JOC Article

Photochemical Cycloaddition of Mono-, 1,1-, and 1,2-Disubstituted Olefins to a Chiral 2(5*H*)-Furanone. Diastereoselective Synthesis of (+)-Lineatin

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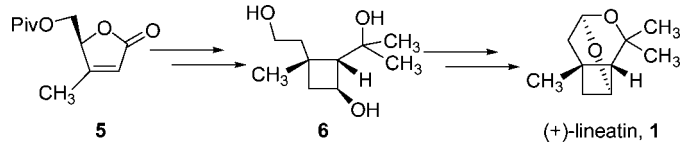

The photochemical [2 + 2] cycloaddition of (*S*)-4-methyl-5-*O*-pivaloyloxymethyl-2(5*H*)-furanone, **5**, to vinyl acetate, vinyl pivalate, *tert*-butyl vinyl ether, 1,1-diethoxyethylene, and (*Z*)- and (*E*)-1,2-dichloroethylene has been studied. A practical synthesis of (+)-lineatin from **5** has been developed via the functionalized cyclobutane **6**.

Introduction

The cyclobutane monoterpene (+)-lineatin, **1** (Scheme 1), isolated in 1977,[1] is the main component of the female-produced pheromone of the ambrosia beetle, *Trypodendron lineatum* Olivier, which is responsible for coniferous forest infestation in Europe and North America. The natural occurrence, biological activity, and unusual structural features of lineatin have attracted considerable synthetic interest that has culminated in various synthesis of (+)-**1**, with total yields between 0.2 and 4%.[2] In most of these syntheses, the enantiomeric purity depends on the optical resolution of a key intermediate.

We have recently accomplished a formal synthesis of (+)-**1** in an overall yield of 14% starting from the suitable chiral 2(5*H*)-furanone **5**.[3] Our synthesis contemplated a late oxidation step of the bicyclic ether intermediate **3** to furnish the keto lactone **2**, which had already been converted into **1**.[2e] Compound **3** was readily accessed from the functionalized cyclobutane **4** via oxycyclization and deoxygenation. Due to the high volatility of **3**, concentration of its solution or its purification always has caused a considerable loss of product. This fact prompted us to consider a modified strategy for the preparation of the crucial six-membered lactone intermediate **2**. The alternative synthesis envisioned that this advanced precursor would be obtained through a more straightforward route involving oxidation of the cyclobutane triol **6**, which in turn would be also prepared from **4** by deoxygenation of the secondary alcohol. In both synthetic pathways, a major challenge was the construction of the functionalized cyclobutane with the correct regio- and stereochemistry. It was envisaged that the pivotal cyclobutane intermediate **4** could be obtained by a [2 + 2] photochemical reaction involving lactone **5** and a suitable substituted alkene.

Herein, we report in detail our investigations on the photochemical [2 + 2] cycloaddition of 2(5*H*)-furanone **5** to several enol esters and enol ethers, to ketene diethyl ketal, and to (*Z*)- and (*E*)-1,2-dichloroethylene. Also, an improved synthesis of (+)-lineatin is reported.

Results and Discussion

Photochemical Study. When this work was initiated, we were not aware of any photochemical addition of vinyl esters or ethers to chiral 2(5*H*)-furanones. Accordingly, our first task was to study the photochemical reaction of **5** to unsymmetrical oxyalkenes **7**, which was visualized as a convenient method to prepare **4**, provided the reaction would proceed with the desired stereo- and regiochemical control.

Considering the head-to-head (HH)/head-to-tail (HT) regioselectivity, the anti/syn facial approaches, and the exo/endo stereoselectivity, this photochemical reaction could lead to the formation of up to eight isomers (Scheme 2). In most examples of the [2 + 2] photocycloaddition of cyclic enones to electron-rich alkenes, the formation of HT adducts is favored, although the regioselectivity of the process results from a balance between

(1) MacConnell, J. G.; Borden, J. H.; Silverstein, R. M.; Stokkink, E. *J. Chem. Ecol.* **1977**, *3*, 549–561.

(2) (a) Mori, K.; Sasaki, M. *Tetrahedron* **1980**, *36*, 2197–2208. (b) Slessor, K. N.; Oehlschlager, A. C.; Johnston, B. D.; Pierce, H. D.; Grewal, S. K.; Wickremesinghe, L. K. G. *J. Org. Chem.* **1980**, *45*, 2290–2297. (c) Mori, K.; Uematsu, T.; Minobe, M.; Yanagi, K. *Tetrahedron* **1983**, *39*, 1735–1743. (d) Kandil, A. A.; Slessor, K. N. *J. Org. Chem.* **1985**, *50*, 5649–5655. (e) Mori, K.; Nagano, E. *Liebigs Ann. Chem.* **1991**, 341–344.

(3) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Parella, T. *Org. Lett.* **2004**, *6*, 1449–1452.

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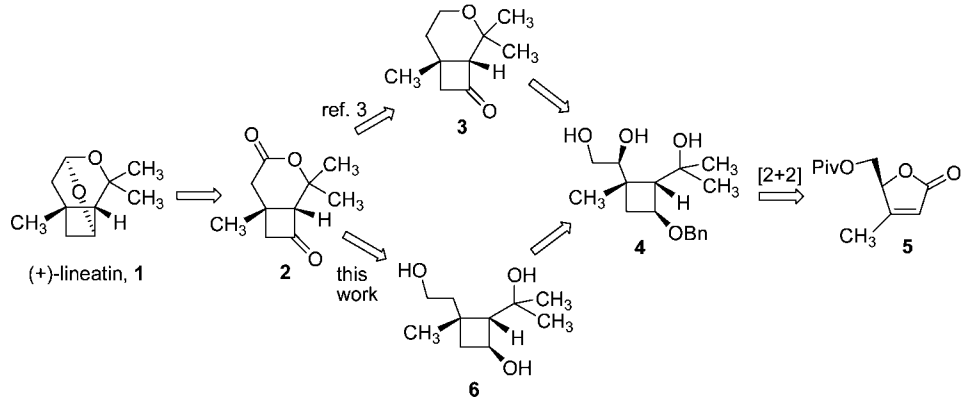
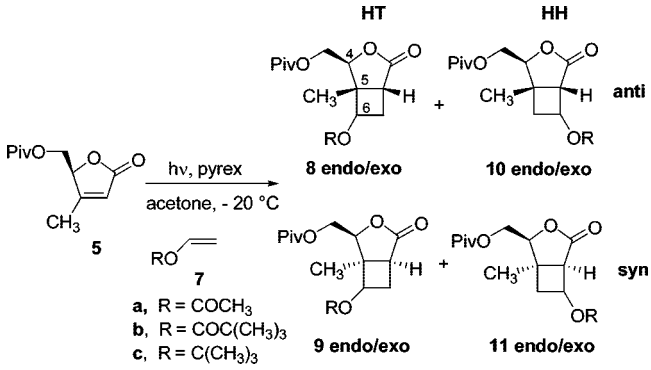
SCHEME 1. Retrosynthetic Analysis of (+)-Lineatin, (+)-1



SCHEME 2. [2 + 2] Photochemical Cycloaddition of 5 to 7a−c



electronic and steric effects. Thus, it has been reported that modifications in either the substrates or the reaction conditions can modulate the regiochemical outcome of the photochemical process.[4] In the present study, we expected that both the pivaloyloxymethyl and β-methyl substituents of the lactone could influence the regio- and stereochemical outcome of the cycloaddition, favoring the formation of the anti-HH isomers **10 endo/exo**.

Irradiation of an acetone solution of lactone **5** and a 10-fold excess of vinyl acetate, **7a**, with a high-pressure mercury lamp through a Pyrex filter for 3 h at −20 °C resulted in the formation of a mixture (28:25:15:14:10:8) of six of the eight possible isomers in 95% global yield, among which, after repeated column chromatography, only the main photoadducts HT-anti, **8a exo** and **8a endo** (Figure 1), could be identified (vide infra). In search for a better selectivity, we decided to employ the more sterically demanding olefins vinyl pivalate, **7b**, and *tert*-butyl vinyl ether, **7c**. Thus, the photoreaction of **5** with pivalate **7b** furnished a mixture (44:13:12:11:11:5:4) of seven cycloadducts in 82% overall yield, from where the major cycloadduct HT-anti, **8b endo**, could be isolated by column chromatography. Finally, irradiation of **5** with the ether **7c**, in which the bulky substituent is closer to the double bond, gave a 29:22:19:12:9:8:1 mixture of seven cycloadducts in 87% yield, from which the three major adducts, the HT-anti **8c endo** and **8c exo** and the HH-anti **10c endo**, were identified. In all the reactions studied, analysis of the mixture by GC−MS indicated that all the compounds within a series possessed identical masses and fragmentation patterns consistent with the expected cycloadducts.

The regio- and stereochemistry of the major photocycloadducts could be assigned with the help of 1D and 2D NMR experiments. The regioselectivity of the addition was established by analysis of the ^{13}C NMR spectra wherein the signal of the carbon atom C-5 in the HT isomers (**8a−c**) appears at lower field ($\delta \sim 47-50$) compared to the HH isomer **10c** ($\delta \sim 36$), due to the deshielding effect of the cyclobutane oxy-substituent. The opposite trend is observed in the chemical shift of C-1 ($\delta \sim 38-40$ in the HT isomers and $\delta \sim 53$ in the HH isomer).[5] The ^{13}C NMR spectra also give information about the facial selectivity. It is known from previous work[6] that the signal of the angular carbon methyl group, because of the larger "steric compression" due to the cis arrangement of the methyl and the pivaloyloxymethyl substituents in the anti isomers, appears high field shifted (∼18 ppm) compared to the syn isomers (∼21 ppm). Thus, the photoadducts **8a−c** and **10c endo** show δ around 18 ppm, while the isomers **8a** and **8c exo**, in which the angular methyl group is even more sterically hindered, exhibit δ around 11 ppm, indicating that all the isolated adducts come

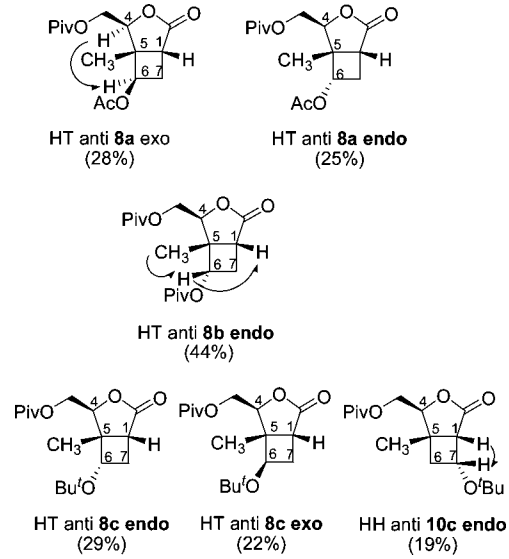


FIGURE 1. Major photocycloadducts from the [2 + 2] photochemical cycloaddition of 2(5*H*)-furanone **5** to olefins **7a−c** and selected NOE difference experiments.

(4) (a) Lange, G. L.; Decicco, C.; Lee, M. *Tetrahedron Lett.* **1987**, *28*, 2833–2836. (b) Lange, G. L.; Organ, M. G.; Lee, M. *Tetrahedron Lett.* **1990**, *31*, 4689–4692. (c) Suishu, T.; Shimo, T.; Somekawa, K. *Tetrahedron* **1997**, *53*, 3545–3556. (d) Bach, T. *Synthesis* **1998**, 683–703.

(5) Rustullet, A.; Alibés, R.; de March, P.; Figueredo, M.; Font, J. *Org. Lett.* **2007**, *9*, 2827–2830.

(6) Alibés, R.; Bourdelande, J. L.; Font, J.; Gregori, A.; Parella, T. *Tetrahedron* **1996**, *52*, 1267–1278.

SCHEME 3. [2 + 2] Photochemical Cycloaddition of 5 to 12

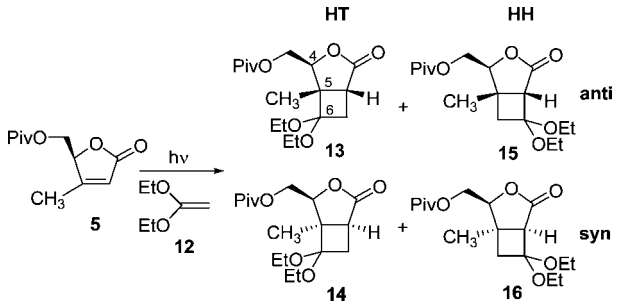


TABLE 1. [2 + 2] Photocycloaddition of 2(5*H*)-Furanone 5 to Ketene Ketal 12

entry	solvent	*t*	yield (%)[a]	**13**:**14**: (**15**+**16**)	HT:HH (%)	anti:syn[b] (%)
1	acetone	8 h	25	64:32:4	96:4	66:34
2	acetonitrile	35 min	85	63:31:6	94:6	67:33
3	ether	1.5 h	80	51:42:7	93:7	55:45
4	hexane	1.7 h	69	47:46:7	93:7	50:50

[a] Isolated yield of the mixture of adducts after column chromatography purification. [b] The anti/syn ratio of the HT isomers.

from antifacial approaches of the reactants. The results of NOE difference experiments provided additional support to the stereochemical assignment (Figure 1).

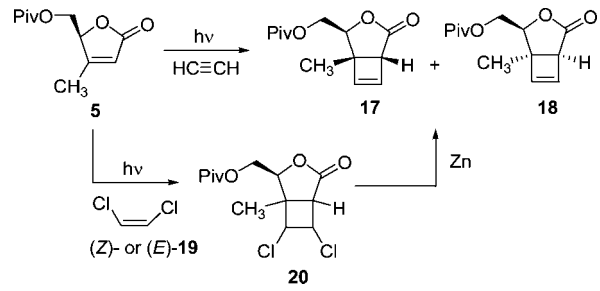
The complexity of the mixtures obtained from the photoreaction of vinyl esters and ether to furanone **5** and the HT regioselectivity of the addition, which is contrary to our synthetic interests, led us to consider the alternative cycloaddition of 1,1-diethoxyethylene, **12**, to lactone **5**, wherein the number of possible cycloadducts is limited to four (Scheme 3).[7]

First, irradiation of **5** and a 5-fold excess of **12** was carried out in acetone through a Pyrex filter at −20 °C, and after 8 h, a mixture of the four possible cycloadducts **13**−**16** was isolated in only 25% yield (Table 1, entry 1). When the photoreaction was performed in acetonitrile through a quartz filter, the overall yield increased to 85% (entry 2). Unfortunately, chromatographic separation of the major adducts was not possible, and NMR analysis of the mixture had to be performed. The HT regiochemistry of the major adducts **13** and **14** was established by HMBC experiments, wherein a correlation between the acetal carbon atom C-6 and proton H-4 is observed in both isomers, while the anti/syn relative configuration was determined through the chemical shift of the angular methyl group in the ^{13}C NMR spectra, as indicated previously.

Next, the reaction was also performed in ether and hexane to study the influence of the solvent polarity (entries 3 and 4). It was found that the regioselectivity remained essentially unaltered, while the facial selectivity decreased from 67:33 in acetonitrile to 55:45 and 50:50 in ether and hexane, respectively.

As in the case of the vinyl esters and ethers, the photocycloaddition of the ketene ketal afforded preferentially the undesired HT isomers. These results indicate that the electronic effects prevail over the steric effects in determining the regioselectivity of the process. The observed regioselectivity is consistent with a mechanism in which formation of the initial bond occurs selectively between C-3 of the 2(5*H*)-furanone triplet and the less substituted end of the alkene, delivering a triplet 1,4-biradical intermediate that closes to furnish a HT photoadduct.[8]

SCHEME 4. [2 + 2] Photochemical Cycloaddition of 5 to 1,2-Dichloroethylene and Subsequent Zn-Promoted Dechlorination



In view of the former results, we considered the possibility of introducing the functionality present in the cyclobutane ring of the target compound **4** from a double bond in a regioselective fashion. Initially, we considered the straightforward preparation of the *anti* cyclobutene **17** (Scheme 4) by photochemical cycloaddition of **5** to acetylene,[9] but this reaction occurred in low yield (35%) and scarce anti facial selectivity (6%). Therefore, a more convenient, two-step protocol based on the photochemical [2 + 2] reaction of lactone **5** with either (*E*)- or (*Z*)-1,2-dichloroethylene, (*E*)- or (*Z*)-**19**, followed by Zn-promoted dechlorination was applied.[10]

Accordingly, an acetone solution of lactone **5** and a 5-fold excess of (*E*)-**19** was irradiated through a Pyrex filter with a high-pressure mercury lamp for 10 h at −20 °C, affording a mixture of seven isomeric dichlorocycloadducts (as evidenced by GC−MS and NMR analysis of the crude product) in 32% combined yield (Table 2, entry 1). Similar results were found by using (*Z*)-**19** (entry 2). However, when the photochemical reaction of **5** with (*E*)-**19** was performed in acetonitrile, after 10 h of irradiation through a quartz filter, a mixture of seven isomers was obtained in 76% yield (entry 3). A faster, cleaner, and better yielding reaction (89%) was achieved with (*Z*)-**19** in acetonitrile (entry 4).

To get a deeper insight into the factors controlling the stereochemistry of these photoadditions, the major dichlorocycloadducts were isolated by repeated column chromatography. Stereochemical assignments of the individual isomers were assessed by detailed analysis of their ^{1}H and ^{13}C NMR spectra and by NOE difference experiments (Figure 2).

It was concluded that the photocycloaddition proceeds in a highly diastereoselective manner affording mainly anti cycloadducts. Interestingly, in the reactions sensitized by acetone, identical ratio of cycloadducts was obtained from either (*Z*)- or (*E*)-**19**. By contrast, when the reactions were performed under direct excitation (entries 3 and 4), the ratio of adducts was different. Considering exclusively the anti cycloadducts **21**−**24**, it can be observed that starting from (*E*)-**19**, the trans relative configuration of the chlorine atoms is slightly favored over the cis (57:43), and from (*Z*)-**19**, the predominance of the trans

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(9) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Fu, X.; Racamonde, M.; Alvárez-Larena, A.; Piniella, J. F.; Parella, T. *J. Org. Chem.* **2003**, *68*, 1283–1289.

(10) Alibés, R.; de March, P.; Figueredo, M.; Font, J.; Racamonde, M.; Rustullet, A.; Alvárez-Larena, A.; Piniella, J. F.; Parella, T. *Tetrahedron Lett.* **2003**, *44*, 69–71.

TABLE 2. [2 + 2] Photochemical Cycloaddition of 5 to (*E*)- and (*Z*)-19

entry	olefin	filter	solvent	*t*	yield (%)[a]	**21**:**22**:**23**:**24**:**25**:**others** (%)[b,c]	anti:syn (%)	anti cis:trans (%)
1	(*E*)-**19**	Pyrex	acetone	10 h	32	33:26:10:18:8:4:1	87:13	32:68
2	(Z)-**19**	Pyrex	acetone	8 h	45	35:25:10:16:7:5:2	86:14	30:70
3	(*E*)-**19**	quartz	acetonitrile	12 h	76	25:23:7:29:11:4:1	84:16	43:57
4	(Z)-**19**	quartz	acetonitrile	7 h	89	35:28:14:11:6:5:1	88:12	29:71

[a] Isolated yield. [b] Isomer ratio from GC analysis of the crude product. [c] *Others* are syn cycloadducts whose configuration could not be assigned.

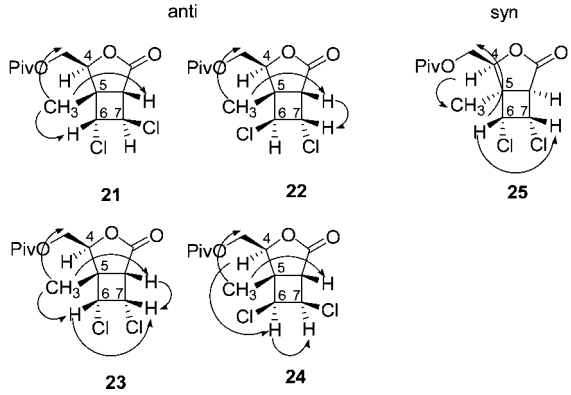
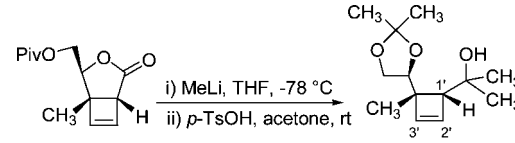


FIGURE 2. Dichlorocycloadducts **21**−**25** and selected NOE difference experiments.

relationship is even higher (71:29), indicating that the stereochemistry of the alkene component is lost in the reaction course.[11,12]

Next, we studied the reductive elimination of the dichlorocycloadducts under different reaction conditions. Attempted dechlorination with activated Zn in refluxing glacial acetic acid, acetonitrile,[13] or dry ethanol[14] met with failure, returning unaltered starting material. Treatment of the mixture of dichlorocycloadducts **20** with acetic anhydride and activated zinc in toluene at 85 °C under mechanical stirring, following Huet conditions,[15] afforded, after 72 h of reaction, the diastereomeric cyclobutenes **17** and **18** in a ratio 81:19 and 59% yield, along with the dichlorocycloadduct **22** (23%). Similarly, when the mixture of adducts **20** was treated with activated Zn in refluxing 80% EtOH for 7 h, it afforded **17** and **18** in 69% yield and recovered **22** (25%). Attempts to drive the process to completion by increasing the reaction temperature or carrying out the reaction under pressure in a sealed vessel caused loss of yield, presumably due to decomposition of the cyclobutene products. It was finally found that treatment of the mixture **20** with activated Zn in 80% EtOH in a sealed vessel at 105 °C under microwave irradiation (CEM Discover microwave reactor, IR temperature monitoring) for 20 min delivered a mixture of **17** and **18** in 88:12 ratio and 79% yield.[16] For synthetic purposes, cyclobutene **17** was conveniently prepared by photochemical reaction of **5** with (*Z*)-**19** in acetonitrile, followed by Zn dechlorination under microwave irradiation in 64% overall yield.

SCHEME 5



Synthesis of (+)-Lineatin. With the anti cycloadduct **17** on hand, the synthesis of the pheromone was continued by treating it with an excess of methyl lithium in THF at −78 °C, followed by reaction with acetone containing a catalytic amount of *p*-toluenesulfonic acid at room temperature to deliver the acetonide **26** in 80% overall yield (Scheme 5).

We initially planned to use the cyclobutene π bond to set up the O-functionality at C-2′ by a hydroboration process, in which the hydroxyl or dioxolane oxygen atoms could direct the approach of the hydroborating agent to the endo hindered face of the olefin.[17] In practice, treatment of **26** with BH_3-THF provided, after oxidation with H_2O_2, a chromatographically separable 20:15:27:38 mixture of the four possible isomeric alcohols **27**−**30** in 89% yield (Figure 2). The regio- and stereochemistries of these cyclobutanols were assigned by 1D and 2D NMR spectroscopy. The connectivity was established by HMBC experiments, wherein one of the methylene protons H-4 correlates with the carbon atom C-4′ for isomers **27** and **29** and with C-1″ for isomers **28** and **30**. The configuration at the stereogenic center C-1 was inferred by the NOESY correlations shown in Figure 3. These assignments reflect the lack of regioselectivity of the process and a moderate preference of the borane to attack from the less hindered side of the double bond (65:35), which is opposite to the potentially directing oxygen atoms of the substrate. Moreover, the double bond of **26** resisted hydroboration by other more sterically demanding reagents, such as disiamylborane and 9-borabicyclo[3.3.1]nonane (9-BBN).

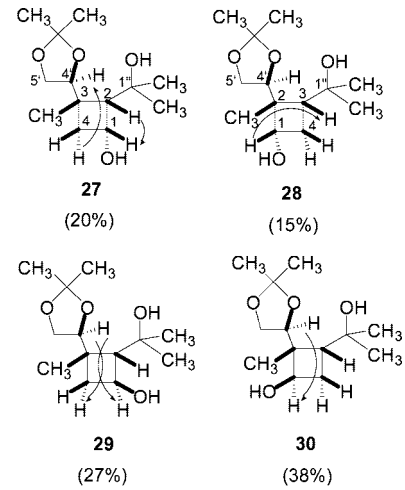


FIGURE 3. Products **27**−**30** of the hydroboration−oxidation step and relevant NOESY correlations.

(11) Loutfy, R. O.; de Mayo, P. *Can. J. Chem.* **1972**, *50*, 3465–3471.
(12) Nelly, J. F. D.; Nelly, J. M.; McMurry, B. H. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1933–1941.
(13) Shimo, T.; Somekawa, K.; Kuwakino, J.; Yemura, H.; Kumamoto, S.; Tsuge, O.; Kanemasa, S. *Chem. Lett.* **1984**, 1503–1504.
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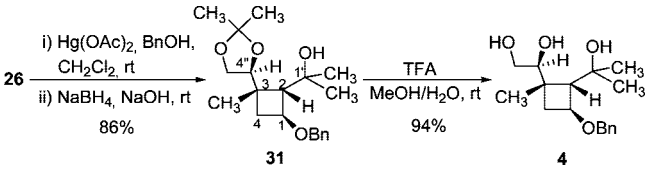
(15) (a) Gauvry, N.; Comoy, C.; Lescop, C.; Huet, F. *Synthesis* **1999**, 574–575. (b) Gauvry, N.; Lescop, C.; Huet, F. *Eur. J. Org. Chem.* **2006**, 5207–5218.
(16) *Microwave in Organic Synthesis*; Loupy, A., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2002; Chapters 2 and 4.
(17) For examples of directed hydroborations, see: (a) Evans, D. A.; Fu, G. C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1992**, *114*, 6671–6679. (b) Garrett, C. E.; Fu, G. C. *J. Org. Chem.* **1998**, *63*, 1370–1371, and references therein.

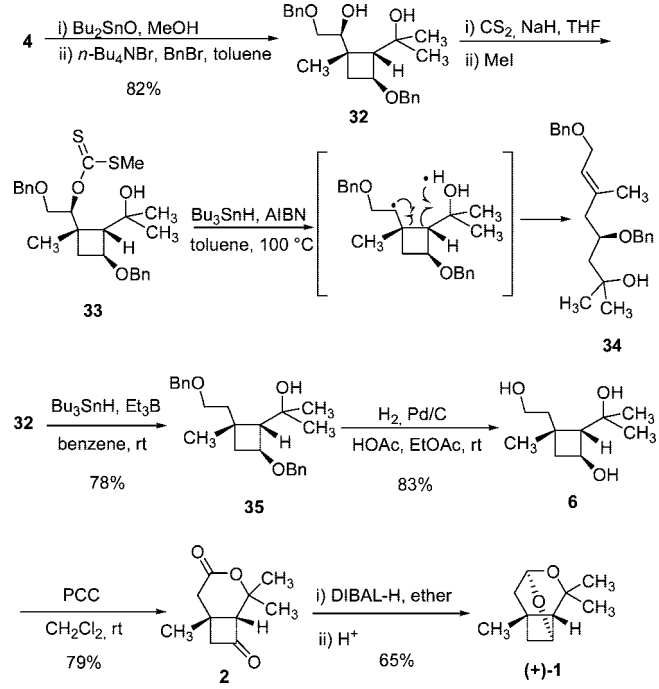
SCHEME 6



In contrast to hydroboration, the oxymercuration−demercuration of **26** proved to be highly regio- and stereoselective, leading exclusively to the alcohol **29** in 92% yield. Since protection of the secondary hydroxyl group was necessary for pursuing our modified synthetic approach, we decided to investigate a benzyloxymercuration−demercuration[18] that would give rise directly to the protected compound. Gratifyingly, treatment of **26** with mercuric acetate and benzyl alcohol in CH_2Cl_2 in the presence of perchloric acid for 24 h, followed by demercuration with alkaline sodium borohydride, afforded the benzyl derivative **31** as a single isomer in 86% yield (Scheme 6). It seems reasonable to assume that the formation of **31** is a consequence of selective coordination of $Hg(OAc)_2$ to the basic groups of the substrate guiding its addition to the endo face of the olefin,[19] followed by anti, regioselective addition of the benzyl alcohol at the less hindered carbon atom C-2′. Although the configuration at C-1 in **31** is opposite to that in the target pheromone, we knew from our previous work that the C-1 configuration could be changed at a late stage of the route.[3] Removal of the acetonide protecting group of **31** under standard conditions (TFA in $MeOH/H_2O$) led to the pivotal intermediate **4**.

Selective benzyl protection of the triol to the dibenzylate **32** was achieved using organotin chemistry in 82% overall yield (Scheme 7). At this juncture, removing the secondary alcohol of **32** by the Barton−McCombie procedure was targeted for attention.[20] Initial attempts to prepare the thiocarbonylimidazolyl derivative by reaction of **32** with TCDI met with failure, recovering only unreacted starting material. On the contrary, sequential treatment of diol **32** with carbon disulfide and methyl iodide in the presence of NaH resulted indeed in the clean formation of the xanthate **33** in 92% yield, which when exposed to the action of tri-*n*-butyltin hydride/AIBN in toluene at 100 °C afforded exclusively the ring-opened products **34**, presumably via β-radical elimination with release of ring strain to produce a secondary radical which collapses with the hydride.[21] Similar radical ring-opening reactions on cyclobutylcarbinyl radicals have already been reported,[22] and it has been suggested that the amount of ring-opening products increases at higher temperature.[23] As a consequence, the required reduction was performed following Oshima's procedure,[24] by treating the dithiocarbonate **33** with *n*-Bu_3SnH and triethylborane in benzene

SCHEME 7



at room temperature. Under these conditions, the desired deoxygenated derivative **35** was obtained in 78% yield from diol **32**, along with smaller amounts of open chain byproducts.

With **35** on hand, the final steps to the target compound were conducted via well-established reactions. Hydrogenolysis (Pd/C) of the benzyl ethers led in 83% yield to the triol **6**, which was oxidized with pyridinium chlorochromate[25] in CH_2Cl_2 to deliver directly the key intermediate **2** (79% yield), whose enantiomeric purity was checked by chiral GC (Lipodex B). It was previously described that reduction of the bicyclic keto lactone (+)-**2** with DIBAL-H, followed by acid-catalyzed acetalization, furnished lineatin in 70−74% yield.[2e] We were able to reproduce this transformation in 65% yield.[26] The spectral data and optical rotation of (+)-**1** are in accordance with those reported in the literature.[2e]

Conclusions

In summary, we have investigated thoroughly the photochemical [2 + 2] cycloaddition of 2(5*H*)-furanone **5** to several enol esters and ethers, **7a**−**c**, ketene diethyl ketal, **12**, and (*Z*)- and (*E*)-1,2-dichloroethylene, (*Z*)- and (*E*)-**19**. In the reaction with the unsymmetrical alkenes, the HT regioisomers predominate, indicating that the electronic effects are more important than the steric effects in determining the regioselectivity of these reactions. The photochemical cycloaddition to (*Z*)- and (*E*)-**19** proceeded with high facial diastereoselectivity. Zn-Promoted dechlorination under microwave irradiation gave the anti adduct **17** in good yield, which has been used as a precursor to synthesize (+)-lineatin. This linear, 11-step synthesis has an

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overall yield of 11% from lactone **5** and improves our previously reported approach regarding simplicity with a comparable yield.

Experimental Section

General Methods: See the Supporting Information for details.

General Procedure for the Photochemical Reactions. Irradiations were performed in a small conventional photochemical reactor (two-necked vessel fitted with a Pyrex or quartz immersion-type cooling jacket) using a high-pressure 125 W mercury lamp (Cathodeon HPK-125). Methanol at −15 °C was used for refrigeration of the immersion well jacket. The vessel was externally cooled at −20 °C with a dry ice−CCl_4 bath. The reaction mixture was initially degassed by passage of oxygen-free argon through the solution for 10 min and then irradiated under an atmosphere of argon. The progress of the reaction was monitored by GC or ^{1}H NMR analysis of aliquot samples.

(1*R*,4*S*,5*R*,6*R*)-6-Acetoxy-6-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (8a exo) and (1*R*,4*S*,5*R*,6*S*)-6-Acetoxy-6-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (8a endo). A solution of 2(5*H*)-furanone **5** (150 mg, 0.71 mmol) and vinyl acetate, **7a** (0.61 mL, 7.1 mmol), in acetone (70 mL) was irradiated through a Pyrex filter for 3 h. Evaporation of the solvent and chromatography (hexane−EtOAc 5:1) afforded a 28:25:10:15:14:8 mixture of six cycloadducts (200 mg, 0.68 mmol, 95% yield). Repeated column chromatography (from hexane to hexane−EtOAc 9:1) allowed us to isolate the major component **8a exo** (28%) as a white solid and enriched fractions of **8a endo** (25%).

8a exo: Mp 72−73 °C (from EtOAc−pentane); $[\alpha]_D$ −32.2 (*c* 0.81, $CHCl_3$); IR (KBr) 2982, 1781, 1739, 1466, 1175 cm^{-1}; MS (CI, NH_3) 316 ($[M + NH_4]^+$, 100), 299 ($[M + H]^+$, 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 (t, J = 8.2 Hz, 1H), 4.85 (dd, J = 2.8, 1.9 Hz, 1H), 4.34 (dd, J = 12.6, 2.8 Hz, 1H), 4.01 (dd, J = 12.6, 1.9 Hz, 1H), 2.71 (dd, J = 8.8, 2.9 Hz, 1H), 2.58 (ddd, J =12.3, 8.8, 8.2 Hz, 1H), 2.55 (ddd, J = 12.3, 8.2, 2.9 Hz, 1H), 2.08 (s, 3H), 1.18 (s, 12H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.1, 177.6, 170.7, 82.4, 72.2, 62.9, 50.2, 38.6, 38.6, 29.6, 27.1, 20.4, 10.7. Anal. Calcd for $C_{15}H_{22}O_6$: C, 60.39; H, 7.43. Found: C, 60.23; H, 7.48.

8a endo: ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.81 (ddd, J = 8.1, 4.7, 1.7 Hz, 1H), 4.73 (t, J = 3.8 Hz, 1H), 4.34 (dd, J = 12.3, 3.8 Hz, 1H), 4.05 (dd, J = 12.3, 3.8 Hz, 1H), 2.95 (ddd, J = 14.0, 9.3, 8.1 Hz, 1H), 2.65 (ddd, J = 9.3, 4.7, 1.7 Hz, 1H), 2.22 (dt, J = 14.0, 4.7 Hz, 1H), 2.10 (s, 3H), 1.36 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.7, 177.5, 170.4, 77.9, 73.5, 63.1, 47.8, 40.3, 38.7, 29.6, 27.0, 20.7, 17.7.

(1*R*,4*S*,5*R*,6*S*)-5-Methyl-6-pivaloyloxy-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (8b endo). A solution of 2(5*H*)-furanone **5** (100 mg, 0.47 mmol) and vinyl pivalate, **7b** (0.5 mL, 4.7 mmol), in acetone (70 mL) was irradiated through a Pyrex filter for 8 h. Evaporation of the solvent and chromatography (hexane−EtOAc 5:1) afforded a 44:13:12:11:11:5:4 mixture of seven cycloadducts (131 mg, 0.38 mmol, 82% yield). Repeated column chromatography (from hexane to hexane−EtOAc 9:1) allowed us to isolate the major component **8b endo** as a white solid: mp 60−61 °C (from EtOAc−pentane); $[\alpha]_D$ −7.8 (*c* 3.6, $CHCl_3$); IR (KBr) 2975, 2937, 1776, 1764, 1735, 1481, 1145 cm^{-1}; MS (CI, NH_3) 357 ($[M + NH_4]^+$, 100), 341 ($[M + H]^+$, 5); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (ddd, J = 7.9, 4.1, 2.1 Hz, 1H), 4.62 (dd, J = 3.7, 3.1 Hz, 1H), 4.35 (dd, J = 12.5, 3.1 Hz, 1H), 4.04 (dd, J = 12.5, 3.7 Hz, 1H), 2.96 (ddd, J = 14.1, 9.2, 7.9 Hz, 1H), 2.67 (ddd, J = 9.2, 4.1, 2.1 Hz, 1H), 2.19 (ddd, J = 14.1, 4.1 Hz, 1H), 1.39 (s, 3H), 1.20 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.1, 177.8, 177.7, 78.0, 73.8, 63.3, 47.8, 40.6, 38.7, 38.6, 29.5, 27.1, 27.0, 17.5. Anal. Calcd for $C_{18}H_{28}O_6$: C, 63.51; H, 8.29. Found: C, 63.43; H, 8.50.

(1*R*,4*S*,5*R*,6*S*)-6-*tert*-Butoxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (8c endo), (1*R*,4*S*,5*R*,6*R*)-6-*tert*-Butoxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (8c exo), and (1*R*,4*S*,5*R*,7*R*)-7-*tert*-Butoxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (10c endo). A solution of 2(5*H*)-furanone **5** (130 mg, 0.61 mmol) and *tert*-butylvinylether, **7c** (0.80 mL, 6.1 mmol), in acetone (70 mL) was irradiated through a Pyrex filter for 8 h. Evaporation of the solvent and chromatography (hexane−EtOAc 6:1) gave a 29:22:19:12:9:8:1 mixture of seven cycloadducts (118 mg, 0.38 mmol, 87% yield). Repeated column chromatography (from hexane to hexane−EtOAc 9:1) provided the major components **8c endo** (29%), **8c exo** (22%), and **10c endo** (19%).

8c endo: Mp 100−102 °C (from EtOAc−pentane); IR (KBr) 2969, 2938, 1762, 1727, 1479, 1187, 1146 cm^{-1}; MS (ESI+) 335 ($[M + Na]^+$, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (dd, J = 5.4, 3.8 Hz, 1H), 4.31 (dd, J = 12.2, 3.8 Hz, 1H), 4.09 (dd, J = 12.2, 5.4 Hz, 1H), 3.87 (ddd, J = 7.8, 6.3, 1.1 Hz, 1H), 2.78 (ddd, J = 12.9, 9.1, 7.8 Hz, 1H), 2.47 (ddd, J = 9.1, 6.1, 1.1 Hz, 1H), 2.10 (ddd, J = 12.9, 6.3, 6.1 Hz, 1H), 1.30 (s, 3H), 1.20 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.2, 178.0, 77.9, 74.0, 70.2, 63.4, 49.3, 39.5, 38.7, 33.5, 28.1, 27.1, 18.2.

8c exo: Mp 70−72 °C (from EtOAc−pentane); IR (KBr) 2973, 2934, 1767, 1735, 1458, 1145 cm^{-1}; MS (ESI+) 335 ($[M + Na]^+$, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.41 (dd, J = 2.7, 2.3 Hz, 1H), 4.31 (dd, J = 12.5, 2.7 Hz, 1H), 4.12 (dd, J = 8.2, 7.3 Hz, 1H), 4.01 (dd, J = 12.5, 2.3 Hz, 1H), 2.57 (ddd, J = 9.9, 2.1, 1.0 Hz, 1H), 2.43 (ddd, J = 11.8, 7.3, 2.1 Hz,1H), 2.33 (ddd, J = 11.8, 9.9, 8.2 Hz, 1H), 1.15 (s, 3H), 1.10 (s, 18H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 179.3, 177.8, 82.4, 73.7, 69.6, 63.1, 51.0, 38.6, 38.4, 34.8, 28.4, 27.1, 11.1.

10c endo: Mp 93−95 °C (from EtOAc−pentane); $[\alpha]_D$ +29.0 (*c* 0.39, $CHCl_3$); IR (KBr) 2972, 2932, 1765, 1730, 1476, 1145 cm^{-1}; MS (CI, NH_3) 329 ($[M + NH_4]^+$, 99), 274 ($[M + NH_4 - C_4H_9]^+$, 40), 257 ($[M - C_4H_9O]^+$, 100); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (ddd, J = 8.5, 7.6 Hz, 1H), 4.34 (dd, J = 2.9, 2.1 Hz, 1H), 4.30 (dd, J = 12.3, 2.9 Hz, 1H), 4.02 (dd, J = 12.3, 2.1 Hz, 1H), 2.93 (ddd, J = 7.6, 4.1, 0.9 Hz, 1H), 2.35 (ddd, J = 12.1, 8.5, 4.1 Hz, 1H), 2.22 (dd, J = 12.1, 8.5 Hz, 1H), 1.21 (s, 3H), 1.20 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.8, 174.5, 83.5, 74.6, 63.3, 62.3, 52.9, 43.1, 38.6, 36.3, 27.9, 27.1, 18.5. Anal. Calcd for $C_{17}H_{28}O_5$: C, 65.36; H, 9.03. Found: C, 65.15; H, 8.77.

(1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-6,6-Diethoxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (13 and 14) and (1*S*,4*S*,5*S*)- and (1*R*,4*S*,5*R*)-7,7-Diethoxy-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (15 and 16). A solution of lactone **5** (100 mg, 0.47 mmol) and 1,1-diethoxyethylene, **12** (0.31 mL, 2.35 mmol), in acetonitrile (70 mL) was irradiate through a quartz filter for 35 min. Evaporation of the solvent and column chromatography (hexane−EtOAc 12:1) afforded a 63:31:6 mixture of **13**, **14**, and **15/16** (132 mg, 0.40 mmol, 85% yield). Repeated column chromatography (hexane−EtOAc 12:1) provided enriched fractions of **13** and **14** which were analyzed. All attempts to obtain enriched fractions of compounds **15** and **16** were unsuccessful.

13: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (dd, J = 3.2 Hz, 1H), 4.38 (dd, J = 12.3, 3.2 Hz, 1H), 4.04 (dd, J = 12.3, 3.2 Hz, 1H), 3.20−3.55 (m, 4H), 2.49 (m, 3H), 1.30 (s, 3H), 1.20 (s, 9H,), 1.15 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.5, 178.4, 103.4, 78.1, 63.5, 58.0, 57.6, 53.6, 38.7, 38.2, 34.3, 27.1, 14.9, 13.4; MS (CI + NH_3) 345 ($[M + NH_4]^+$, 100).

14: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (dd, J = 12.6, 7.6 Hz, 1H), 4.47 (dd, J = 12.6, 2.3 Hz, 1H), 4.28 (dd, J = 7.6, 2.3 Hz, 1H), 3.40 (m, 4H), 2.49 (m, 2H), 2.34 (dd, J = 12.8, 9.8 Hz, 1H), 1.37 (s, 3H), 1.20 (s, 9H), 1.15 (m, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.2, 177.9, 101.1, 84.8, 64.1, 58.2, 57.7, 54.7, 39.0, 38.7, 33.0, 27.1, 14.9, 16.5; MS (CI + NH_3), 345 ($[M + NH_4]^+$, 100). Anal. Calcd for $C_{17}H_{28}O_6$ (from a mixture of **13** and **14**): C, 62.18; H, 8.59. Found: C, 62.19; H, 8.60.

(1*S*,4*S*,5*S*,6*R*,7*R*)-6,7-Dichloro-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (21) and its Stereoisomers

(1*S*,4*S*,5*S*,6*S*,7*S*)- (22), (1*S*,4*S*,5*S*,6*R*,7*S*)- (23), (1*S*,4*S*,5*S*,6*S*,7R)- (24), and (1*R*,4*S*,5*R*,6*R*,7*S*)-6,7-Dichloro-5-methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]heptan-2-one (25). A solution of 2(5*H*)-furanone **5** (600 mg, 2.8 mmol) and (*Z*)-1,2-dichloroethylene, **19** (1.1 mL, 14.1 mmol), in acetonitrile (280 mL) was irradiated through a quartz filter for 7 h. Evaporation of the solvent and chromatography (hexane−EtOAc 5:1) afforded a mixture of seven dichlorocyclobutane stereoisomers (774 mg, 2.50 mmol, 89% yield) in a ratio of 35:28:14:11:6:5:1. Repeated column chromatography (from hexane−EtOAc 8:1 to hexane−EtOAc 3:1) provided analytical samples of **21**−**25**.

21: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.99 (t, J = 4.1 Hz, 1H), 4.35 (dd, J = 12.4, 4.1 Hz, 1H), 4.32 (m, 2H), 4.16 (dd, J = 12.4, 4.1 Hz, 1H), 2.97 (dd, J = 3.0 Hz, 1H), 1.5 (s, 3H), 1.20 (s, 9H); ^{1}H NMR (500 MHz, C_6D_6) δ 4.56 (dd, J = 5.0, 4.5 Hz, 1H), 4.02 (dd, J = 12.1, 4.5 Hz, 1H), 3.83 (dd, J = 12.1, 5.0 Hz, 1H), 3.77 (dd, J = 5.6, 4.7 Hz, 1H), 3.72 (dd, J = 5.6, 1.4 Hz, 1H), 2.51 (dd, J = 4.7, 1.4 Hz, 1H), 1.15 (s, 9H), 0.60 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.5, 172.6, 79.0, 66.7, 62.4, 57.5, 52.7, 46.7, 38.7, 27.0, 19.5; MS (CI/NH_3) 327 ([M + NH_4]$^+$, 66), 325 ([M + NH_4]$^+$, 100), 256 ([M − 2Cl]$^+$, 83); HRMS (FAB+) calcd for [$C_{13}Cl_2H_{18}O_4$+H]$^+$ 309.0660, found 309.0671. Anal. Calcd for $C_{13}Cl_2H_{18}O_4$: C, 50.50; H, 5.87. Found: C, 50.17; H, 5.53.

22: Mp 128−129 °C (from pentane−EtOAc); $[\alpha]_D$ +20.9 (*c* 1.05, $CHCl_3$); IR (ATR) 2987, 2962, 1786, 1736, 1478, 1162 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.53 (dd, J = 9.5, 8.2 Hz, 1H), 4.52 (dd, J = 2.6, 1.7 Hz, 1H), 4.40 (dd, J = 8.2, 1.0 Hz, 1H), 4.39 (dd, J = 12.7, 2.6 Hz, 1H), 4.03 (dd, J = 12.7, 1.7 Hz, 1H), 3.24 (dd, J = 9.5, 1.0 Hz, 1H), 1.35 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.4, 171.2, 81.9, 65.2, 62.4, 55.9, 48.0, 47.1, 38.6, 27.1, 13.2; MS (CI/NH_3) 327 ([M + NH_4]$^+$, 58), 325 ([M + NH_4]$^+$, 100), 256 ([M − 2Cl]$^+$, 47). Anal. Calcd for $C_{13}Cl_2H_{18}O_4$: C, 50.50; H, 5.87. Found: C, 50.46; H, 5.84.

23: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.03 (dd, J = 8.3, 7.8 Hz, 1H), 4.99 (dd, J = 3.5, 2.9 Hz, 1H), 4.60 (dd, J = 7.8, 2.6 Hz, 1H), 4.40 (dd, J = 12.5, 3.5 Hz, 1H), 4.12 (dd, J = 12.5, 2.9 Hz, 1H), 3.24 (dd, J = 8.3, 2.6 Hz, 1H), 1.45 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.6, 171.5, 79.2, 64.9, 62.8, 52.0, 50.5, 47.4, 38.7, 27.1, 18.5; MS (CI/NH_3) 327 ([M + NH_4]$^+$, 20), 325 ([M + NH_4]$^+$, 27), 256 ([M − 2Cl]$^+$, 100); HRMS (FAB+) calcd for [$C_{13}Cl_2H_{18}O_4$+H]$^+$ 309.0660, found 309.0685.

24: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.78 (dd, J = 6.4, 1.5 Hz, 1H), 4.65 (dd, J = 6.4, 1.0 Hz 1H), 4.53 (dd, J = 2.8, 1.6 Hz, 1H), 4.37 (dd, J = 12.7, 2.8 Hz, 1H), 4.03 (dd, J = 12.7, 1.6 Hz, 1H), 3.08 (s, 1H), 1.50 (s, 3H), 1.15 (s, 9H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 177.4, 173.5, 82.1, 62.4, 59.7, 58.9, 51.1, 50.1, 38.6, 27.1 (CH_3, $(CH_3)_3C$), 14.7 (CH_3); MS (CI/ NH_3) 325 ([M + NH_4]$^+$, 26), 256 ([M − 2Cl]$^+$,100). Anal. Calcd for $C_{13}Cl_2H_{18}O_4$: C, 50.50; H, 5.87. Found: C, 50.17; H, 5.53.

25: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.88 (dd, J = 6.5, 1.4 Hz, 1H), 4.63 (d, J = 6.5 Hz, 1H), 4.31 (m, 3H), 3.15 (s, 1H), 1.60 (s, 3H), 1.25 (s, 9H); ^{1}H NMR (500 MHz, C_6D_6) δ 4.07 (dd, J = 6.3, 1.3 Hz, 1H), 4.00 (dd, J = 12.3, 6.9 Hz 1H), 3.99 (d, J = 6.3 Hz, 1H), 3.96 (dd, J = 12.3, 4.5 Hz, 1H), 3.53 (dd, J = 6.9, 4.5 Hz, 1H), 2.40 (dd, J = 1.3 Hz, 1H), 1.20 (s, 9H), 1.10 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 178.4, 173.4, 83.2, 61.2, 58.7, 55.2, 51.9, 51.0, 39.2, 27.5, 18.0; HRMS (FAB+) calcd for [$C_{13}Cl_2H_{18}O_4$−Cl]$^+$ 273.0894, found 273.0893.

(1*R*,4*S*,5*S*)- and (1*S*,4*S*,5*R*)-5-Methyl-4-pivaloyloxymethyl-3-oxabicyclo[3.2.0]hept-6-en-2-one (17 and 18). A solution of 2(5*H*)-furanone **5** (600 mg, 2.8 mmol) and (*Z*)-**19** (1.1 mL, 14.1 mmol) in acetonitrile (280 mL) was irradiated using a high-pressure 125 W mercury lamp (Cathodeon HPK-125) for 7 h. Evaporation of the solvent and column chromatography (hexane−EtOAc 3:1) afforded a diastereomeric mixture of the dichlorocyclobutane derivatives.

The resulting crude was dissolved in (80%) aqueous EtOH (3.6 mL), and activated Zn dust (3.6 g, 55.0 mmol) was added. The mixture was irradiated under pressure in a focused microwave reactor at 105 °C for 20 min. After cooling, the reaction mixture was filtered through Celite. The solid was washed several times with EtOH and EtOAc. Evaporation of the solvent gave a residue, which was subjected to column chromatography (hexane−EtOAc 12:1) to afford the syn cycloadduct **18** (58 mg, 0.24 mmol, 9% yield) ant the anti cycloadduct **17** (429 mg, 1.80 mmol, 64% yield).[3]

2-{(1*R*,4*S*)-4-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-4-methyl-2-cyclobutenyl}-2-propanol (26). To a solution of **17** (900 mg, 4.83 mmol) in anhydrous THF (90 mL) at −78 °C was added, dropwise, MeLi 1.6 M in ether (18.1 mL, 28.98 mmol), and the mixture was stirred at −78 °C for 1 h and at room temperature for 2 h. Then, saturated solution of NH_4Cl (40 mL) was slowly added, the organic layer was separated, and the aqueous phase was successively extracted with CH_2Cl_2 and EtOAc. The organic extracts were washed with brine, dried, and the solvents removed to give a crude which was dissolved in acetone (12 mL). To this solution was added *p*-TsOH 0.05 M in acetone (0.6 mL, 0.03 mmol). After being stirred for 12 h, the reaction mixture was diluted with CH_2Cl_2 and successively washed with a saturated aqueous solution of $NaHCO_3$ and brine before being dried and concentrated. The product was purified by chromatography (hexane−EtOAc 4:1) to give **26** (873 mg, 3.86 mmol, 80% yield) as a colorless oil.[3]

(1*R*,2*S*,3*S*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-2-(1-hydroxy-1-methylethyl)-3 methylcyclobutanol (27) and Its Stereoisomer (1*R*,2*R*,3*R*)- (29) and (1*S*,2*R*,3*R*)-2-[(4*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-3-(1-hydroxy-1-methylethyl)-2-methylcyclobutanol (28) and Its Stereoisomer (1*S*,2*S*,3*S*)-30. To a stirred solution of 1 M BH_3-THF (0.45 mL, 0.45 mmol) in dry THF (1 mL) at −15 °C was added dropwise a solution of **26** (50 mg, 0.22 mmol) in dry THF (1 mL). The mixture was stirred at −15 °C for 7 h and quenched by careful addition of water. Then, 3 M NaOH (0.6 mL) and 30% H_2O_2 (0.36 mL) were successively added, and the mixture was stirred for 15 h at room temperature. The mixture was poured into brine containing 2% hydrochloric acid (5 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried, and evaporated to give a residue which was purified by column chromatography (hexane−EtOAc 3:1) to furnish **27** (10 mg, 0.04 mmol, 19% yield), **28** (7 mg, 0.03 mmol, 13% yield), **29** (18 mg, 0.07 mmol, 33% yield), and **30** (13 mg, 0.05 mmol, 24% yield) as colorless oils.

27: $[\alpha]_D$ −80.0 (*c* 0.05, $CHCl_3$); IR (ATR) 3419 (br), 2969, 1455, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.21 (t, J = 6.5 Hz, 1H), 4.81 (d, J = 3.5 Hz, 1H), 4.51 (m, 1H, H-1), 4.10 (dd, J = 8.4, 6.5 Hz, 1H), 3.98 (s, 1H), 3.78 (dd, J = 8.4, 6.5 Hz, 1H), 2.02 (d, J = 6.3 Hz, 1H), 1.81 (dd, J = 12.6, 5.4 Hz, 1H), 1.56 (d, J = 12.6 Hz, 1H) 1.44 (s, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 109.6, 79.9, 73.7, 69.2, 65.5, 57.6, 44.4, 39.2, 29.1, 27.7, 26.1, 24.8, 22.2; MS (FAB+) 245 ([M + H]$^+$, 87), 227 ([M − OH]$^+$, 100); HRMS (FAB+) calcd for [$C_{13}H_{24}O_4$+H]$^+$ 245.1753, found 245.1766.

28: $[\alpha]_D$ −27.0 (*c* 0.15, $CHCl_3$); IR (ATR) 3419 (br), 2969, 1455, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.79 (t, J = 6.8 Hz, 1H), 4.13 (dd, J = 8.9, 6.8 Hz, 1H), 3.86 (s, 1H), 3.83 (dd, J = 8.9, 6.8 Hz, 1H), 3.77 (m, 1H), 2.19 (ddd, J = 10.5, 7.9 Hz, 1H), 2.02 (ddd, J = 12.0, 10.5, 8.7 Hz, 1H), 1.72 (s, 1H), 1.49 (dd, J = 12.0, 7.9 Hz, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 107.7, 74.5, 70.9, 70.4, 66.8, 51.2, 47.6, 30.1, 29.4, 27.3, 26.0, 24.4, 20.8; MS (FAB+) 245 ([M + H]$^+$, 33), 227 ([M − OH]$^+$, 100); HRMS (FAB+) calcd for [$C_{13}H_{24}O_4$+H]$^+$ 245.1753, found 245.1754.

29: $[\alpha]_D$ −53.0 (*c* 0.15, $CHCl_3$); IR (ATR) 3419 (br), 2969, 1455, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (t, J = 7.0 Hz, 1H), 4.00 (dd, J = 8.2, 7.0 Hz, 1H), 3.78 (m, 1H), 3.74 (dd, J = 8.2, 7.0 Hz, 1H), 3.41 (s, 1H), 2.32 (ddd, J = 12.2, 9.3, 7.0 Hz, 1H), 2.23 (t, J = 9.3 Hz, 1H), 1.80 (ddd, J = 12.2, 9.3, 3.3 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.25 (s, 3H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 109.3, 76.8, 71.1, 69.1, 65.5, 51.7, 48.6, 29.7, 29.5, 27.4, 26.0, 24.7, 15.3; MS (FAB+) 245 ([M

+ H]$^+$, 10), 227 ([M − OH]$^+$, 100); HRMS (FAB+) calcd for [$C_{13}H_{24}O_4$+H]$^+$ 245.1753, found 245.1752.

30: [α]$_D$ −3.7 (*c* 1.21, $CHCl_3$); IR (ATR) 3419 (br), 2969, 1455, 1157 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.41 (t, *J* = 6.9 Hz, 1H), 4.25 (m, 1H), 3.97 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.70 (dd, *J* = 8.2, 6.9 Hz, 1H), 3.65 (s, 1H), 2.29 (s, 1H), 1.88 (dd, *J* = 11.2, 7.5 Hz, 1H), 1.86 (d, *J* = 8.6 Hz, 1H), 1.52 (dd, *J* = 11.2, 8.1 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H), 1.20 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 109.6, 78.4, 70.9, 66.0, 65.6, 64.0, 39.7, 36.4, 29.5, 27.5, 26.0, 24.7, 22.6; MS (FAB+) 245 ([M + H]$^+$, 39), 227 ([M − OH]$^+$, 90), 169 (100), 154 (82); HRMS (FAB+) calcd for [$C_{13}H_{24}O_4$+H]$^+$ 245.1753, found 245.1749.

2-{(1*S*,2*S*,4*S*)-4-(Benzyloxy)-2-[(4*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methylcyclobutyl}-2-propanol (31). To a stirred solution of **26** (78 mg, 0.34 mmol) in CH_2Cl_2 (1 mL) were added, successively, benzyl alcohol (89 μL, 0.86 mmol), mercuric acetate (135 mg, 0.43 mmol), and 70% perchloric acid (1 μL). The resulting mixture was stirred at room temperature for 24 h. Then, the mixture was added to cold CH_2Cl_2 (20 mL) and washed with cold H_2O (10 mL), and the aqueous phase was extracted with CH_2Cl_2 (10 mL). The combined organic phase was dried, filtered, and concentrated. The resulting residue was dissolved in THF (3 mL) and added to a vigorously stirred ice-cooled mixture of $NaBH_4$ (13 mg, 0.34 mmol) in THF (3 mL) and aqueous pH 8 solution (3 mL). After 15 min, the reaction mixture was washed with water and the aqueous phase was extracted with CH_2Cl_2. The combined organic phase was dried, filtered, and concentrated. Column chromatography of the resulting residue (from hexane−EtOAc 20:1 to hexane−EtOAc 12:1) afforded **31** (99 mg, 0.30 mmol, 86%) as a colorless oil.[3]

2-[1*S*,2*S*,4*S*)-4-(Benzyloxy)-2-[(1*S*)-2-(benzyloxy)-1-hydroxyethyl]-2-methylcyclobutyl]-2-propanol (32). A suspension of triol **4** (191 mg, 0.65 mmol) and Bu_2SnO (178 mg, 0.71 mmol) in MeOH (4 mL) was heated at reflux until the solution became clear. The solvent was evaporated to dryness to give a residue, which was dissolved in dry toluene (4 mL). Then, tetrabutylammonium bromide (209 mg) and benzyl bromide (85 μL, 0.71 mmol) were added. The mixture was stirred for 24 h at the reflux temperature, cooled to room temperature, and washed successively with a 10% solution of Na_2SO_3 and brine. The organic layer was dried, and the solvent was removed. The crude material was purified by column chromatography (hexane−EtOAc 3:2) to afford diol **32** (205 mg, 0.53 mmol, 82% yield) as a colorless oil: [α]$_D$ +83.7 (*c* 0.45, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 10H), 4.54 (m, 2H), 4.41 (m, 2H), 4.00 (m, 2H), 3.80 (br s, 1H), 3.52 (dd, *J* = 9.5, 2.5 Hz, 1H), 3.50 (br s, 1H), 3.44 (dd, *J* = 9.5, 8.3 Hz, 1H), 2.05 (d, *J* = 9.5 Hz, 1H), 1.99 (dd, *J* = 11.1, 7.0 Hz, 1H), 1.45 (dd, *J* = 11.1, 7.9 Hz, 1H), 1.32 (s, 3H), 1.24 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.9, 138.1, 128.9, 128.8, 128.3, 128.2, 128.1, 128.0, 74.0, 73.9, 71.5, 71.0, 70.9, 70.8, 64.5, 38.6, 38.1, 30.0, 28.7, 24.3; HRMS (MALDI) calcd for [$C_{24}H_{32}O_4$+Na]$^+$ 407.2193, found 407.2180.

(*E*)- or (*Z*)-(4*S*)-4,8-Dibenzyloxy-2,6-dimethyl-6-octen-2-ol (34). To a stirred solution of diol **32** (40 mg, 0.10 mmol) in dry THF (2 mL) were added CS_2 (64 μL, 1.0 mmol) and NaH (60% in oil, 11 mg, 0.26 mmol) under an Ar atmosphere. The mixture was stirred at room temperature for 2 h. Then, MeI (130 μL, 2.5 mmol) was added and the mixture was stirred for 1 h. After neutralization with AcOH, the solvent was removed to afford **33** (45 mg, 0.095 mmol) as a pale yellow solid which was subjected to the following reaction without further purification. To a heated (100 °C) solution of tributyltin hydride (100 μL, 0.38 mmol) in dry toluene (0.7 mL) was added a solution of azobisisobutyronitrile AIBN (5 mg, 0.03 mmol) in dry toluene (0.5 mL), and a solution of **33** in dry toluene (2 mL) was added dropwise under an Ar atmosphere. The reaction mixture was heated for 20 min. After cooling, the contents were directly subjected to column chromatography (from hexane to hexane−EtOAc 10:1) to furnish a mixture 1.3:1 of two products (23 mg, 0.06 mmol, 66% yield). Repeated column chromatography allowed obtaining enriched fractions of the major product **34** which was analyzed by NMR spectra.

34: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 10H), 5.50 (m, 1H), 4.74 (d, *J* = 10.9 Hz, 1H), 4.52 (m, 2H), 4.48 (d, *J* = 10.9 Hz, 1H), 4.08 (d, *J* = 6.4 Hz, 2H), 3.95 (m, 1H), 2.58 (dd, *J* = 13.8, 4.1 Hz, 1H), 2.20 (dd, *J* = 13.8, 7.7 Hz, 1H), 1.80 (m, 1H), 1.72 (s, 1H), 1.60 (m, 1H), 1.20 (s, 6H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 137.6, 136.3, 128.6, 128.4, 128.1, 128.0, 127.7, 127.6, 124.8, 124.7, 76.0, 72.2, 70.7, 70.2, 66.4, 46.0, 44.2, 31.1, 28.3, 17.1.

2-[(1*S*,2*S*,4*S*)-4-(Benzyloxy)-2-[2-(benzyloxyethyl]-2-methylcyclobutyl]-2-propanol (35). To a solution of diol **32** (154 mg, 0.40 mmol) in dry THF (7 mL) were added CS_2 (253 μL, 4.2 mmol), in one portion, and NaH (60% in oil, 40 mg, 1.06 mmol) under an Ar atmosphere, and the mixture was stirred for 2 h at room temperature. Then, MeI (523 μL, 8.4 mmol) was added, and the mixture was stirred at room temperature for 1 h. After neutralization with AcOH, the solvent was removed to afford **33** (175 mg, 0.37 mmol, 92% yield) as a pale yellow solid. To a stirred solution of the above xanthate in benzene (8 mL), Bu_3SnH (293 μL, 1.09 mmol) and Et_3B (1 M in hexane, 1.1 mL) were added and the mixture was stirred for 2 h 30 min at room temperature. Removal of the solvent afforded an oily residue, which was subjected to column chromatography (hexane−EtOAc 4:1) to afford **35** (115 mg, 0.31 mmol, 78% yield from **32**) as a colorless oil.

33: ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.30 (m, 10H), 6.06 (dd, *J* = 5.2, 3.6 Hz, 1H), 4.52 (s, 2H), 4.44 (m, 2H), 4.08 (m, 1H), 3.83 (dd, *J* = 11.1, 5.2 Hz, 1H), 3.73 (br s, 1H), 3.70 (dd, *J* = 11.1, 3.6 Hz, 1H), 2.56 (s, 3H), 2.50 (dd, *J* = 11.5, 7.3 Hz, 1H), 2.14 (d, *J* = 9.1 Hz, 1H), 1.54 (dd, *J* = 11.5, 8.2 Hz, 1H), 1.41 (s, 3H), 1.27 (s, 3H), 1.22 (s, 3H).

35: [α]$_D$ +97.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.35 (m, 10H), 4.51 (s, 2H), 4.48 (m, 2H), 4.08 (m, 1H), 3.53 (m, 2H), 2.20 (dd, *J* = 10.7, 7.2 Hz, 1H), 2.07 (d, *J* = 9.0 Hz, 1H), 1.97 (m, 2H), 1.49 (dd, *J* = 10.7, 8.1 Hz, 1H), 1.29 (s, 6H), 1.20 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 138.1, 136.1, 128.1, 128.0, 127.4, 127.3, 127.3, 127.2, 72.9, 71.2, 70.1, 70.1, 67.5, 62.9, 39.2, 35.5, 33.8, 29.7, 29.2, 28.3; HRMS (MALDI) calcd for [$C_{24}H_{32}O_3$+Na]$^+$ 391.2244, found 391.2247.

(1*S*,2*S*,3*S*)-3-(2-Hydroxyethyl)-2-(1-hydroxy-1-methylethyl)-3-methylcyclobutan-1-ol (6). A stirred solution of alcohol **35** (100 mg, 0.27 mmol) in a 30:1 mixture of EtOAc and HOAc (6 mL) was hydrogenated over 10% Pd/C (309 mg) under a flow of H_2 for 1 h. The catalyst was removed by filtration over Celite, and the solvent was evaporated and the residue purified by column chromatography (hexane−EtOAc 1:3) to afford **6** (41 mg, 0.21 mmol, 83% yield) as a colorless oil: [α]$_D$ +54.6 (*c* 0.61, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.28 (m, 1H), 3.69 (m, 2H), 2.26 (dd, *J* = 10.9, 7.9 Hz, 1H), 1.87 (m, 2H), 1.81 (d, *J* = 9.0 Hz, 1H), 1.44 (dd, *J* = 10.9, 9.1 Hz, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 71.5, 65.9, 64.1, 59.9, 41.7, 38.5, 33.3, 29.8, 29.4, 28.2; HRMS (CI+/CH_4) calcd for [$C_{10}H_{21}O_3$−H_2O]$^+$ 171.1385, found 171.1386.

(1*R*,6*S*)-2,2,6-Trimethyl-3-oxabicyclo[4.2.0]octan-4,8-dione (2). To a solution of triol **6** (50 mg, 0.26 mmol) in dry CH_2Cl_2 (5 mL) was added PCC (215 mg, 1.00 mmol). The mixture was stirred for 4 h at room temperature, filtrated over Celite, and concentrated, and the resulting residue was purified by column chromatography (hexane−EtOAc 1:1) to give **2** (38 mg, 0.21 mmol, 79% yield) as colorless crystals: mp 135−8 °C (from EtOAc−pentane); [α]$_D$ +209.1 (*c* 0.93, acetone); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.95 (br s, 1H,), 2.89 (m, 2H), 2.83 (d, *J* = 16.8 Hz, 1H), 2.71 (d, *J* = 16.8 Hz, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.40 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 205.6, 170.0, 80.5, 69.8, 58.0, 40.1, 29.5, 28.1, 26.9, 26.7.

(1*R*,4*S*,5*R*,7*R*)-3,3,7-Trimethyl-2,9-dioxatricyclo[3.3.1.0^{4,7}]nonane (1). To a solution of **2** (28 mg, 0.15 mmol) in dry ether (1.5 mL) at −78 °C was added dropwise a 1.0 M solution of DIBAL-H in hexane (0.36 mL, 0.36 mmol), and the mixture was stirred 30 min at −78 °C and 1.5 h at 0 °C. The reaction mixture was pored

into ice-cold 10% aqueous tartaric acid (2 mL) and stirred for 20 min. The two layers were separated, and the organic extracts was successively washed with saturated $NaHCO_3$ and brine, dried, and concentrated by distillation through a Vigreux column under atmospheric pressure to give **1** (14 mg, 0.08 mmol, 65% yield): $[\alpha]_D$ +81.1 (*c* 0.46, $CDCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 5.08 (d, J_1 = 3.2 Hz, 1H), 4.49 (t, J = 3.9 Hz, 1H), 2.10 (ddd, J = 12.6, 3.2 Hz, 1H), 1.95 (dd, J = 12.6, 2.1 Hz, 1H), 1.90 (d, J = 3.9 Hz, 1H), 1.73 (dt, J = 10.0, 3.9 Hz, 1H), 1.65 (d, J = 10.0 Hz, 1H), 1.23 (s, 3H), 1.17 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 93.2, 71.9, 66.2, 48.5, 43.8, 42.5, 38.7, 29.3, 28.2, 26.7.

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Supporting Information Available: General experimental procedures, full assignment of ^1H and ^{13}C NMR spectra, and ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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