# First Total Synthesis of the Sex Pheromone of the Oleander Scale *Aspidiotus nerii*: An Unusual Sesquiterpenic Functionalized Cyclobutane

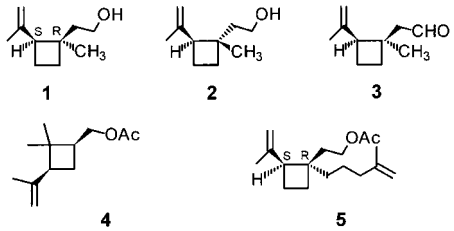
**Inés Petschen,[a] Alfredo Parrilla,[a] M. Pilar Bosch,[a] Cristina Amela,[a] Ana A. Botar,[b] Francisco Camps,[a] and Angel Guerrero*[a]**

**Abstract:** The first total synthesis of the sex pheromone of the oleander scale *Aspidiotus nerii* (**5**), an economically important polyphagous pest, is described. The synthesis is based on a stereocontrolled and completely regioselective intramolecular *exo*-cyclization of *cis*-epoxynitrile **9** to afford cyclobutane alcohol *t*-**10** stereoselectively. Introduction of the unusual 4-methylpent-4-enyl group onto the cyclobutane skeleton was effected through Wittig reaction of aldehyde **17b** with the bulky ylide 3,3-(ethylenedioxy)butylidenetriphenylphosphorane. This process requires protection of the primary hydroxy group of **10** with a nonbulky protecting agent, like methoxymethyl (MOM) but not tetrahydropyranyl (THP), as confirmed by molecular modelling studies. After selective transformations to manipulate the three acid-sensitive protecting functionalities present, that is, the *tert*-butyldimethylsilyl (TBDMS), ethylene acetal, and MOM groups, compound **5** was obtained in 26.4% overall yield from *t*-**10b**. In a different approach, complete cleavage of these protecting groups in **19b** furnished keto diol **31**, which after regioselective acetylation of the primary alcohol and Wittig reaction afforded acetate **5** in 21.4% overall yield from *t*-**10b**. The synthetic material exhibited spectroscopic features identical to those of the natural material and showed remarkable biological activity in field tests.

**Keywords:** *Aspidiotus nerii* · natural products · pheromones · protecting groups · synthesis design · total synthesis

## Introduction

Cyclobutane derivatives are remarkable compounds not only as natural products,[1–6] but also in their versatility to be transformed into a variety of compounds by ring enlargement or ring-opening reactions.[7–14] Some of them, such as the cyclobutane nucleosides cyclobut-A and cyclobut-G (BHCG), are also important in the pharmaceutical field, because they are potent inhibitors of the replication of herpes simplex type-1 and type-2 viruses, *varicella zoster* virus and human citomegalo virus, and they also exhibit activity against HIV.[15–18] However, in the pheromone field very few structures containing a cyclobutane ring are known[19] (Scheme 1). Grandisol (1*R*,2*S*)-(+)-*cis*-2-isopropenyl-1-methylcyclobutylethanol (**1**), is the most important constituent of the aggregation pheromone of the cotton boll weevil *Anthonomus grandis*,[20] and has been found in other beetles like *Tripodendron signatum*,[21] *Pityophthorus pityographus*,[22] *Pityogenes bidentatus*, *P. quadridens* and *P. calcaratus*[23] and *Curculio caryae*.[24] Its *trans* isomer, fragranol (**2**), has been identified in extracts of the plant *Artemisia fragrans*.[25] Grandisol and its oxidation product grandisal (**3**) have also been found as the aggregation pheromone components of *Pissodes strobi* and *P. nemorensis*.[26, 27] A structurally related analogue (1*R*,3*R*)-(+)-*cis*-2,2-dimethyl-3-isopropenylcyclobutylmethanol acetate (**4**), has been described as the sex pheromone of the citrus mealybug *Planococcus citri*.[28]




Scheme 1. Cyclobutane derivatives known in the pheromone field.

The oleander scale *Aspidiotus nerii* (Homoptera: Diaspididae) is a polyphagous pest of many tropical and subtropical areas. It has been reported from hosts corresponding to more than 100 plant families,[29] and is particularly important in the

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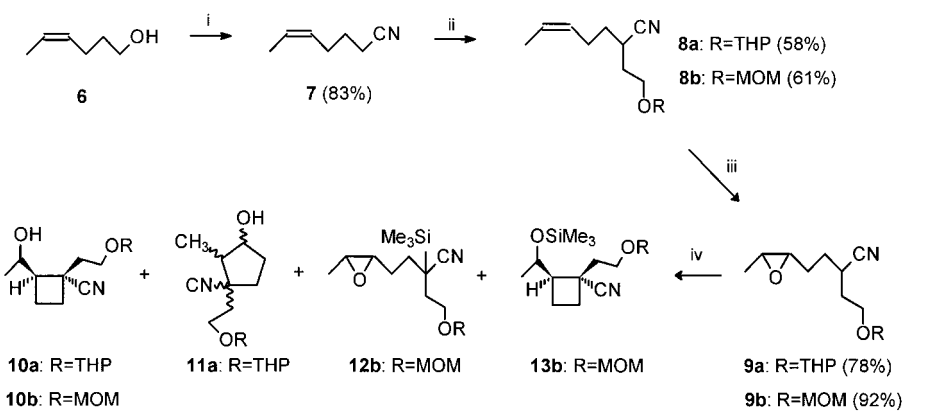
damage caused to lemon trees, olive trees, and ornamental plants, like oleander. The scale is sap-sucking and produces general weakening of the tree, discoloration of leaves and severe deterioration of the fruit quality.[30] The sex pheromone is presumably produced by the female's pygidial gland and released through the rectum, like in other scales.[31]

Very recently, we reported the complete structural characterization and absolute configuration of the sex pheromone of the oleander scale, as (1*R*,2*S*)-*cis*-2-isopropenyl-1-(4′-methylpent-4′-en-1′-yl)cyclobutylethanol acetate (**5**), an unusual sesquiterpenic functionalized cyclobutane[32] (Scheme 1). Noteworthy structural features of **5** are the sterically congested quaternary carbon of the cyclobutane ring, the presence of the 4-methylpent-4-enyl group, an unusual homoprenylated chain,[33] and the two differently substituted isopropenyl functionalities. The well-known difficulty associated with the construction of the small-size rings, the strain induced by the chains, particularly on the quaternary carbon, and the additional transannular strain[34] made the total synthesis of the pheromone a real challenge. We describe herein the first total synthesis of the pheromone **5** through a convenient regio- and stereocontrolled intramolecular *exo*-cyclization of a duly functionalized *cis*-epoxynitrile **7**.

## Results and Discussion

Preparation of (*Z*)-hept-5-enenitrile (**7**) was performed by three different reaction sequences: a) Wittig reaction of the phosphonium salt of 5-bromovaleronitrile with acetaldehyde in toluene and *t*BuOK as base in 60% yield,[35] b) alkylation of 1-bromo-3-chloropropane with lithium acetylide followed by methylation of the terminal acetylene, cyanation and reduction to the *cis* nitrile **7** (24% overall yield, 4 steps),[36] and c) nucleophilic substitution of the mesylate of (*Z*)-hex-4-enol (**6**) with sodium cyanide (83% yield). Because of the simplicity and overall yield, this latter route was preferred for large-scale preparation of nitrile **7** (Scheme 2).

Initially, we decided to perform the proposed synthetic sequence with R = tetrahydropyranyl. Monoalkylation of **7**




Scheme 2. Synthesis of intermediate cyclobutane derivatives **10a** and **10b**. i) 1) MsCl, $Et_3N$, 2) NaCN/DMSO; ii) LDA, $Br(CH_2)_2OR$/THF:HMPA

**Abstract in Spanish:** *Se describe la primera síntesis total de la feromona sexual del piojo blanco Aspidiotus nerii (**5**), una importante plaga polífaga. La síntesis se basa en una ciclación exo intramolecular, estereocontrolada y completamente regioselectiva, del cis-epoxinitrilo **9** para dar lugar de manera estereoselectiva al ciclobutano alcohol t-**10**. La introducción del poco frecuente grupo 4-metil-4-pentenilo en el esqueleto ciclobutánico se consiguió por reacción de Wittig del aldehido **17b** con el voluminoso iluro 3,3-(etilendioxi)butilidentrifenilfosforano. Este proceso requiere la protección del grupo hidroxilo primario de **10** con un agente protector poco voluminoso, como el MOM pero no el THP, como se confirmó por estudios de modelización molecular. Tras selectivas transformaciones para manipular las tres funcionalidades presentes sensibles al medio ácido, esto es los grupos TBDMS, etilen acetal y MOM, se obtuvo el compuesto **5** en un 26.4% de rendimiento global desde t-**10b**. En otra aproximación, se procedió a la desprotección completa de los grupos protectores en **19b** para obtener el ceto diol **31**, el cual por acetilación regioselectiva del alcohol primario y reacción de Wittig condujo al acetato **5** en un 21.4% de rendimiento global desde t-**10b**. El material sintético exhibió idénticas características espectroscópicas que las del producto natural y mostró una notable actividad biológica en pruebas de campo*

was accomplished by metalation with lithium diisopropylamide (LDA) followed by reaction with 2-(2-bromoethoxy)-tetrahydropyran in THF/hexamethyl phosphoramide (HMPA) 3:2. The monoalkylated product **8a** was obtained in 58% yield along with 20% of the bis-alkylated derivative. Epoxidation under standard conditions afforded *cis*-epoxide **9a** in 78% yield (Scheme 2).

For the construction of the cyclobutane ring a number of processes have been developed, such as photochemical cycloaddition of olefins,[37] thermal cycloaddition of electrophilic and nucleophilic olefins,[38–40] cycloaddition of ketenes with olefins,[41] or intramolecular cyclizations.[42–44] We decided to follow the base-induced cyclization of δ-epoxynitriles developed by Stork and Cohen.[45] These compounds cyclized to give preferentially the smallest ring (cyclobutane vs. cyclopentane) when both ends of the epoxide are equally substituted, the regioselectivity is due to a more ready attainment of the necessary co-planar arrangement of the attacking group, epoxide carbon and oxide leaving groups. The epoxide stereochemistry directs the regioselectivity of the ring-opening, and thus while *cis*-epoxynitriles yielded cyclobutanes preferentially, similarly substituted *trans*-epoxides afforded mixtures of four- and five-membered ring products.[36] In our case, a systematic study of the intramolecular cyclization reaction of **9a** under a variety of conditions was undertaken (Table 1).



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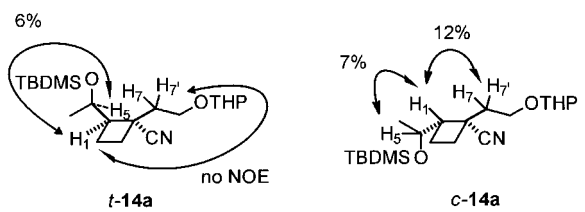
Table 1. Cyclization reaction of epoxide **9a** under different conditions.

| Entry | Base[a] | Ratio **9a**:base | Reaction conditions addition of **9a**; reaction | Products: yield[b] (t/c) |
|---|---|---|---|---|
| 1 | LiHMDS | 1:4 | 0 °C/3.5 h; 25 °C/5 h | **10a**: 24 (n. d.); **11a**: 6 |
| 2 | LiHMDS | 1:3.3 | 0 °C/20 min; reflux 10 min | **10a**: 61 (80/20); **11a**: 14 |
| 3 | LiHMDS | 1:4 | 0 °C/20 min; reflux 1 h | **10a**: 41 (n. d.); **11a**: 11 |
| 4 | LDA[c] | 1:2 | −78 °C/15 min; −20 °C/45 min, 0 °C/90 min | **10a**: 39 (85/15); **11a**: 7 |

[a] Benzene was used as solvent in LiHMDS reactions, while THF was preferred when LDA was used as base. [b] Yields of isolated product (mixture of diastereomers) after careful purification by column chromatography on neutral alumina. [c] Inverse addition, that is the base was added to the epoxide.

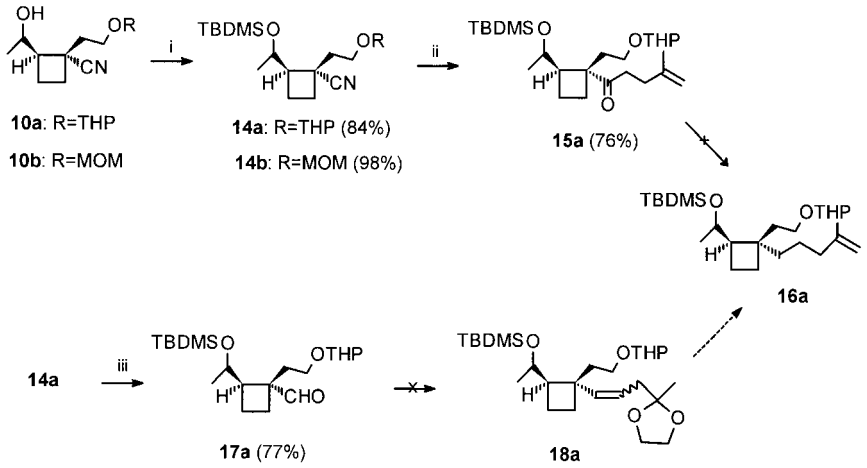
The best conditions found for cyclization of **9a** were utilization of lithium hexamethyldisilazide (LiHMDS) in a substrate/base ratio of 1:3.3 in benzene, addition of the epoxide at 0 °C for 20 min and reflux for 10 min (entry 2). Under these conditions, cyclobutane **10a** was obtained (61 %) as a mixture of *trans* and *cis* isomers in a 80:20 ratio along with cyclopentane **11a** (14 %) (Scheme 2). The two compounds resulted from the 4-*exo*- and 5-*endo*-attack of the cyano anion on the epoxide.[46] In our hands, the conditions described by Stork and Cohen[45] did not lead to the best yield of **10a** in terms of stereo- and regioselectivity. The reaction was also stereoselective, the major isomer (*t*-**10a**) had the required relative configuration, that is with the tetrahydropyranyloxyethyl and 1-hydroxyethyl groups on the same side of the ring. This result agrees with the assumption of Stork[45] that the cyano anion in the allenic structure of the metal salt is more sterically demanding than a normal alkyl group.

The regioisomers **10a** and **11a** were characterized by $^1H-^1H$ correlation (DQCOSY) and $^1H-^{13}C$ NMR (HETCOR) experiments, as well as by PDC/DMF oxidation to the corresponding methyl ketone [IR: $\tilde{\nu}=1712\ cm^{-1}$, $^1H$ NMR: $\delta=2.19$ (s, 3H, $CH_3CO$), $^{13}C$ NMR: $\delta=204.6$] and methyl cyclopentanone [IR: $\tilde{\nu}=1749\ cm^{-1}$, $^1H$ NMR: $\delta=1.25$ (d, 3H, $J=7.2$ Hz, $CH_3CH$), $^{13}C$ NMR: $\delta=214.5$], respectively. The stereomeric *cis* and *trans* configuration was determined by NOE experiments on the correponding *tert*-butyldimethylsilyl (TBDMS) ethers *c*-**14a** and *t*-**14a** (Scheme 3). Thus, selective irradiations of protons $H_1$, $H_5$ and $H_7$ produced NOE effect (6–7 %) between $H_1$ and $H_5$ in both compounds, and $H_1$ and $H_7$ (12 %) in *c*-**14a** , while no effect was observed between these two protons in *t*-**14a**. In this way, the major stereoisomer with *trans* stereochemistry was assigned to the structure with the two oxygenated functions on the same side of the ring, as in target compound **5**.




Scheme 3. NOE experiments on *t*-**14a** and *c*-**14a**.

With *t*-**14a** in hand, the next objective was transformation of the cyano group into the 4-methylpent-4-enyl group. Conversion of nitrile **14a** into ketone **15a**, through the intermediate imine, was not problematic since reaction with the required 3-methylbut-3-enyllithium, prepared in situ by metalation of 1-iodo-3-methylbut-3-ene with *t*BuLi in pentane/diethyl ether,[47] occurred cleanly in a one-step process in 76 % yield. However, different approaches to proceed with this synthetic sequence were not successful (Scheme 4). Thus,




Scheme 4. Possible routes to diol-protected **16a.** i) TBDMSCl, imidazole/DMF; ii) 1) 3-methylbut-3-enyllithium (for R = THP), 2) $Al_2O_3$ chromatography; iii) DIBAH/hexane.

extensive efforts to achieve Wolff–Kishner reduction (toluene-*p*-sulfonyl hydrazine/EtOH, hydrazine hydrate/EtOH) of **15a** to effect the desired CO →$CH_2$ transformation to **16a** were unsuccessful. In another approach, ketone **15a** was reduced to the corresponding alcohol (LAH/diethyl ether 76 %) but reductive cleavage of the hydroxy group after transformation into a suitable leaving group (thiocarbonyldiimidazole/$Bu_3SnH$,[48] NaH/$CS_2$/MeI[49]) also proved futile. In another approach, Wittig reaction of aldehyde **17a**, obtained by reduction of **14a** with diisobutylaluminum hdyride (DIBAH) (77 %), with the required ylide 3,3-(ethylenedioxy)butylidenetriphenylphosphorane[50] under a variety of conditions to build compound **18a** was also unsuccessful. In

order to explain this failure, we carried out energy minimization calculations of aldehyde **17a** and the intermediate betaine in the latter Wittig reaction, and compared them with those determined for analogous compounds with the OH-protected as the less bulky methoxymethyl (MOM) ether (**17b**) and the corresponding betaine. The compounds were built with the HYPERCHEM 3.0 module, and fully geometry-optimized with the molecular-mechanics force-field (method AMBER) with a 0.01 kcal mol$^{-1}$ energy gradient convergence. A systematic conformational search was performed on the rotable C–C bonds around the dihedral angles and involved the alkyl chains with an increment of 120°. Every generated conformation was minimized up to 2000 iterations. The results showed that **17a** and its betaine presented minimum-energy conformations of higher energy (ca. 7 kcal mol$^{-1}$ difference in each case) than the corresponding analogues with the MOM group. Moreover, in the conformations of the former structures a marked steric hindrance between the tetrahydropyranyloxyethyl and the *tert*-butyldimethylsilyloxyethyl was apparent, while this strain appeared to be relieved in the MOM-containing conformations. This led us to consider substitution of the THP protecting group of the primary alcohol by the less bulky MOM moiety in the complete synthetic sequence. Besides, utilization of the MOM protecting group implied lack of any additional stereogenic centre, as occurred with the THP function, and greatly facilitated interpretation of the spectroscopic features of the cyclic structures.

Cyclization of the MOM derivative **9b**, prepared in a similar manner to **9a**, was also attempted under several reaction conditions (Table 2). The best conditions were found to be addition of **9b** to LiHDMS at 0 °C, followed by stirring at 20 °C for 20 min and then refluxing for a further 15 min (entry 3). The reaction products consisted of a 79:21 mixture of *t*/*c*-**10b** (60% yield) along with 2% of *t*-**13b**, and they were separated by careful column chromatography. In none of the cases studied was the cyclopentane derivative **11b** from the 5-*endo* attack detected, this implied that cyclization was completely regioselective. The reaction was also stereoselective and the major isomer (*t*-**10b**) had the required relative configuration, that is with the methoxymethyloxyethyl and 1-hydroxyethyl groups on the same side of the ring. Assignment of compounds was determined by DQCOSY and HECTOR experiments.

Characterization of *cis*- and *trans*-**10b** was carried out by NOESY and ROESY experiments on the silyl derivatives **14b**. In the case of *c*-**14b** a clear correlation was observed between $H_5$ with $H_7$ and $H_{7'}$, whereas no correlation was found in the *trans* isomer (see Scheme 3 for numbering). In the same regard, cyclobutane methine $H_1$ resonates at lower field ($\delta =$ 2.66, q, $J = 9.9$ Hz) in *t*-**10b** than in *c*-**10b** ($\delta = 2.27$, q, $J =$ 9.5 Hz) due to the paramagnetic effect induced by the vicinal cyano group. On the contrary and for the same reason, methine $H_5$ resonates at higher field in *t*-**10b** ($\delta = 3.80$, m) than in *c*-**10b** ($\delta = 4.07$, dq, $J = 9.5$, $J' = 6.5$ Hz). Moreover, treatment of *c*-**10b** and *t*-**10b** with neutral alumina in hexane/AcOEt 1:1 for three days produced a partial cyclization of the *cis* isomer to the corresponding lactone, while *t*-**10b** remained completely unaltered. Formation of the lactone can be visualized through formation of the corresponding imine intermediate followed by hydrolysis. Likewise, treatment of both isomers with DIBAH in hexane produced reduction of *c*-**10b** to the aldehyde followed by concomitant cyclization to the corresponding hemiacetal, while *t*-**10b** underwent the expected reduction with no hemiacetal detected.

Reduction of nitrile **14b** with DIBAH furnished the corresponding aldehyde **17b** in 90% yield, which was subjected to the key Wittig reaction with the bulky ylide 3,3-(ethylenedioxy)butylidenetriphenylphosphorane. The reaction was carried out at low temperature, in the presence of 5.6 equiv of ylide and in THF as solvent. To our satisfaction, and as predicted from the molecular modeling studies, the reaction proceeded successfully to give alkene **18b** (85–98% *Z*) in 82% yield (Scheme 5). This reaction represents a convenient entry to the 4-methylpent-4-enyl group, an unusual but biogenetically interesting chain. Hydrogenation of the double bond was initially tried on $PtO_2$/MeOH at atmospheric or medium pressure. However, the reaction was capricious and not reproducible, and led in many instances to hydrogenolysis products. After extensive experimentation with other catalysts under different conditions, we found that Pd/C in 5% molar concentration in EtOH at room temperature provided complete hydrogenation of the double bond to furnish **19b** in 90% yield, without concomitant formation of hydrolysis or hydrogenolysis products. Cleavage of the silyl ether (TBAF/THF) followed by oxidation (PDC/DMF) gave ketone **21b**, which was selectively hydrolyzed to diketone **22b** with Amberlyst A15 resin in 92.5% overall yield from **19b** (Scheme 6). Bis-Wittig reaction of diketone **22b** was effected with five equivalents of ylide per carbonyl group in THF, and a slight excess of the phosphonium salt in order to ensure complete absence of base in the reaction mixture. Under these conditions, diolefin **23b** was obtained in 79% yield without epimerization of the configuration of the cyclobutane carbon in the $\alpha$-position to the carbonyl (Scheme 5).

Table 2. Cyclization reaction of epoxide **9b** under different conditions.

| Entry | Base[a] | Ratio **9b**:base | Reaction conditions | Products: yield[b] (*t*/*c*) |
|---|---|---|---|---|
| 1 | LiHMDS | 1:4 | base to 0 °C + **9b**, 0 °C/3.5 h, 20 °C/6 h | **10b**: 26 (91:9); **9b**: 10; *t*-**13b**: 12; **12b**: 5 |
| 2 | LiHMDS | 1:3.3 | base to 0 °C + **9b**, 20 °C/20 min, reflux 35 min | **10b**: 47 (79/21); **12b**: 10; *t*-**13b**: 8; *c*-**13b**: 2 |
| 3 | LiHMDS | 1:3.3 | base to 0 °C + **9b**, 20 °C/20 min, reflux 15 min | **10b**: 60 (79/21); *t*-**13b**: 2 |
| 4 | LiHMDS[c] | 1:3.3 | **9b** to 0 °C + base, 20 °C/20 min, reflux 15 min | **10b**: 45 (73/27); *t*-**13b**: 5; *c*-**13b**: 2 |
| 5 | KHMDS | 1:3.3 | base to 0 °C + **9b**, 20 °C/20 min, reflux 15 min | **10b**: 28 (89/11) |
| 6 | LDA | 1:2.5 | base to −78 °C + **9b**, −20 °C/45 min, 0 °C/2 h | **10b**: 30 (67/33) |

[a] Benzene was used as solvent in LiHMDS reactions, whereas THF was preferred when LDA was utilized as base. [b] Yields of isolated product after careful purification by column chromatography on neutral alumina. [c] Inverse addition, that is the base was added to the epoxide.



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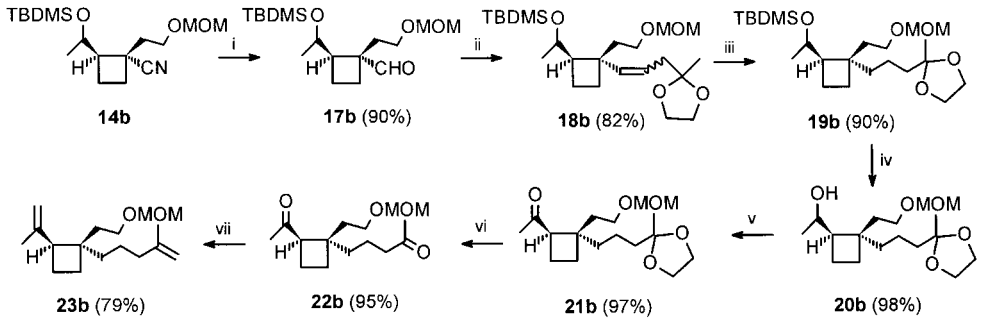
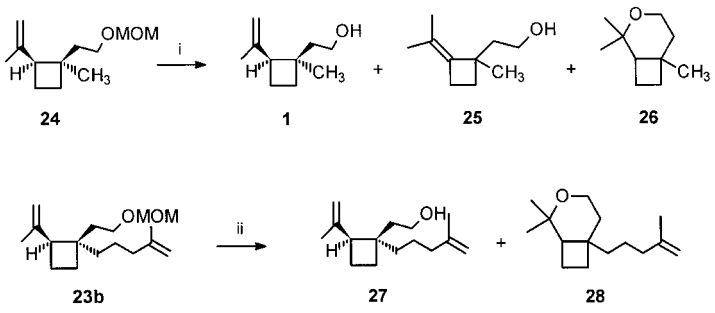


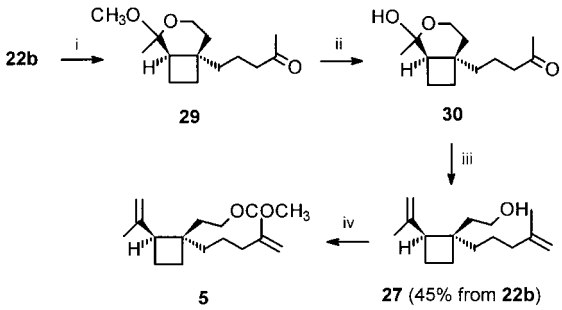

Scheme 5. Synthesis of diene **23b.** i) DIBAH/hexane; ii) $Ph_3P{=}CHCH_2C(OCH_2CH_2O)CH_3$/THF; iii) $H_2$, Pd/C, EtOH; iv) TBAF/THF; v) PDC/DMF; vi) Amberlyst A15 resin/acetone/$H_2O$; vii) $Ph_3P{=}CH_2$ (5 equiv per carbonyl)/THF.

Before proceeding, a number of model studies for hydrolysis of the MOM group in structures with a vinyl group were undertaken. When 10-methoxymethylundecenyl ether was subjected to various cleavage reagents (AcOH/MeOH/$H_2O$ (2:2:1),[51] trifluoroacetic acid/MeOH,[52] $BF_3/Et_2O$,[53] $Me_3SiBr/CH_2Cl_2$,[53] pyridinium *p*-toluenesulfonate (PPTS)/EtOH, AG 50Wx4 resin[54] or Dowex 50Wx4 resin[55]/MeOH, and $Me_3SiCl/Et_4NBr$,[56]), the best yields of the corresponding alcohol were obtained with PPTS/EtOH (0.5 equiv at reflux for 15 h: 97%; 0.02 equiv at reflux for 73 h: 96%), AG 50Wx4 resin (room temperature for 21 h: 99%) and Dowex 50Wx4 resin (room temperature for 48 h: 92%). The two latter resins were, therefore, good candidates for the mild hydrolysis of a close analogue of **23b**, like the MOM derivative of grandisol **24**. However, for each resin up to six-fold in weight of resin and several days of reaction at room temperature were required to drive hydrolysis to completion. However, under these conditions mixtures of the hydrolysis product **1**, the isomerized alcohol **25** and the cyclic ether **26** were obtained (Scheme 6). In spite of this result, we decided to perform the hydrolysis of **23b** since we could expect feasible transformation of ether **28** into alcohol **27** under basic conditions. However, in this case, a 12-fold in weight of Dowex 50Wx4 resin was required and the target alcohol **27** was obtained in only 20% yield along with cyclic ether **28** (30%). Use of PPTS/EtOH needed 15 h at reflux for complete reaction, but again mixtures of **27** and **28** were obtained as well as other unidentified products. Trials to protect the *exo*-methylene group of **24** with bromine unavoidably led to cleavage of the MOM group with concomitant cyclization to form mono-




Scheme 6. Attempted hydrolysis of MOM derivative **23b** and its analogue **24**. i) AG 50W-X4 resin/MeOH or Dowex 50W-X4 resin/MeOH; ii) Dowex 50W-X4 resin/MeOH or PPTS/EtOH.

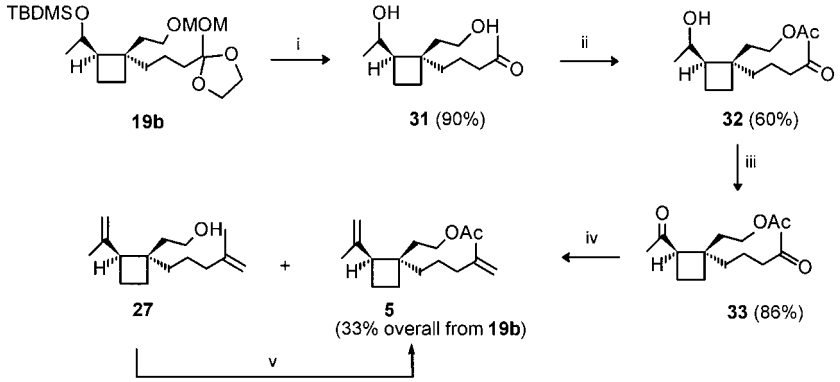
brominated and nonbrominated cyclic ether **26**. To circumvent the difficulties encountered with the MOM-cleavage in the presence of the double bond(s), we decided to hydrolyze the protecting group on diketone **22b** (Scheme 7). Treatment of this compound with Dowex 50Wx4 resin in MeOH afforded acetal **29**, which upon purification on silica gel was partly cleaved to hemiacetal **30**. Therefore, to optimize the formation of the hemiacetal, crude **29** was treated with $SiO_2$ in hexane to afford the unstable hemiacetal **30**. This was immediately subjected to a Wittig reaction with a large excess of methylenetriphenylphosphorane (30 equiv/




Scheme 7. Route for the synthesis of pheromone **5** from **22b**. i) Dowex 50W-X4/MeOH; ii) $SiO_2$/hexane; iii) $Ph_3P{=}CH_2$ (30 equiv per carbonyl)/THF; iv) $Ac_2O/Et_3N/DMAP/CH_2Cl_2$.

carbonyl group) to provide alcohol **27** in 45% overall yield from **22b**. The alcohol was stereomerically pure, without epimerization at the stereogenic center in the $\alpha$-position to the carbonyl group. Finally, acetylation of **27** under standard conditions afforded acetate (±)-**5** in 26.4% overall yield from **14b** (Scheme 7).

In an alternative approach compound **19b** was fully hydrolyzed with HCl/MeOH to afford dihydroxy ketone **31** in 90% yield (Scheme 8). Then, regioselective acetylation of the primary alcohol was accomplished through a modification of the procedure described by Posner and Oda[57] ($Al_2O_3$ W-200-N/AcOEt; 12 d, room temperature). Under these conditions acetate **32** was obtained in 60% yield, along with 25% of unreacted diol **31** which was recycled.[58] Oxidation of **32** with pyridinium dichromate (PDC)/DMF furnished **33** (86% yield), which underwent a Wittig reaction with the required ylide (5 equiv of salt per carbonyl group) to afford a mixture of the expected pheromone **5** (30% yield) and alcohol **27** (42% yield). This latter compound was acetylated under standard conditions in a quantitative manner to provide acetate **5** in 71% total yield. Overall, this new approach allowed us to obtain the target product **5** in 21.4% yield from **14b** (Scheme 8). The synthetic material exhibited spectroscopic features identical to those of the natural material (Figures 1 and 2) and showed fairly good attractant activity in the field, as it will be reported in due course.




Scheme 8. Alternative route for the synthesis of pheromone **5.** i) HCl/MeOH; ii) $Al_2O_3$ W-200-N/AcOEt; iii) PDC/DMF; iv) $Ph_3P{=}CH_2$; v) $Ac_2O/Et_3N/DMAP/CH_2Cl_2$.

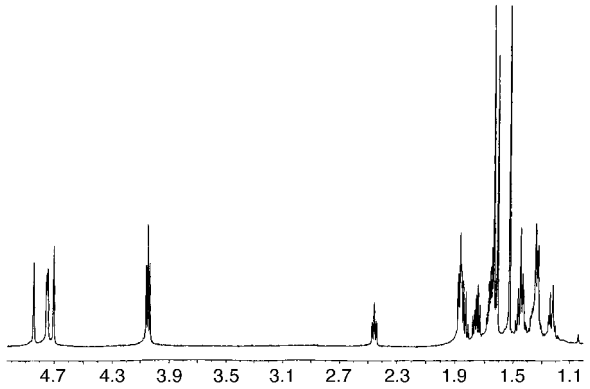



Figure 1. $^1$H NMR (600 MHz) spectrum of the natural pheromone in $C_6D_6$.[32]

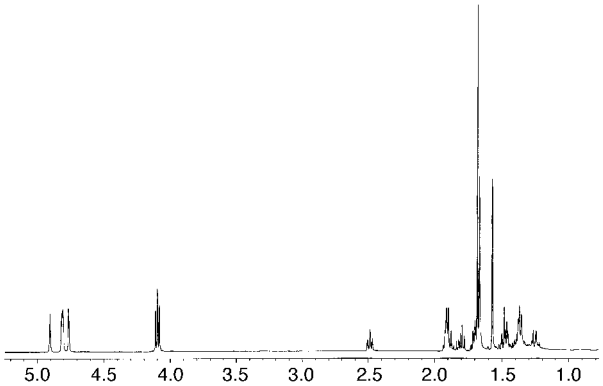



Figure 2. $^1$H NMR (500 MHz) spectrum of the synthetic pheromone (±)-**5** in $C_6D_6$.

## Experimental Section

**General**: Elemental analyses were carried out on Carlo Erba models 1106 and EA 1108. IR spectra were recorded on a FT-IR Bomem MB-120 instrument. $^1$H and $^{13}$C NMR spectra were obtained in $CDCl_3$ solutions on a Varian Gemini 200 and Unity 300 spectrometers, at 200 and 300 MHz for $^1$H and 25 and 75 MHz for $^{13}$C, respectively. In special cases for $^1$H NMR a Varian VXR-500 (500 MHz) was also used. Chemical shifts are expressed in $\delta$ scale relative to internal $Me_4Si$ or to the $CHCl_3$ signal (7.26 ppm) present in $CDCl_3$. GC analyses were run on Carlo Erba Series 4130 using a SPB-5 (30 m × 0.25 mm i.d.) capillary column, or on a Fisons MFC 800 equipped with a EC-1 (30 m × 0.25 mm i.d.). GC-MS were run on a Fisons MD800 coupled to a GC equipped with a HP-1 (30 m × 0.20 mm) or BP-20 (30 m × 0.22 mm) column. Exact mass measurements were done on a Autospec-Q instrument at 70 eV and source temperature 225 °C. Analytical-grade reagents were obtained from commercial sources and used without further purification. Anhydrous solvents were prepared as follows: tetrahydrofuran, diethyl ether and pentane by distillation over Na/benzophenone, hexane and acetonitrile over calcium hydride, benzene from sodium, methylene chloride over $P_2O_5$, triethylamine and pyridine over KOH, dimethyl sulfoxide over $CaH_2$ under vacuum. Anhydrous dimethylformamide was obtained commercially.

**(*Z*)-5-Heptenenitrile (7)**: To a solution of (*Z*)-hex-4-enol (**6**) (25 g, 0.25 mol) in $CH_2Cl_2$ (625 mL) at −10 °C was added anhydrous triethylamine (105 mL, 76 g, 0.75 mol). Then mesyl chloride (43 mL, 62.5 g, 0.55 mol) was added dropwise over 30 min. The mixture was stirred for 10 min and poured into ice. The organic phase was washed with HCl (1N), $NaHCO_3$ (saturated solution), and brine. After drying ($MgSO_4$) the mixture, the solvent was removed under vacuum and the corresponding mesylate (44 g) subjected to the next step without purification. The crude product was dissolved in anhydrous DMSO (600 mL), and dried NaCN (55 g, 1.12 mol) was added. The mixture was brought to reflux for 2 h, cooled and poured into ice/water. The organic material was extracted with pentane, washed with water, and dried ($MgSO_4$) to leave a residue, which was purified by distillation to furnish nitrile **7** (22.5 g, 83 % from **6**), as a colorless oil. B.p.: 100 °C/20 mm Hg; IR (film): $\tilde{\nu}$ = 3014, 2937, 2867, 2246, 1656, 1454, 1427, 838, 702 cm$^{-1}$; $^1$H NMR (200 MHz): $\delta$ = 5.55 (m, 1H), 5.30 (m, 1H), 2.33 (t, $J$ = 7.2 Hz, 2H), 2.20 (q, $J$ = 7.2 Hz, 2H), 1.72 (qt, $J$ = 7.2 Hz, 2H), 1.62 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (50 MHz): $\delta$ = 127.6, 126.2, 119.8, 25.5, 25.2, 16.3, 12.8; MS (EI): *m/z* (%): 108 (6), 81 (30), 80 (19), 69 (29), 68 (21), 67 (23), 55 (79), 54 (29), 53 (19), 41 (100); anal. calcd (%) for $C_7H_{11}N$: C 77.01, H 10.16, N 12.83; found: C 76.86, H 10.28, N 12.88.

**(*Z*)-2-(2-Methoxymethyloxyethyl)hept-5-enenitrile (8b)**: A solution of nitrile **7** (6.64 g, 60.9 mmol) in anhydrous THF (180 mL) was cooled to −78 °C. To the solution was added dropwise with a cannula freshly prepared LDA (50.7 mL of a 1.2 M solution), and the mixture was stirred for 30 min under Ar at this temperature. The mixture was then added via a cannula to a solution of 2-bromoethoxymethoxymethane (12.36 g, 73 mmol) in anhydrous THF (77 mL) and the resulting mixture stirred for 30 min. The reaction was quenched with $NH_4Cl$ (saturated solution), the aqueous layer extracted with pentane, and the organic phases combined, washed with brine, and dried ($MgSO_4$). The solvent was removed and the residue purified by distillation under vacuum to yield the expected product **8b** (7.32 g, 61 %) along with the bis-alkylated compound (1.91 g, 11 %).

**Compound 8b**: B.p.: 75–79 °C/12 mm Hg; IR (film): $\tilde{\nu}$ = 3014, 2931, 2237, 1420, 1213, 1149, 1112, 1043, 919 cm$^{-1}$; $^1$H NMR (200 MHz): $\delta$ = 5.50 (m, 1H), 5.30 (m, 1H), 4.60 (s, 2H), 3.66 (t, $J$ = 6.0 Hz, 2H), 3.35 (s, 3H), 2.80 (m, 1H), 2.25 (q, $J$ = 7.4 Hz, 2H), 1.85 (m, 2H), 1.68 (m, 2H), 1.62 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (50 MHz): $\delta$ = 127.94, 126.01, 121.72, 96.51, 64.41, 55.35, 32.42, 31.97, 27.95, 24.40, 12.83; MS (CI, $CH_4$): *m/z* (%): 198 (57) [$M^+$+1], 167 (22), 166 (100); anal. calcd (%) for $C_{11}H_{19}NO_2$: C 66.97, H 9.71, N 7.10; found: C 66.85, H 9.76, N 7.02.

**(*Z*)-2,2-Bis(2-methoxymethyloxyethyl)hept-5-enenitrile**: B.p.: 115–117 °C/0.2 mm Hg; IR (film): $\tilde{\nu}$ = 3014, 2933, 2231, 1442, 1213, 1153, 1108, 1039, 918 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta$ = 5.50 (m, 1H), 5.30 (m, 1H), 4.60 (s, 4H), 3.70 (t, $J$ = 6.9 Hz, 4H), 3.35 (s, 6H), 2.19 (m, 2H), 1.96 (t, $J$ = 6.9 Hz, 4H), 1.63 (m, 2H), 1.60 (d, $J$ = 6.6 Hz, 3H); $^{13}$C NMR (300 MHz): $\delta$ = 128.31, 125.32, 122.94, 96.52, 63.77, 55.42, 38.13, 36.66, 35.85, 22.07, 12.74; MS (CI, $CH_4$): *m/z* (%): 286 (20) [$M^+$+1], 254 (100); anal. calcd (%) for $C_{15}H_{27}NO_4$: C 63.13, H 9.54, N 4.91; found: C 63.20, H 9.65, N 4.91.

**(*Z*)-2-(2-Tetrahydropyranyloxyethyl)hept-5-enenitrile (8a)**: Following a similar procedure as above, compound **8a** was obtained in 58 % yield along with 20 % of the bis-alkylated product. B.p.: 98-99 °C/0.08 mm Hg; IR (film): $\tilde{\nu}$ = 3000, 2935, 2860, 2240, 1650, 1440, 1350, 1140, 1120, 1070, 1030 cm$^{-1}$; $^1$H NMR (diastereomeric mixture): $\delta$ = 5.4 (dm, $J$ = 10.5 Hz, 2H), 4.6 (m, 1H), 3.9 (m, 2H), 3.52 (m, 2H), 2.82 (m, 1H), 2.26 (m, 2H),



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1.88–1.4 (c, 10H), 1.64 (d, $J = 5.7$ Hz, 3H); $^{13}$C NMR (diastereomeric mixture): $\delta = 128.06, 125.9, 121.9, 99.4, 98.6, 64.4, 64.1, 62.6, 62.1, 32.5, 32.4, 32.0, 31.9, 30.6, 30.5, 38.05, 28.0, 25.4, 24.44, 24.4, 19.6, 19.3, 12.9$; MS (EI): *m/z* (%): 169 (4), 109 (15), 94 (9), 85 (100), 69 (12), 67 (18), 55 (25).

**(*Z*)-5,6-Epoxy-2-(methoxymethyloxyethyl)heptanenitrile (9b)**: To a solution of the monoalkylated nitrile **8b** (9.29 g 47.2 mmol) in $CH_2Cl_2$ (155 mL) was added at 0 °C *m*-chloroperbenzoic acid (70%, 12.1 g, 48.9 mmol). The mixture was stirred at room temperature for 4.5 h and washed successively with $Na_2SO_3$ (saturated solution), NaOH (1N), and water, and dried ($MgSO_4$). The solvent was removed under vacuum to leave the expected compound **9b** (9.3 g, 92%) after flash column chromatography purification. IR (film): $\tilde{\nu} = 2993, 2954, 2237, 1454, 1392, 1211, 1151, 1110, 1039, 918$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 4.609, 4.606$ (s, 2H), 3.68 (t, $J = 6.0$ Hz, 2H), 3.35 (s, 3H), 3.06 (m, 1H), 2.90 (m, 2H), 1.9–1.7 (c, 6H), 1.28 (d, $J =$ 5.4 Hz, 3H); $^{13}$C NMR (300 MHz) (diastereomeric mixture): $\delta = 121.41, 121.28, 96.49, 64.25, 56.19, 55.75, 55.36, 52.77, 52.52, 32.62, 32.28, 29.58, 29.00, 28.63, 28.12, 25.56, 24.95, 13.18, 13.14$; MS (CI, $CH_4$) *m/z* (%): 214 (7) [$M^+$], 182 (40), 152 (100); anal. calcd (%) for $C_{11}H_{19}NO_3$: C 61.95, H 8.98, N 6.57; found: C 61.83, H 9.04, N 6.56.

**(*Z*)-5,6-Epoxy-2-(2-tetrahydropyranyloxyethyl)heptanenitrile (9a):** Following a similar procedure as for **9b**, **9a** was obtained in 78% yield after column chromatography on alumina (III). IR (film): $\tilde{\nu} = 3000, 2940, 2870, 2240, 1450, 1350, 1135, 1070, 1030, 980, 870, 810$ cm$^{-1}$; $^1$H NMR (diastereomeric mixture): $\delta = 4.58$ (m, 1H), 3.86 (m, 2H), 3.51 (m, 2H), 3.05 (m, 1H), 2.9 (m, 2H), 1.9–1.4 (c, 12H), 1.27 (d, $J = 5.7$ Hz, 3H); $^{13}$C NMR (diastereomeric mixture): $\delta = 121.5, 99.47, 99.44, 98.68, 98.63, 64.3, 63.97, 63.95, 62.71, 62.65, 62.2, 62.16, 56.25, 56.2, 55.8, 52.8, 52.6, 32.71, 32.66, 32.38, 32.31, 30.56, 30.48, 29.61, 29.54, 29.05, 28.98, 28.76, 28.7, 28.3, 28.21, 25.6, 25.35, 25.04, 24.97, 19.69, 19.66, 19.38, 19.34, 13.23, 13.18$; MS (EI): *m/z* (%): 253 ([$M^+$], 2), 152 (9), 110 (9), 101 (12), 85 (100), 67 (16), 57 (22), 55 (19).

***t*-2-(1-Hydroxyethyl)-1-(2-tetrahydropyranyloxyethyl)cyclobutyl-*r*-1-carbonitrile (10a)**: At 0 °C anhydrous benzene (400 mL) was added to lithium hexamethyldisilazide (67 mL of a 1M solution in hexane). Then, epoxide **9a** (5.2 g, 20.3 mol) in anhydrous benzene (45 mL) was added dropwise under argon. The mixture was stirred for 15 min at room temperature and for 8 min at reflux. The reaction was quenched by treatment with HCl (0.5N), and the organic material extracted with diethyl ether, washed with brine, and dried. After evaporation of the solvent, the residue was purified by column chromatography on alumina (III), eluting with hexane/ethyl acetate (75:25) to obtain a mixture of isomers **10a** (3.183 g, 61%), and with hexane/ethyl acetate (65:35) to furnish a mixture of isomers **11a** (0.728 g, 14%).

**Compound 10a** (mixture of diastereomers) IR (film): $\tilde{\nu} = 3444, 2948, 2230, 1442, 1376, 1354, 1122, 1075, 1003$ cm$^{-1}$; $^{13}$C NMR (75 MHz): $\delta = 123.94, 123.79, 99.26, 99.01, 66.75, 66.63, 64.60, 64.57, 62.31, 62.21, 50.68, 50.77, 35.06, 34.92, 30.62, 30.51, 30.01, 29.96, 29.39, 29.26, 25.23, 20.64, 20.07, 20.06, 19.32, 19.30$.

**Compound 11a** (mixture of diastereomers) IR (film): $\tilde{\nu} = 3438, 2943, 2873, 2110, 1737, 1454, 1353, 1258, 1201, 1122, 1078, 1033, 870$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 4.61$ (m, 1H), 4.05 (m, 1H), 3.85 (m, 2H), 3.69 (m, 1H), 3.54 (m, 1H), 2.25 (m, 1H), 2.05 (m, 1H), 1.95 (m, 1H), 1.85 (m, 1H), 1.8 (m, 1H), 1.65 (m, 1H), 1.6 (m, 1H), 1.58 (m, 1H), 1.54 (m, 1H), 1.52 (m, 1H), 1.4 (m, 1H), 1.22 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (major diastereomer) (75 MHz): $\delta = 122.26, 99.04, 77.85, 64.28, 62.32, 51.36, 45.26, 37.3, 34.85, 31.87, 30.54, 25.33, 19.38, 13.62$.

***t*-2-(1-Hydroxyethyl)-1-(2-methoxymethyloxyethyl)cyclobutyl-*r*-1-carbonitrile (10b):** To a mixture of lithium hexamethyldisilazide (48 mL of a 1M solution in hexane) and anhydrous benzene (260 mL) was added dropwise epoxide **9b** (3.1 g, 14.5 mmol) at 0 °C under an inert atmosphere. The mixture was stirred for 20 min at room temperature, and then immersed in an oil bath at 110 °C wherein it was further stirred for 15 min. After cooling, the reaction mixture was treated with HCl (0.5N), and extracted with diethyl ether, and the organic phases were combined and washed with $NaHCO_3$ and NaCl (saturated solution). After drying the mixture with $MgSO_4$, the solvent was removed under vacuum and the residue purified by careful flash chromatography on silica gel. Cyclobutane **10b** was obtained as a mixture of isomers (1.488 g, 48% of *t*-**10**; 0.372 g, 12% of *c*-**10**) along with trimethylsilyl derivative *t*-**13b** (0.064 g, 2%).

**Compound *t*-10:** IR (film): $\tilde{\nu} = 3475, 2931, 2885, 2225, 1442, 1375, 1213, 1153, 1110, 1039, 921$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 4.62$ (s, 2H), 3.82 (m, 1H), 3.80 (m, 1H), 3.72 (dt, $J = 9.9$ Hz, $J' = 6.0$ Hz, 1H), 3.36 (s, 3H), 2.66 (q, $J = 9.9$ Hz, 1H), 2.43 (m, 1H), 2.35 (dt, $J = 14.4$ Hz, $J' = 6.9$ Hz, 1H), 2.03 (m, 1H), 2.02 (m, 1H), 1.93 (dt, $J = 14.4$ Hz, $J' = 6.0$ Hz, 1H), 1.70 (m, 1H), 1.08 (d, $J = 6.0$ Hz, 3H); $^{13}$C NMR (300 MHz): $\delta = 123.70, 96.54, 66.80, 64.75, 55.55, 50.74, 34.95, 30.55, 29.36, 20.65, 20.17$; MS (EI): *m/z* (%): 152 (9, [$M^+ - OCH_2OCH_3$]), 125 (12), 94 (18), 81 (21), 45 (100).

**Compound *c*-10:** IR (film): $\tilde{\nu} = 3467, 2962, 2931, 2885, 2229, 1444, 1375, 1213, 1153, 1110, 1041, 919$ cm$^{-1}$; $^1$H NMR (500 MHz): $\delta = 4.63$ (s, 2H), 4.07 (dq, $J =$ 9.5 Hz, $J' = 6.5$ Hz, 1H), 3.79 (ddd, $J = 10.4$ Hz, $J' = 7.5$ Hz, $J'' =$ 5.4 Hz, 1H), 3.73 (dt, $J = 10.5$ Hz, $J' = 6.0$ Hz, 1H), 3.39 (s, 3H), 2.33 (m, 1H), 2.27 (q, $J = 9.5$ Hz, 1H), 2.13 (ddd, $J = 14.2$ Hz, $J' =$ 7.2 Hz, $J'' =$ 5.5 Hz, 1H), 2.01 (m, 1H), 1.97 (m, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.12 (d, $J =$ 6.5 Hz, 3H); $^{13}$C NMR (300 MHz): $\delta = 122.48, 96.42, 69.74, 64.49, 55.61, 51.62, 39.53, 38.71, 29.84, 20.72, 19.80$; MS (EI): *m/z* (%): 152 (7), 125 (11), 110 (21), 45 (100).

**Compound *t*-13b**: IR (film): $\tilde{\nu} = 2954, 2931, 2883, 2229, 1444, 1373, 1251, 1153, 1114, 1091, 1045, 919, 842, 750, 734$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta =$ 4.62 (s, 2H), 3.90–3.64 (c, 3H), 3.36 (s, 3H), 2.72 (q, $J = 9.9$ Hz, 1H), 2.4–1.5 (c, 6H), 1.06 (d, $J = 6.3$ Hz, 3H), 0.12 (s, 9H); $^{13}$C NMR (300 MHz): $\delta =$ 123.80, 96.57, 68.02, 64.70, 55.29, 50.30, 34.66, 30.04, 28.13, 20.45, 20.41, 0.73; MS (EI): *m/z* (%): 240 (11, [$M^+ - CH_2OCH_3$]), 210 (11), 117 (20), 75 (42), 73 (100), 45 (88); anal. calcd (%) for: $C_{14}H_{27}NO_3Si$: C 58.91, H 9.53, N 4.91; found: C 58.86, H 9.66, N 4.88.

***t*-2-(1-*tert*-Butyldimethylsilyloxyethyl)-1-(2-methoxymethyloxyethyl)cyclobutyl-*r*-1-carbonitrile (14b)**: To a solution of *t*-**10b** (2.52 g, 11.8 mmol) in anhydrous DMF (50 mL) were added imidazole (4.74 g, 69.6 mmol) and *tert*-butyldimethylsilyl chloride (5.05 g, 33.5 mmol). The mixture was stirred at room temperature overnight, quenched with water and extracted with $CH_2Cl_2$. The organic layer was washed with brine, dried ($MgSO_4$), and the solvent removed. The crude product was purified by flash column chromatography on silica gel to afford **14b** (3.80 g, 98%). IR (film): $\tilde{\nu} =$ 2952, 2929, 2229, 1471, 1373, 1255, 1155, 1114, 1087, 1043, 925 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 4.60$ (s, 2H), 3.82 (dq, $J = 8.7$ Hz, $J' = 6.3$ Hz, 1H), 3.75 (ddd, $J = 10.0$ Hz, $J' = 7.5$ Hz, $J'' = 5.4$ Hz, 1H), 3.68 (dt, $J = 9.9$ Hz, $J' = 7.2$ Hz, 1H), 3.35 (s, 3H), 2.72 (dt, $J = 10.8$ Hz, $J' = 8.7$ Hz, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 2.06 (m, 1H), 2.05 (m, 1H), 1.88 (m, 1H), 1.76 (ddd, $J = 21.6$ Hz, $J' = 10.8$ Hz, $J'' = 9.0$ Hz, 1H), 1.05 (d, $J = 6.0$ Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); $^{13}$C NMR (300 MHz): $\delta = 123.76, 96.51, 67.97, 64.63, 50.46, 50.31, 34.48, 29.75, 28.11, 25.78, 20.49, 20.45, 17.91, -3.13, -4.81$; MS (EI): *m/z* (%): 181 (10), 107 (10), 89 (30), 75 (32), 73 (31), 45 (100); anal. calcd (%) for $C_{17}H_{33}NO_3$: C 62.34, H 10.16, N 4.28; found: C 62.31, H 10.21, N 4.31.

***t*-2-(1-*tert*-Butyldimethylsilyloxyethyl)-1-(2-tetrahydropyranyloxyethyl)cyclobutyl-*r*-1-carbonitrile (14a)**: Following a similar procedure as for **14b**, the mixture of *c/t*-**10a** furnished a blend of *cis*- and *trans*-**14a** which could be separated by careful column chromatography on alumina (II). Compound *t*-**14a** was obtained in 67% yield as a mixture of diastereomers, with *c*-**14a** in 17% yield. *t*-**14a**: IR (film): $\tilde{\nu} = 2950, 2925, 2110, 1471, 1371, 1255, 1118, 1080, 1035, 833$ cm$^{-1}$; $^1$H NMR (300 MHz): $\delta = 4.59$ (m, 1H), 4.0 (m, 1H), 3.85 (m, 1H), 3.83 (m, 1H), 3.59 (m, 1H), 3.5 (m, 1H), 2.72 (dt, $J = 11.6$ Hz, $J' = 10$ Hz, 1H), 2.3 (m, 1H), 2.16 (m, 1H), 2.08 (m, 1H), 2.05 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H), 1.7 (m, 2H), 1.6 (m, 1H), 1.5 (m, 2H), 1.45 (m, 1H), 1.02 (d, $J = 6$ Hz, 3H), 0.05 (ds, 6H), 0.85 (s, 9H); $^{13}$C NMR (mixture of diastereomers) (300 MHz): $\delta = 123.9, 123.8, 99.0, 98.8, 67.9, 64.5, 64.2, 62.2, 62.1, 50.5, 34.7, 34.5, 30.5, 30.46, 29.65, 29.62, 29.1, 28.2, 25.7, 25.3, 20.43, 20.4, 19.4, 19.3, 17.9, -3.18, -4.8, -4.9$.

**Ketone 15a**: In a 50-mL flask was placed, under oxygen-free argon, 1-iodo-3-methylbut-3-ene (321 mg, 1.63 mmol) in anhydrous hexane/diethyl ether 3:2 (16 mL). The solution was cooled to −78 °C and *t*BuLi (2.1 mL of a 1.6M solution in pentane) was added dropwise under vigorous stirring. The reaction mixture was stirred for 5 min at −78 °C and for 1 h at room temperature. Then, the mixture was again cooled to −78 °C and a solution of cyclobutane **14a** (300 mg, 0.82 mmol) in pentane (3 mL) added. After 15 min of stirring at this temperature and 1 h at room temperature, the reaction mixture was treated with $NH_4Cl$ (saturated solution) and stirred for a further 30 min. The organic material was extracted with diethyl ether and washed with brine and dried ($MgSO_4$). Evaporation of the solvent left a residue which was chromatographed on alumina (III) to furnish ketone **15a**

(331 mg, 76%) as a mixture of diastereomers. IR (film): $\tilde{\nu}=3074$, 2952, 1701, 1649, 1255, 1122, 1082, 1033, 833 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=4.68$ (s, 2H), 4.54 (t, $J=3$ Hz, 1H), 3.98 (dq, $J=9.2$ Hz, $J'=6.1$ Hz, 1H), 3.69 (m, 1H), 3.45 (dm, $J=9.6$ Hz, 2H), 3.42 (m, 1H), 2.8 (m, 2H), 2.52 (m, 1H), 2.45 (dt, $J=14$ Hz, $J'=4.8$ Hz, 1H), 2.25 (m, 2H), 2.20 (m, 1H), 2.06 (dt, $J=14$ Hz, $J'=4.8$ Hz, 1H), 1.8 (m, 1H), 1.76 (m, 1H), 1.71 (m, 3H), 1.65 (m, 1H), 1.56 (m, 1H), 1.5 (m, 2H), 1.48 (m, 1H), 1.46 (m, 2H), 1.02 (d, $J=6.1$ Hz, 3H), 0.11 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H); $^{13}C$ NMR (mixture of diastereomers) (300 MHz): $\delta=212.3$, 212.1, 145.2, 145.1, 110.0, 99.3, 98.2, 69.6, 69.5, 63.7, 63.2, 62.3, 61.4, 54.4, 54.3, 48.5, 48.4, 34.7, 31.6, 31.0, 30.9, 30.4, 30.2, 26.1, 26.0, 25.4, 22.7, 22.6, 22.1, 21.8, 21.3, 19.6, 19.0, 18.9, 18.8, 18.0, −3.6, −3.7, −3.9; anal. calcd (%) for $C_{25}H_{46}O_4Si$: C 68.44, H 10.58; found: C 68.78, H 10.55.

***t*-2-(1-*tert*-Butyldimethylsilyloxyethyl)-1-(2-tetrahydropyranyloxyethyl)cyclobutyl-*r*-1-carbaldehyde (17a)**: To a solution of nitrile **14a** (60 mg, 0.16 mmol) in hexane (2 mL) was added at −45 °C DIBAH (0.25 mL of a 1M solution) under argon. The mixture was stirred at 0 °C for 1 h. Then MeOH (1 mL) and $H_2SO_4$ (1N, 1 mL) were added, and the product was extracted with hexane, washed with $NaHCO_3$ (saturated solution) and water, and dried ($MgSO_4$). The solvent was removed to leave a residue, which was purified by column chromatography on silica gel to furnish aldehyde **17a** (45 mg, 77%). IR (film) $\tilde{\nu}=2952$, 2929, 2896, 2856, 1716, 1471, 1257, 1120, 833 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=9.49$ (s, 1H), 4.58 (m, 1H), 3.8 (m, 1H), 3.6 (m, 1H), 3.5 (m, 1H), 3.3 (m, 1H), 2.45 (m, 1H), 2.3 (m, 1H), 2.25 (m, 1H), 2.20 (m, 1H), 2.0 (m, 1H), 1.88 (m, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.50 (m, 2H), 1.4 (m, 1H), 0.85 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H).

***t*-2-(1-*tert*-Butyldimethylsilyloxyethyl)-1-(2-methoxymethyloxyethyl)cyclobutyl-*r*-1-carbaldehyde (17b)**: A solution of **14b** (1.08 g, 3.33 mmol) in anhydrous hexane (95 mL) was cooled at −55 °C under Ar. To the solution was added dropwise DIBAH (6 mL of a 1M solution), the reaction mixture was stirred for 1 h and quenched with $H_2SO_4$ (1N). After extraction with hexane, the organic phases were combined and washed with $NaHCO_3$ (saturated solution) and brine, and dried ($MgSO_4$). The solvent was removed under vacuum and the residue purified by flash column chromatography on silica gel to afford the corresponding aldehyde **17b** (0.99 g, 90%). IR (film): $\tilde{\nu}=2956$, 2931, 2885, 2858, 1716, 1257, 1112, 1085, 1056, 918, 833, 775, 734 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=9.49$ (s, 1H), 4.51 (d, $J=6.6$ Hz, 1H), 4.46 (d, $J=6.6$ Hz, 1H), 3.84 (dq, $J=9.0$ Hz, $J'=6.0$ Hz, 1H), 3.55 (m, 1H), 3.46 (m, 1H), 3.26 (s, 3H), 2.39 (m, 1H), 2.37 (m, 1H), 2.25 (q, $J=9.3$ Hz, 1H), 2.01 (dt, $J=14.0$ Hz, $J'=5.0$ Hz, 1H), 1.75 (m, 1H), 1.60 (m, 1H), 1.50 (m, 1H), 1.01 (d, $J=6.0$ Hz, 3H), 0.86 (s, 9H), 0.082 (s, 3H), 0.056 (s, 3H); $^{13}C$ NMR (300 MHz): $\delta=202.93$, 96.22, 68.27, 63.47, 55.20, 53.38, 49.40, 28.14, 25.9, 20.63, 19.18, 19.07, 17.83, −4.55, −3.23; MS (CI, $CH_4$): *m/z* (%): 299 (7), 270 (16), 269 (97), 211 (56), 169 (56), 159 (96), 137 (100); anal. calcd (%) for $C_{17}H_{34}O_4Si$: C 61.77, H 10.37; found: C 61.60, H 10.41.

**Alkene 18b:** Anhydrous THF (200 mL) was added under argon to a 250-mL three-necked round-bottomed flask, containing dried 3,3-(ethylenedioxy)butyltriphenylphosphonium iodide (5.97 g, 11.8 mmol). The mixture was cooled to −65 °C and then *n*BuLi (5.5 mL of a 1.6M solution in hexane, 8.8 mmol) was added dropwise and stirred for 30 min. The mixture was then warmed to 0 °C and stirred for a further 15 min. After cooling again to −65 °C, aldehyde **17b** (0.528 g, 1.6 mmol) in anhydrous THF (15 mL) was added dropwise. The mixture was stirred for 30 min at −65 °C and at room temperature until the almost complete disappearance of the aldehyde (monitored by TLC: 20–40 min). After quenching with $NH_4Cl$ (saturated solution), the organic material was extracted with hexane, washed with $NH_4Cl$ (saturated solution) and brine, and dried ($MgSO_4$). The solvent was removed to leave a crude product, which was purified by flash column chromatography on silica gel to yield alkene **18b** (0.561 g, 82%) as mixture of *Z*/*E* isomers, with *Z* as the major isomer (85–98%).

***Z* isomer**: IR (film): $\tilde{\nu}=3014$, 2956, 2931, 2883, 2858, 1473, 1373, 1255, 1147, 1110, 1082, 835, 773 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=5.63$ (dt, $J=11.7$ Hz, $J'=1.8$ Hz, 1H), 5.27 (dt, $J=11.4$ Hz, $J'=6.9$ Hz, 1H), 4.59 (s, 2H), 3.94 (s, 4H), 3.86 (dq, $J=9.6$ Hz, $J'=6.0$ Hz, 1H), 3.55 (m, 2H), 3.34 (s, 3H), 2.43 (ddd, $J=15.0$ Hz, $J'=7.8$ Hz, $J''=1.5$ Hz, 1H), 2.18 (ddd, $J=15.0$ Hz, $J'=6.7$ Hz, $J''=1.5$ Hz, 1H), 2.17 (q, $J=9.6$ Hz, 1H), 2.08 (m, 1H), 2.04 (m, 1H), 1.87 (m, 1H), 1.85 (m, 1H), 1.72 (m, 1H), 1.51 (m, 1H), 1.33 (s, 3H), 0.98 (d, $J=6.0$ Hz, 3H), 0.86 (s, 9H), 0.061 (s, 3H), 0.054 (s, 3H); $^{13}C$ NMR (300 MHz): $\delta=139.37$, 121.74, 109.73, 96.43, 69.12, 65.45, 64.71, 64.66, 55.07, 52.48, 44.92, 38.07, 32.40, 28.85, 25.97, 23.95, 21.08, 20.56, 17.94, −4.50, −3.40; MS (CI, $CH_4$): *m/z* (%): 159 (9), 89 (10), 87 (100); anal. calcd (%) for $C_{23}H_{44}O_5Si$: C 64.44, H 10.34; found: C 64.62, H 10.41.

**1-(4,4-Ethylenedioxypentyl)-c-2-(1-hydroxyethyl)-*r*-1-(2-methoxymethyloxyethyl)cyclobutane (20b)**: Hydrogenation of alkene **18b** was carried out by addition of the alkene (135 mg, 0.32 mmol) at 0 °C to a hydrogen-saturated mixture of Pd/C (17 mg, 0.016 mmol) and deoxygenated ethanol (1 mL). The mixture was hydrogenated with a balloon of hydrogen and stirred at room temperature for 2.5 h (control by GC). The crude product was filtered through Celite, washed with ethanol and $CH_2Cl_2$, dried ($MgSO_4$), and the solvent removed. After purification by flash column chromatography on silica gel, the pure hydrogenated product **19b** (122 mg, 90%) was obtained. IR (film): $\tilde{\nu}=2952$, 2929, 2883, 2858, 1463, 1373, 1257, 1151, 1108, 1068, 1041, 833, 775 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=4.61$ (s, 2H), 3.92 (m, 4H), 3.82 (dq, $J=9.3$ Hz, $J'=6.0$ Hz, 1H), 3.58 (dt, $J=9.3$ Hz, $J'=6.9$ Hz, 1H), 3.48 (dt, $J=9.3$ Hz, $J'=6.9$ Hz, 1H), 3.35 (s, 3H), 2.06 (q, $J=9.3$ Hz, 1H), 1.87 (ddd, $J=9.1$ Hz, $J'=6.4$ Hz, $J''=2.7$ Hz, 2H), 1.74 (m, 1H), 1.56 (m, 2H), 1.53 (m, 2H), 1.48 (m, 1H), 1.44 (m, 1H), 1.36 (m, 1H), 1.32 (m, 2H), 1.32 (s, 3H), 0.98 (d, $J=6.0$ Hz, 3H), 0.87 (s, 9H), 0.083 (s, 3H), 0.057 (s, 3H); $^{13}C$ NMR (300 MHz): $\delta=110.17$, 96.34, 69.28, 64.69, 64.49, 64.46, 55.06, 49.94, 42.45, 40.23, 39.75, 32.44, 27.16, 26.01, 23.64, 21.38, 19.47, 19.16, 17.95, −4.16, −3.45; MS (CI, $CH_4$): *m/z* (%): 175 (38), 149 (48), 89 (63), 87 (100); exact mass: calcd for $C_{23}H_{46}O_5Si$: 430.311453; found: 430.312062.

A mixture of **19b** (93 mg, 0.22 mmol) in anhydrous THF (15 mL) was cooled to 0 °C and then "dry" TBAF (0.574 g, 2.2 mmol) in anhydrous THF (15 mL) was added. The mixture was stirred at room temperature overnight, the solvent removed under vacuum, and water/$CH_2Cl_2$ was added. The organic phase was washed with brine and dried ($MgSO_4$), and the solvent evaporated. The residue was purified by flash column chromatography on silica gel to obtain compound **20b** (67 mg, 98%). IR (film): $\tilde{\nu}=3477$, 2948, 1885, 1461, 1377, 1215, 1149, 1109, 1060, 1039, 919 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=4.60$ (s, 2H), 3.91 (m, 4H), 3.79 (dq, $J=9.6$ Hz, $J'=6.3$ Hz, 1H), 3.64 (dt, $J=9.6$ Hz, $J'=7.5$ Hz, 1H), 3.53 (ddd, $J=9.6$ Hz, $J'=8.4$ Hz, $J''=4.8$ Hz, 1H), 3.34 (s, 3H), 2.06 (dt, $J=14.1$ Hz, $J'=7.8$ Hz, 1H), 1.89 (q, $J=9.0$ Hz, 1H), 1.77 (m, 1H), 1.71 (m, 1H), 1.59 (m, 1H), 1.58 (m, 1H), 1.52 (m, 1H), 1.42 (m, 1H), 1.40 (m, 2H), 1.35 (m, 1H), 1.32 (m, 1H), 1.31 (m, 1H), 1.29 (s, 3H), 1.02 (d, $J=6.3$ Hz, 3H); $^{13}C$ NMR (300 MHz), 110.06, 96.42, 68.14, 64.60, 55.34, 51.75, 42.31, 40.34, 39.81, 32.18, 29.26, 23.76, 20.74, 19.46, 18.64; MS (CI, $CH_4$): *m/z* (%): 149 (49), 87 (100); anal. calcd (%) for $C_{17}H_{32}O_5$: C 64.53, H 10.19; found: C 64.29, H 10.37.

**Oxidation of 20b**: A solution of alcohol **20b** (56 mg, 0.18 mmol) in anhydrous DMF (5 mL) was cooled to 0 °C and then pyridinium dichromate (0.677 g, 1.80 mmol) was added. The mixture was stirred at room temperature overnight, water was added and the organic material extracted with hexane/diethyl ether (1:1). The organic layer was washed with brine, dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was purified by column chromatography to yield ketone acetal **21b** (54 mg, 97%). IR (film): $\tilde{\nu}=2950$, 2933, 2883, 1703, 1151, 1109, 1060, 1041, 916, 732 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=4.54$ (s, 2H), 3.93 (m, 4H), 3.41 (t, $J=7.5$ Hz, 2H), 3.31 (s, 3H), 3.04 (t, $J=8.1$ Hz, 1H), 2.28 (m, 1H), 2.07 (s, 3H), 1.81 (m, 1H), 1.78 (m, 1H), 1.74 (m, 1H), 1.72 (m, 1H), 1.66 (m, 1H), 1.54 (m, 1H), 1.52 (m, 2H), 1.45 (m, 1H), 1.44 (m, 2H), 1.31 (s, 3H); $^{13}C$ NMR (300 MHz): $\delta=208.82$, 109.91, 96.36, 64.67, 63.76, 55.19, 53.79, 45.66, 40.13, 39.69, 32.79, 30.74, 28.60, 23.83, 18.88, 16.83; MS (EI): *m/z* (%): 99 (27), 87 (100), 45 (83); anal. calcd (%) for $C_{17}H_{30}O_5$: C 64.94, H 9.62; found: C 64.87, H 9.75.

**Diketone 22b**: To a mixture of the acetal **21b** (71 mg, 0.23 mmol) in acetone (560 μL) and water (16 μL) was added Amberlyst A-15 resin (11 mg). The mixture was stirred at room temperature overnight, filtered, extracted with hexane, and washed with brine and dried ($MgSO_4$). After removal of the solvent, the crude product was purified by column chromatography to furnish diketone **22b** (58 mg, 95%). IR (film): $\tilde{\nu}=$ 2935, 2887, 1716, 1703, 1359, 1151, 1109, 1070, 1041, 918 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta=4.54$ (s, 2H), 3.42 (td, $J=8.1$ Hz, $J'=1.8$ Hz, 2H), 3.31 (s, 3H), 3.06 (t, $J=8.4$ Hz, 1H), 2.46 (t, $J=6.9$ Hz, 2H), 2.28 (m, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 1.80 (m, 1H), 1.74 (m, 1H), 1.71 (m, 2H), 1.65 (m, 1H), 1.60 (m, 2H), 1.49 (m, 2H); $^{13}C$ NMR (75 MHz): $\delta=208.72$, 208.35, 96.35, 63.70, 55.16, 53.66, 45.51, 43.67, 39.29, 32.60, 30.62, 29.93, 28.51, 18.51, 16.91; MS (EI): *m/z* (%): 209 (1), 149 (4), 147 (5), 123 (11), 107 (13), 95 (17), 79



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(10), 71 (14), 45 (100), 43 (63); anal. calcd (%) for $C_{15}H_{26}O_4$: C 66.64, H 9.69; found: C 66.59, H 9.89.

***c*-2-Isopropenyl-*r*-1-(2-methoxymethyloxyethyl)-1-(4-methylpent-4-enyl)-cyclobutane (23b)**: In a three-necked round-bottomed flask were placed methyltriphenylphosphonium bromide (0.394 g, 1.10 mmol), previously dried overnight at 80 °C/0.1 mm Hg, and anhydrous THF (2 mL). The mixture was cooled to −78 °C and then *n*BuLi (0.50 mL of a 1.76 M solution in hexane, 0.88 mmol) was added dropwise. The ylide was stirred for 1 h at room temperature, cooled again to −78 °C and then diketone **22b** (29 mg, 0.11 mmol) dissolved in anhydrous THF (300 μL) was added. The reaction mixture was stirred for 3 h at room temperature, quenched with $NH_4Cl$ (saturated solution) and extracted with hexane. The organic phases were washed with $NH_4Cl$ (saturated solution) and brine, and dried ($MgSO_4$). Removal of the solvent left a residue, which was chromatographed on silica flash to afford diene **23b** (22.5 mg, 79%). IR (film): $\tilde{\nu}$ = 3080, 2933, 2881, 1647, 1454, 1149, 1109, 1039, 887, 757 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 4.87 (br, 1H), 4.72 (br, 2H), 4.68 (br, 1H), 4.59 (s, 2H), 3.47 (m, 2H), 3.35 (s, 3H), 2.64 (t, $J$ = 9.0 Hz, 1H), 2.01 (m, 2H), 1.97 (m, 1H), 1.78 (m, 1H), 1.75 (m, 1H), 1.72 (s, 3H), 1.69 (s, 3H), 1.67 (m, 1H), 1.64 (m, 1H), 1.56 (m, 1H), 1.47 (m, 1H), 1.44 (m, 2H), 1.37 (m, 1H); $^{13}C$ NMR (75 MHz): $\delta$ = 145.8, 145.2, 110.4, 109.9, 96.4, 64.6, 55.1, 49.1, 44.6, 39.9, 38.4, 32.6, 27.7, 23.9, 22.5, 22.3, 19.3; MS (EI): *m/z* (%): 177 (2), 151 (4), 121 (16), 109 (10), 107 (11), 95 (12), 93 (16), 81 (18), 79 (11), 68 (13), 67 (17), 55 (10), 45 (100); exact mass: calcd for $C_{17}H_{30}O_2$: 266.2246; found: 266.2251.

**Hydrolysis of 24 with AG 50Wx4 resin**: To AG 50Wx4 resin (180 mg), previously washed with MeOH, was added compound **24** (30 mg, 0.15 mmol) in MeOH (2 mL). The suspension was protected from light and stirred for five days at room temperature, and the resin was filtered and washed thoroughly with MeOH and $CHCl_3$. The solvent was removed under vacuum, and the oily residue purified by column chromatography on silica flash to afford cyclic ether **26** (4 mg, 17%) along with a mixture of grandisol (**1**) and its isomer **25** (10 mg, 33%) in a 37:63 ratio, respectively.

**Compound 26:** IR (film): $\tilde{\nu}$ = 2970, 2950, 2529, 2862, 1463, 1215, 1072, 918, 734 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 3.60 (m, 2H), 2.0–1.2 (c, 7H), 1.16 (s, 3H), 1.13 (s, 3H), 1.01 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 70.8, 57.8, 47.8, 35.5, 34.1, 32.8, 28.1, 26.4, 24.9, 18.3; MS (EI): *m/z* (%): 154 ([$M^+$], 1), 139 (87), 111 (52), 81 (93), 80 (14), 79 (16), 71 (28), 69 (100), 68 (39), 67 (42), 55 (27), 53 (16), 43 (39), 41 (44).

**Compound 1**: IR (film): $\tilde{\nu}$ = 3330, 3080, 2948, 2867, 1647, 1456, 1375, 1053, 885 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 4.83 (q, $J$ = 1.2 Hz, 1H), 4.64 (br, 1H), 3.66 (m, 2H), 2.54 (t, $J$ = 9.3 Hz, 1H), 2.05–1.30 (c, 7H), 1.67 (s, 3H), 1.17 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 145.2, 109.7, 60.0, 52.5, 41.3, 36.9, 29.3, 28.4, 23.2, 19.1; MS (EI): *m/z* (%): 154 ($M^+$, 0.6), 121 (6), 111 (8), 109 (24), 69 (17), 68 (100), 67 (73), 56 (17), 55 (13), 53 (18), 43 (8), 41 (23).

**Compound 25**: $^1H$ NMR (300 MHz): $\delta$ = 3.67 (m, 2H), 2.1–1.3 (c, 7H), 1.59 (s, 3H), 1.47 (s, 3H), 1.22 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 138.9, 123.4, 60.7, 44.8, 42.2, 28.9, 26.4, 24.0, 19.4, 18.8; MS (EI): *m/z* (%): 154 ([$M^+$], 12), 139 (25), 125 (14), 121 (41), 111 (38), 109 (31), 107 (20), 95 (23), 93 (35), 91 (23), 83 (31), 81 (48), 79 (35), 77 (24), 69 (42), 68 (27), 67 (100), 56 (22), 55 (65), 53 (34), 43 (43), 41 (56).

**Hydrolysis of 23b with Dowex 50Wx4 resin**: To Dowex 50Wx4 resin (99 mg), previously washed with MeOH, was added compound **23b** (8.2 mg, 0.031 mmol) dissolved in MeOH (2 mL). The suspension was protected from light and stirred for five days at room temperature, and the resin was filtered and washed thoroughly with MeOH and $CHCl_3$. The solvent was removed and the residue purified by column chromatography to give compounds **27** (approx. 20% yield) and **28** (approx. 30% yield).

**Compound 27**: For spectroscopic data see below.

**Compound 28**: $^1H$ NMR (300 MHz): $\delta$ = 4.72 (br, 1H), 4.68 (br, 1H), 3.58 (m, 2H), 2.1–1.3 (c, 13H), 1.71 (s, 3H), 1.14 (s, 3H), 1.01 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 146.0, 109.8, 70.8, 57.8, 47.0, 39.6, 39.0, 38.2, 31.5, 29.7, 26.3, 25.2, 22.4, 22.1, 18.3; MS (EI): *m/z* (%): 207 ([$M^+ - CH_3$], 20), 179 (34), 149 (24), 136 (13), 135 (21), 123 (75), 121 (23), 109 (21), 108 (17), 107 (25), 95 (33), 93 (45), 81 (43), 79 (35), 69 (100), 67 (51), 55 (48), 53 (29), 43 (73), 41 (95); exact mass: calcd for $C_{15}H_{26}O$: 222.198366; found: 222.197476.

**Hydrolysis of 22b with Dowex 50 W4 resin**: In a 10-mL flask was placed Dowex 50Wx4 resin (22.1 mg), which was thoroughly washed with MeOH. Then, **22b** (30.6 mg, 0.11 mmol) in MeOH (0.7 mL) was added. The mixture was light-protected and stirred for 48 h at room temperature. The resin was filtered and thoroughly washed with MeOH and $CHCl_3$. The solvent was removed to leave cyclic acetal **29** (29 mg). IR (film): $\tilde{\nu}$ = 2983, 2943, 1716, 1373, 1218, 1168, 1080, 1043, 842 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 3.51 (c, 2H), 3.14 (s, 3H), 2.40 (t, $J$ = 6.3 Hz, 2H), 2.12 (s, 2H), 1.96–1.20 (c, 11H), 1.08 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 209.16, 98.53, 56.91, 47.62, 45.91, 44.06, 39.48, 38.38, 30.38, 29.91, 29.69, 19.20, 18.94, 18.31; MS (EI): *m/z* (%): 225 (16), 151 (20), 127 (25), 123 (36), 108 (32), 95 (35), 93 (51), 85 (36), 81 (40), 80 (28), 79 (61), 71 (21), 67 (26), 55 (32), 43 (100).

**Hemiacetal 30**: A mixture of the acetal **29**, hexane (6 mL), and silica flash (1.2 mg) (activated at 400 °C for 48 h and deactivated with 4.8% of water) was stirred at room temperature for 4 h. The mixture was filtered, and the silica washed successively with AcOEt and hexane. The solvent was removed under vacuum and the residue, which was characterized as hemiacetal **30** (28.7 mg), immediately subjected to the next step without purification. IR (film): $\tilde{\nu}$ = 3419, 2939, 2887, 1714, 1371, 1359, 1166, 1076, 1064, 906 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 3.82 (td, $J$ = 12.0 Hz, $J'$ = 2.4 Hz, 1H), 3.56 (ddd, $J$ = 11.5 Hz, $J'$ = 4.8 Hz, $J''$ = 2.7 Hz, 1H), 2.42 (t, $J$ = 6.6 Hz, 2H), 2.13 (s, 3H), 2.01 (t, $J$ = 9.6 Hz, 1H), 1.90–1.30 (c, 11H), 1.22 (s, 3H); $^{13}C$ NMR (75 MHz): $\delta$ = 209.07, 96.03, 57.20, 44.95, 43.98, 39.38, 30.77, 29.95, 29.62, 26.49, 18.90, 18.32; MS (EI): *m/z* (%): 208 (12), 123 (42), 122 (64), 95 (57), 91 (30), 81 (48), 79 (53), 55 (24), 53 (23), 43 (100).

***r*-1-(2-Hydroxyethyl)-*c*-2-isopropenyl-1-(4-methylpent-4-enyl)cyclobutane (27)**: A mixture of methyl triphenylphosphonium bromide (2.8 g, 7.8 mmol) and anhydrous THF (4 mL) was cooled to −78 °C under argon. Then, BuLi (4.6 mL of a 1.36 M solution in THF, 6.24 mmol) was added and the mixture stirred for 10 min at −78 °C and at room temperature for 1 h. The mixture was cooled again at −78 °C and then a solution of hemiacetal **30** (28.7 mg, 0.13 mmol) in anhydrous THF (1 mL) was added. The mixture was stirred for 10 min at −78 °C and 24 h at room temperature, quenched with $NH_4Cl$ (saturated solution), and extracted with hexane and diethyl ether. The organic phases were combined and washed with $NH_4Cl$ (saturated solution), brine and dried ($MgSO_4$). The solvent was removed and the crude product purified by column chromatography on silica flash to furnish the expected alcohol **27** (11.2 mg, 45% overall yield from **22b**). IR (film): $\tilde{\nu}$ = 3344, 3078, 2968, 2935, 2894, 1647, 1454, 1373, 1051, 885 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 4.87 (s, 1H), 4.72 (s, 2H), 4.68 (s, 1H), 3.60 (m, 2H), 2.63 (t, $J$ = 9.0 Hz, 1H), 1.99 (m, 2H), 1.96 (m, 1H), 1.79 (m, 1H), 1.72 (s, 3H), 1.70 (m, 1H), 1.69 (s, 3H), 1.66 (m, 1H), 1.60 (m, 1H), 1.55 (m, 1H), 1.43 (m, 2H), 1.34 (m, 1H); $^{13}C$ NMR (75 MHz): $\delta$ = 145.79, 145.38, 110.36, 109.93, 59.53, 49.18, 44.70, 39.97, 38.36, 36.05, 27.84, 23.88, 22.49, 22.36, 19.34; MS (EI): *m/z* (%): 177 (5), 139 (36), 121 (38), 109 (24), 108 (61), 107 (35), 95 (36), 93 (46), 91 (81), 81 (66), 80 (43), 79 (38), 69 (100), 68 (97), 67 (64), 55 (30), 53 (88), 43 (36), 41 (66); anal. calcd (%) for $C_{15}H_{26}O$: C 81.02, H 11.78; found: C 80.92, H 12.01.

***r*-1-(2-Acetoxyethyl)-*c*-2-isopropenyl-1-(4-methylpent-4-enyl)cyclobutane (5)**: A mixture of the alcohol **27** (11.2 mg, 0.050 mmol) dissolved in anhydrous $CH_2Cl_2$ (1 mL), anhydrous $Et_3N$ (18 μL, 0.13 mmol), and small crystals of 4-(dimethylamino)pyridine (DMAP) was brought to 0 °C. Then acetic anhydride (20.8 μL, 0.22 mmol) was added and the mixture stirred for 1 h. After quenching with water, the organic material was extracted with $CH_2Cl_2$, washed with $NaHCO_3$ (saturated solution) and dried ($MgSO_4$). Evaporation of the solvent afforded a residue which, upon purification on column chromatography on silica flash, yielded pheromone **5** (13 mg, 98%). IR (film): $\tilde{\nu}$ = 3080, 2964, 2933, 2858, 1741, 1647, 1454, 1368, 1238, 887 $cm^{-1}$; $^1H$ NMR (300 MHz): $\delta$ = 4.88 (s, 1H), 4.72 (s, 2H), 4.69 (s, 1H), 4.02 (t, $J$ = 8.1 Hz, 2H), 2.65 (t, $J$ = 9.0 Hz, 1H), 2.02 (s, 3H), 2.00 (m, 2H), 1.90 (m, 1H), 1.82 (m, 1H), 1.75 (m, 1H), 1.72 (s, 3H), 1.68 (s, 3H), 1.67 (m, 1H), 1.65 (m, 1H), 1.57 (m, 1H), 1.49 (m, 1H), 1.44 (m, 2H), 1.37 (m, 1H); $^{13}C$ NMR (75 MHz): $\delta$ = 171.17, 145.74, 145.03, 110.61, 110.00, 61.68, 48.99, 44.55, 39.73, 38.36, 31.39, 27.59, 23.87, 22.48, 22.36, 21.08, 18.29; MS (EI): *m/z* (%): 189 (5), 121 (79), 119 (25), 108 (33), 107 (49), 105 (25), 94 (30), 93 (70), 91 (24), 81 (54), 80 (47), 79 (66), 69 (28), 68 (100), 67 (54), 43 (69), 41 (32); anal. calcd (%) for $C_{17}H_{28}O_2$: C 77.22, H 10.67; found: C 77.30, H 10.96.

***r*-1-(2-Hydroxyethyl)-*c*-2-(1-hydroxyethyl)-1-(4-oxopentyl)cyclobutane (31)**: To a 10-mL flask containing **19b** (65 mg, 0.15 mmol) was added HCl (0.5 mL of a 1.2 N solution in methanol). The mixture was stirred at room temperature overnight and then diluted with $CH_2Cl_2$ and water. The aqueous layer was separated and extracted with $CH_2Cl_2$. The organic phase was washed with $NaHCO_3$ (saturated solution) and brine. After drying ($MgSO_4$), evaporation of the solvent gave an oil which was purified by column chromatography on silica gel to yield pure dihydroxy ketone **31**

(31 mg, 90%). IR (film): $\tilde{\nu}$ = 3383, 2962, 2902, 1708, 1367, 1053, 732 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta$ = 3.81 (m, 1H), 3.75 (m, 1H), 3.65 (m, 1H), 3.25 (br s, 1H), 2.41 (t, $J$ = 6.9 Hz, 2H), 2.12 (s, 3H), 2.08 (m, 1H), 1.89 (m, 1H), 1.82 (m, 1H), 1.63 (m, 1H), 1.61 (m, 1H), 1.54 (m, 1H), 1.52 (m, 1H), 1.48 (m, 1H), 1.47 (m, 1H), 1.46 (m, 1H), 1.34 (m, 1H), 1.02 (d, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (75 MHz): $\delta$ = 209.6, 68.0, 59.2, 52.0, 44.0, 42.3, 39.6, 34.8, 30.0, 29.6, 20.7, 19.5, 18.2; MS (EI): *m/z* (%): 171 (1), 134 (19), 126 (19), 125 (11), 124 (15), 123 (17), 121 (10), 111 (15), 109 (28), 108 (74), 107 (18), 97 (23), 95 (38), 93 (25), 79 (27), 71 (26), 69 (21), 67 (19), 55 (35), 43 (100), 41 (29).

**Acetylation of diol 31: *r*-1-(2-acetoxyethyl)-*cis*-2-(1-hydroxyethyl)-1-(4-oxopentyl)-cyclobutane (32)**: A mixture of neutral $Al_2O_3$ W-200-N (1.1 g, Woelm, activity super-I) and diol **31** (25.2 mg, 0.11 mmol), dissolved in anhydrous ethyl acetate (3.3 mL) was stirred at room temperature for 12 days. The mixture was filtered over Celite, washed with ethyl acetate and the solvent removed under vacuum. The crude product was purified by flash column chromatography on silica gel to obtain starting diol (6.3 mg, 25%) and monoacetate **32** (18 mg, 60%). IR (film): $\tilde{\nu}$ = 3240, 2964, 2935, 2902, 1737, 1714, 1367, 1245 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta$ = 4.19 (m, 1H), 4.05 (m, 1H), 3.78 (dq, $J$ = 13.0 Hz, $J'$ = 6.0 Hz, 1H), 2.41 (t, $J$ = 6.9 Hz, 2H), 2.13 (s, 3H), 2.04 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.85 (m, 1H), 1.80 (m, 1H), 1.68 (m, 1H), 1.55 (m, 2H), 1.45 (m, 1H), 1.44 (m, 1H), 1.32 (m, 2H), 1.05 (d, $J$ = 6.0 Hz, 3H); $^{13}$C NMR (75 MHz): $\delta$ = 209.1, 171.2, 68.3, 61.6, 51.2, 44.0, 42.2, 39.8, 30.6, 30.0, 29.6, 21.4, 21.1, 19.3, 18.2; MS (EI): *m/z* (%): 211 ([$M^+$ – OCOCH$_3$], 1), 138 (11), 134 (19), 123 (15), 109 (20), 107 (18), 106 (19), 95 (58), 93 (17), 81 (23), 80 (22), 79 (27), 43 (100).

***r*-1-(2-Acetoxyethyl)-*c*-2-acetyl-1-(4-oxopentyl)cyclobutane (33)**: To a cold solution (0 °C) of hydroxy acetate **32** (14 mg, 0.052 mmol) in anhydrous DMF (1.5 mL) was added pyridinium dichromate (0.196 g, 0.52 mmol). The mixture was stirred at room temperature overnight. Then, water was added and the organic material extracted with hexane/diethyl ether (1:1). The organic phase was washed with brine, dried ($MgSO_4$), and the solvent removed under vacuum, to leave a residue which was chromatographed on silica flash. The diketone **33** was thus obtained in pure form (12 mg, 86% yield). IR (film): $\tilde{\nu}$ = 2948, 2869, 1737, 1714, 1699, 1365, 1242 cm$^{-1}$; $^1$H NMR (300 MHz): $\delta$ = 3.97 (m, 2H), 3.09 (t, $J$ = 8.0 Hz, 1H), 2.47 (t, $J$ = 6.9 Hz, 2H), 2.31 (m, 1H), 2.14 (s, 3H), 2.09 (s, 3H), 2.00 (s, 3H), 1.85 (m, 1H), 1.78 (m, 1H), 1.76 (m, 2H), 1.66 (m, 1H), 1.62 (m, 2H), 1.50 (m, 2H); $^{13}$C NMR (75 MHz): $\delta$ = 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* (%): 208 ([$M^+$ – AcOH], 1), 123 (25), 107 (12), 95 (31), 92 (11), 81 (13), 80 (13), 79 (19), 71 (24), 43 (100).

**Wittig reaction of diketone 33**: ***r*-1-(2-acetoxyethyl)-*c*-2-isopropenyl-1-(4-methylpent-4-enyl)cyclobutane (5)**: A solution of previously dried methyl triphenylphosphonium bromide (0.133 g, 0.37 mmol) in anhydrous THF (1 mL) was cooled to −78 °C. Then *n*BuLi (0.26 mL of a 1.16 M solution in hexane, 0.30 mmol) was added and the mixture stirred for 10 min at −78 °C and 1 h at room temperature. The reaction mixture was cooled again to −78 °C and then diketone **33** (10 mg, 0.037 mmol), dissolved in anhydrous THF (0.3 mL), was added. The reaction mixture was stirred for a further 10 min at −78 °C and for 2 h at room temperature, quenched with $NH_4Cl$ (saturated solution) and brine, and dried ($MgSO_4$). Removal of the solvent led to a residue, which was purified by column chromatography on silica gel to furnish compound **5** (3 mg, 30%) along with the corresponding alcohol **27** (3.5 mg, 42%). This was acetylated (see above) and the obtained acetate **5** combined with the former material (71% total yield).

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