60 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with $NaHCO_3$ (sat.) and dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude residue was dissolved in anhydrous CH_2Cl_2 (30 mL) and Et_3N (2.4 mL, 17 mmol), acetic anhydride (Ac_2O) (1.6 mL, 17 mmol) and 4-dimethylaminopyridine (DMAP) (24.3 mg, 0.21 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (50 mL) and washed with water (2 x 15 mL) and brine (15 mL, a portion of the crude material was purified yielding an 82 % of acetate **36**, see below for full spectroscopical characterization)**.** The crude residue was dissolved in acetone (50 ml) and HCl was added (1 M, 20 ml). The reaction was stirred for 60 min at room temperature. After this time, water (30 ml) was added, and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were successively washed with sat. $NaHCO_3$ (2 X 20 mL), brine (20 ml), dried over $MgSO_4$ and the solvent removed under reduced pressure. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure

to give a crude material containing compound **35**. The crude product was purified by flash column chromatography (silica gel, 30-50% EtOAc/hexane) to give 3.3 g of diketone **35** (62%) as a yellow liquid. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 3.97-3.94 (m, 2H), 3.08 (t, *J*= 8.0 Hz, 1H), 2.47 (t, *J*= 6.7 Hz, 2H), 2.34-2.32 (m, 1H), 2.13 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.85-1.83 (m, 1H), 1.79-1.77 (m, 1H), 1.76-1.74 (m, 2H), 1.67-1.64 (m, 1H), 1.64-1.61 (m, 2H), 1.50-1.48 (m, 2H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 208.7, 208.3, 171.0, 60.7, 53.5, 45.2, 43.5, 39.1, 31.4, 30.6, 30.0, 28.4, 21.0, 18.4, 17.0. **MS (EI)** m/z (%): 225 (M^+-43, 1), 208 (1), 150(7), 138 (7), 123 (26), 95 (45), 79 (23), 71 (23), 43 (100). The data agree with those published by Petschen *et al*. (see ref. 12)

2-(-2-Acetyl-1-(3-(2-methyl-1,3-dioxolan-2-yl)propyl)cyclobutyl)ethyl acetate 36. **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.0-3.94 (m, 6H), 3.08 (t, *J*= 8.3 Hz, 1H), 2.33-2.23 (m, 1H), 2.09 (s, 3H), 2.02 (s, 3H), 1.79-1.72 (m, 4H), 1.69-1.64 (m, 2H), 1.60-1.53 (m, 3H), 1.33 (s, 3H), 1.34-1.28 (m, 1H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 208.5, 170.9, 109.8, 64.6 (2C), 60.8, 53.6, 45.4, 40.0, 39.6, 31.5, 30.6, 28.5, 23.8, 20.9, 18.8, 16.8. **MS (EI)** m/z (%): 297 (M^+-15, 1), 239 (1), 115 (5), 99 (9), 87 (100), 55 (15), 43 (60).

2-(1-(4-Methylpent-4-en-1-yl)-2-(prop-1-en-2-yl)cyclobutyl)ethyl acetate 1. *n*-Butyllithium in hexane (2.5 M, 10 mL) was slowly added over a suspension of methyltriphenylphosphonium bromide (9.2 g, 26 mmol) in anhydrous THF (40 mL) at -78 °C. The resultant mixture was stirred for 30 min at this temperature and the temperature was raised up to - 20 ºC. The solution was cooled again to -78°C and a solution of diketone **35** (2 g, 7.6 mmol) in anhydrous THF (20 mL) was slowly added, and the resultant mixture was allowed to warm to room temperature and stirred for additional 30 min. The reaction was quenched with saturated aqueous NH_4Cl (20 mL)

and extracted with ethyl acetate (2 x 60 mL). The combined organic layers were washed with saturated brine (2 X 30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, 5-15% EtOAc/hexane) to give 1,28 g of sex pheromone **1** (65%) as a yellow liquid along with 253 mg of the corresponding alcohol **37** (15% yield, as a yellow liquid), which was acetylated under standard conditions and the obtained product **1** was combined with the former material (ca. 80 % total yield). **^{1}H NMR** ($CDCl_3$, 300 MHz) δ: 4.88 (s, 1H), 4.72 (s, 2H), 4.68 (s, 1H), 4.03 (t, *J*= 7.7 Hz, 2H), 2.66 (t, *J*= 8.8 Hz, 1H), 2.03 (s, 3H), 2.03-1.94 (m, 2H), 1.94-1.89 (m, 1H), 1.89-1.82 (m, 1H), 1.81-1.75 (m, 1H), 1.72 (s, 3H), 1.69 (s, 3H), 1.64-1.60 (m, 1H), 1.59-1.56 (m, 1H), 1.56-1.51 (m, 1H), 1.51-1.47 (m, 1H), 1.46-1.39 (m, 2H), 1.38-1.31 (m, 1H). **^{13}C{1H} NMR** ($CDCl_3$, 75 MHz) δ: 171.3, 145.9, 145.2, 110.8, 110.2, 61.8, 49.2, 44.7, 39.9, 38.6, 31.6, 27.7, 24.0, 22.6, 22.5, 21.2, 19.4. **MS (EI)** m/z (%): 204 (M^+-60, 1), 189 (1), 121 (43), 107 (28), 93 (45), 79 (41), 68 (71), 43 (100). Data are in full agreement with those previously reported.[12]

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SUPPORTING INFORMATION

Copy of the ^{1}H and ^{13}C NMR are available as Supporting information.

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[18] a) Prakash Rao H.S.; Babu M.; Desai A. Synthesis, Characterization and Spectroscopic Properties of Water Soluble Coumarins Substituted with Oligomeric Alkoxy Functions. *RSC Adv*., **2014**, 4, 11064–11072. b) Purification using column chromatography of some experiments allowed us to unequivocally identify compounds **2** and **14**. Spectroscopical data of both were in fully agreement with those published by Weiler, L., *et al.* (see ref. 16 b) and Tong, X. *et al.* in *Tetrahedron Lett.*, **2014**, *55*, 1682–1685 respectively.

[19] a) THP, TBDPMS and TMS were also evaluated affording lower yields in the protection and/or coupling reaction. b) Reitz, A. B., Nortey, S. O., Maryanoff, B. E., Liotta, D., & Monahan III, R. Stereoselectivity of Electrophile-Promoted Cyclizations of Gamma-Hydroxyalkenes. An Investigation of Carbohydrate-Derived and Model Substrates. *J. Org. Chem.*, **1987**, 52(19), 4191-4202. c) Lambert, K. M., Bobbitt, J. M., Eldirany, S. A., Kissane, L. E., Sheridan, R. K., Stempel, Z. D., Bailey, W. F. Metal-Free Oxidation of Primary Amines to Nitriles through Coupled Catalytic Cycles. *Chemistry–A European Journal*, **2016**, *22*(15), 5156-5159. d) Kong, D., Xue, T., Guo, B., Cheng, J., Liu, S., Wei, J., Hu, W; Yang, Y. Optimization of P2Y12 Antagonist Ethyl 6-(4-((Benzylsulfonyl) carbamoyl) piperidin-1-yl)-5-cyano-2-methylnicotinate (AZD1283) Led to the Discovery of an Oral Antiplatelet Agent with Improved Drug-Like Properties. *J. Med.Chem*. **2019**, *62* (6), 3088-3106.

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b) Adachi S.; Watanabe K.; Iwata Y.; Kameda S.; Miyaoka Y.; Onozuka M.; Mitsui R.; Saikawa Y.; Nakata M. Total Syntheses of Lactonamycin and Lactonamycin Z with Late-Stage A-Ring Formation and Glycosylation. *Angew. Chem. Int. Ed*., **2013**, *52*, 2087–2091. c) Hyun Han J.; Eun Kwon Y.; Sohn J-H.; Hyun Ryu D. A Facile Method for the Rapid and Selective Deprotection Of Methoxymethyl (MOM) Ethers. *Tetrahedron*, **2010**, *66*, 1673–1677.

[21] Deprotection of the silyl group in TBDMS derivative **19** was first attempted using TBAF or HF·Pyr in THF, affording a 62 % yield of **7**. No lactonization reaction was observed. However, the use of hexafluorosilicic acid in acetonitrile at 45 ºC, directly afforded a 53 % yield of lactone **2.** This result prompted us to assay these conditions reaction with the acid labile MOM derivative **21.**

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[24] As can be inferred from the ^{1}H-NMR analysis and according to the literature, only the *E* geometrical estereoisomer was observed in both cases. a) Nakatsuji H.; Ueno K.;

Misaki T.; Tanabe Y. General, Robust, and Stereocomplementary Preparation of β-Ketoester Enol Tosylates as Cross-Coupling Partners Utilizing TsCl-N-Methylimidazole Agents. *Org. Lett.*, **2008**, 2131–2134; b) Brown R.C.; Bataille C.J.; Hughes R.M.; Kenney A.; Luker T.J. Permanganate Oxidation of 1,5,9-Trienes: Stereoselective Synthesis of Tetrahydrofuran-Containing Fragments. *J. Org. Chem*., **2002**, *67*, 8079-8085.

[25] The deprotection-cyclization reaction was carried out with the crude enol tosylate **20**, affording an acceptable 65 % yield of enol lactone **24** after crystallization in AcOEt. The deprotection-cyclization reaction was also assayed using catalytic p-TsOH or 10 % HCl (1M) in MeOH, but lower yields of lactones **24** (52 %) or **25** (42 %) were obtained.

[26] The coupling reaction conditions were originally developed by Cahiez, G. for enol phosphate, see a) Cahiez, G., & Avedissian, H. Efficient Preparation of Terminal Conjugated Dienes By Coupling of Dienol Phosphates with Grignard Reagents under Iron Catalysis. *Synthesis*, **1998**, *8*, 1199-1205; b) Cahiez, G., Habiak, V., & Gager, O. Efficient Preparation of Terminal Conjugated Dienes by Coupling of Dienol Phosphates with Grignard Reagents under Iron Catalysis. *Org. lett*., **2008**, 10, 2389-2392. Further adaptation of this coupling to enol tosylates were later developed by Tanabe, Y., see c) Nishikado, H., Nakatsuji, H., Ueno, K., Nagase, R., & Tanabe, Y. Mild, Efficient, and Robust Method for Stereocomplementary Iron-Catalyzed Cross-Coupling Using (E)-and (Z)-Enol Tosylates. *Synlett*, **2010**, *14*, 2087-2092.

[27] a) Lactone **26** has been previously synthesized in six steps starting from ethyl acetoacetate, being also the key intermediate for the synthesis of other related pheromones as Grandisol, see ref. 13. b) D'Annibale, A., Ciaralli, L., Bassetti, M., & Pasquini, C. Synthesis of Alkyl-Substituted Six-Sembered Lactones through Ring-

Closing Metathesis of Homoallyl Acrylates. An Easy Route to Pyran-2-ones, Constituents of Tobacco Flavor. *J. Org. Chem*, **2007,** *72*(16), 6067-6074.

[28] Wu, J. M., & Li, Y. An Unexpected Product in the Photooxygenation of a Cyclic Enol Ether. *Tetrahedron Letters*, **2001**, *42*, 6737-6739.

[29] Compound **30** could be also obtained in two steps from carbon-carbon coupling reaction of **20** with Grignard derivative of **29** under the developed conditions. A subsequent double deprotection-cyclization sequence of the crude material using H_2SiF_6 in acetonitrile, afforded a 58 % overall yield of the ketone **30**.

[30] a) Stork, G.; Cohen, J.F. Ring Size in Epoxynitrile Cyclization. A General Synthesis of Functionally Substituted Cyclobutanes. Application to (±)-Grandisol. *J. Am. Chem. Soc.*, **1974**, *96*, 5270–5272. b) Mori K.; Fukamatsu K. A New Synthesis of (+)-Grandisol. *Liebigs. Ann. Chem.*, **1992**, *5*, 489–493. c) Kim D.; Kwak Y.-S.; Shin K.-J. A Stereospecific Synthesis of (±)-Grandisol via an Intramolecular Lactone Enolate Alkylation: A Remarkable Regiodivergence in C- Vs O-Alkylation. *Tetrahedron Lett.*, **1994**, *35*, 9211–9212. d) Okano K.; Ebata T.; Koseki K.; Kawakami H.; Matsumoto K.; Matsushita H. Formal Synthesis of (+)-Grandisol from Levoglucosenone. *Chem. Pharm. Bull.*, **1993**, *41*, 861–865. e) Martin T.; Rodriguez C.M.; Martin V.S. A New Approach to Functionalized Cyclobutanes: Stereoselective Synthesis of the Enantiomers of Grandisol and Fragranol. *Tetrahedron Asymmetry*, **1995**, *6*, 1151–1164. f) Han Y.T.; Kim N.J.; Jung J.W.; Yun H.; Lee S.; Suh Y.G. A Versatile Synthetic Approach to Grandisol Monoterpene Pheromone. *Arch. Pharm. Res.*, **2011**, *34*, 1437–1442. g) Craig D.; Funai K.; Gore S.J.; Kang A.; Mayweg A.V.W. Transannular Claisen Rearrangement Reactions for the Synthesis of Vinylcyclobutanes: Formal Synthesis of (±)-Grandisol. *Org. Biomol. Chem.*, **2011**, *9*, 8000–8002.

[31] a) Panda J.; Ghosh S.; Ghosh S. Synthesis of Cyclobutane Fused γ-Butyro Lactones through Intramolecular [2+2] Photocycloaddition. Application in a Formal Synthesis of Grandisol. ARKIVOC, **2001**, *8*, 146–153 and references cited therein b) Demuth M.; Palomer, A.; Sluma H.-D.; Dey A.K.; Krüger C.; Tsay Y.-H. Asymmetric Photocycloadditions with Optically Pure, Spirocyclic Enones. Simple Synthesis of (+)- and (−)-Grandisol. *Angew. Chem.*, **1986**, *25*, 1117–1119, and references cited therein. c) Hoffmann N.; Scharf H.-D. Liebigs. Efficient and Diastereoselective Synthesis of (+)- and (−)-Grandisol and 2-[(1*R*,2*S*)-2-Isopropenylcyclobutyl]ethanol (Dimethylgrandisol) in High Purity. *Ann. Chem*., **1991**, *12*, 1273–1277 and references cited therein.

[32] A few grandisol syntheses has been attempted by the use of a [2+2] lewis acid promoted cycloaddition, see: a) Billups W.E.; Cross J.H.; Smith C.V. A Synthesis of (±)-Grandisol, *J. Am. Chem. Soc*., **1973**, *95*, 3438–3438. b) Narasaka K.; Kusama H.; Hayashi Y. Enantio- and Diastero-Seletive Synthesis of (+)-Grandisol. *Bull. Chem. Soc. Jpn*., **1991**, *64*, 1471–1478. Based on a ring expansion strategy, see: c) Trost B.M.; Keeley D.E. New Synthetic Methods. Seco-Alkylative Approach to Grandisol. *J. Org. Chem*., **1975**, *40*, 2013. d) Frongia A.; Girard C.; Ollivier J.; Piras P.P.; Secci F. Convenient Formal Synthesis of (+)-Grandisol through Lewis Acid Promoted Enantioselective Pinacolic Rearrangement. *Synlett*, **2008**, *18*, 2823–2825. Based on a ring close metathesis strategy, see: e) Graham T.J.A.; Gray E.E.; Burgess J.M.; Goess B. G. An Efficient Synthesis of (±)-Grandisol Featuring 1,5-Enyne Metathesis *J. Org. Chem*., **2010**, *75*, 226–228.

[33] The reactivity of carbonyl derivatives other than ketones and aldehydes is limited when non-stabilized phosphoranes are used. In this particular case, the bicyclic structure of lactone **4** is possibly increasing the carbonyl reactivity towards nucleophiles, see: a)

Murphy, P. J., & Brennan. The Wittig Olefination Reaction With Carbonyl Compounds Other Than Aldehydes And Ketones. *J. Chem. Soc. Rev*., **1998**, *17*, 1-30. b) Lakhrissi, M., & Chapleur, Y. Wittig Olefination of Lactones. *Angew. Chem. Int. Ed.*, **1996**, *35*, 750-752. c) Sabitha, G., Reddy, M. M., Srinivas, D., & Yadov, J. S. Microwave Irradiation: Wittig Olefination of Lactones and Amides. *Tet. Lett.*, **1999**, *40*, 165-166.

[34] Interestingly, when similar Wittig conditions were applied to 1,4 unsaturated lactone **30,** a moderate 70 % yield after column chromatography of the corresponding methylenated product was obtained with no other major products detected. Unfortunately, this product could not be submitted to the subsequent photochemical step due to the intramolecular [2+2] reaction competition.

[35] Possibly, the low yield obtained could be explained due to the fact that the elimination reaction of the intermediate phosphorane betaine is not favored at this temperature, see: Trippett, S., & Walker, D. M. The Phosphobetaines: Preparation and Properties. *J. Chem.Soc. (Resumed)*, **1961**, 1266-1272.

[36] The photochemical reaction could be carried out with compound **3** as a crude material to give compound **34** in ca. 41 % yield. Noticeably, if the reaction time was longer than expected or the crude material was kept at room temperature for a long time prior to purification, a partial deprotection of the ketal moiety to give ketone **4** was observed in some experiments.

[37] Acetylation of the alcohol moiety after lactone **34** opening was necessarily carried out before ketal deprotection, in order to avoid a partial or total intramolecular six-member hemiketal formation, as previously described (see ref. 12 and Supporting experimental file for detailed information).

[38] A reproducible yield of 53 % was obtained for compound **35** from keto-lactone **34** when this three step synthetic sequence was attempted in a 50 g scale.

[39] a) Lombardo L. Methylenation of Carbonyl Compounds with Zn-CH_2Br_2-$TiCl_4$. Applications to Gibberellins. *Tetrahedron Lett*., **1982**, *23*, 4293–4296. b) Lombardo L. Methylenation of Carbonyl Compounds: (+)-3-methylene-cis-p-methane. *Org. Synth*. **1987**, *65*, 81–85.