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C_2-Symmetric Enantiopure Ethanotethered Bis(α,β-butenolides) as Templates for Asymmetric Synthesis. Application to the Synthesis of (+)-Grandisol[1]

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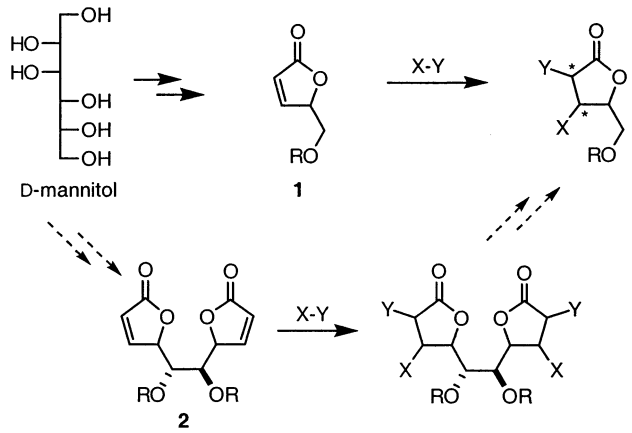
Starting from D-mannitol, we have prepared several C_2-symmetric ethanotethered bis(α,β-butenolides) and studied their [2+2] photocycloaddition reaction with ethylene. The protective groups of the central diol unit have a noticeable influence on the facial selectivity of the cycloaddition, the bis(trimethylsilyloxy) derivatives showing the highest diastereoselectivity. A theoretical conformational analysis of the substrates in the ground state is in good agreement with the diastereofacial selectivity experimentally observed. The bis(photocycloadducts) have been converted into the enantiopure cyclobutanes formally derived from the photoreaction of ethylene with γ-hydroxymethyl-α,β-butenolide, in which only a moderate facial selectivity had been previously found. As an application of these studies, we have developed a highly efficient and stereoselective synthesis of (+)-grandisol.

Introduction

γ-Hydroxymethyl-α,β-butenolide derivatives of type **1** (Scheme 1) have been extensively used as chiral scaffolds in the stereoselective synthesis of many molecules of biological significance.[2] Compounds **1** may be conveniently prepared from D-mannitol, a C_2-symmetric and easily available natural product, through sequences involving an oxidative cleavage step that yields a protected D-glyceraldehyde.[3] A crucial transformation of many synthetic sequences involving **1** is the addition of a reagent XY to the carbon−carbon double bond with concomitant formation of one or two new stereogenic centers. The diastereoselectivity of this process depends on the asymmetric induction effected by the substituent at the γ-carbonyl position of the lactone. In general, the initial attack of the external reagent occurs preferentially by the face opposite to this substituent, but the degree

SCHEME 1. Bidirectional Synthetic Strategy for the Preparation of Enantiopure Polysubstituted γ-lactones



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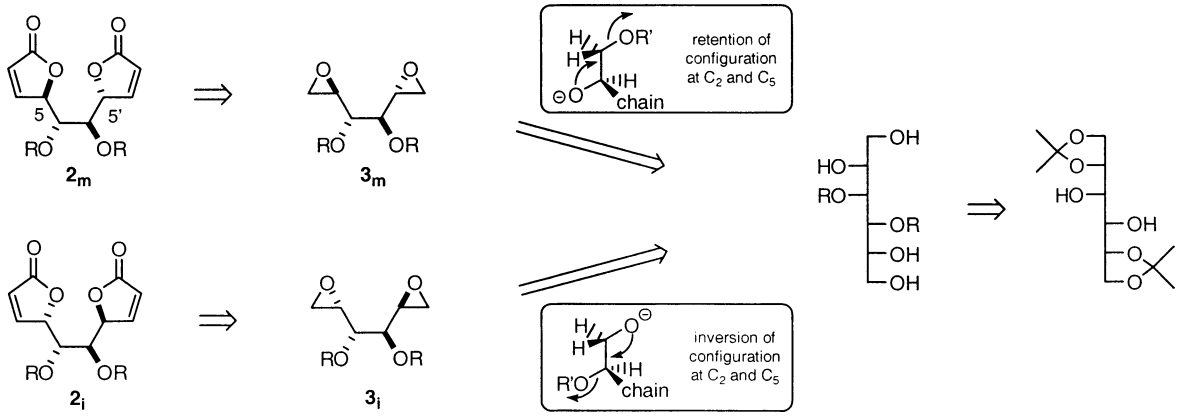
SCHEME 2. Retrosynthetic Analysis for the Preparation of C_2-Symmetric Enantiopure Ethanotethered Bis(α,β-butenolides) Starting from D-Mannitol



of facial discrimination depends on the class of addition reaction and the nature of the R group, steric and electronic factors being at play.[4] We thought that using as substrates C_2-symmetric analogues of **1**, i.e., **2**, the facial selectivity of some addition processes may improve, should a favorable combination of steric and electronic factors increase the accessibility of one of the pair of homotopic diastereofaces of the olefin. After the addition, symmetric cleavage of the products would furnish the formal adducts derived of **1**.

The photochemical [2+2] cycloaddition of enones to olefins has found broad application in the synthesis of natural products as a key step in the preparation of many target molecules containing a cyclobutane ring in their skeleton.[5] However, reports on the use of α,β-unsaturated lactones as substrates for these reactions are quite limited.[4c,d,6] Some of the published studies deal with chiral substrates[6b,e−k,m] and, eventually, culminate in the synthesis of a natural product, but the diastereoselectivities of these photocycloadditions range from low to moderate. In particular, a total synthesis of (+)-grandisol was developed in our laboratories,[7] in which the key step was the formation of a cyclobutane ring through a photochemical addition of ethylene to (*S*)-4-methyl-5-pivaloyloxymethyl-2(5*H*)-furanone, a compound of type **1** that bears a methyl group at the β-carbonyl position. Although this reaction proceeded in good yield, the diastereofacial selectivity was low (24% diasteromeric excess in favor of the anti cycloadduct). For this reason, we decided to investigate the validity of the idea depicted in Scheme 1 using the photocycloaddition of ethylene as a model reaction. We report here the preparation of a series of enantiopure bis(α,β-butenolides) with different protecting groups of the central diol unit, the study of their [2+2] photocycloaddition to ethylene, and its application to the stereoselective synthesis of (+)-grandisol, the main component of the sexual attracting pheromone of the cotton boll weevil, *Anthonomous grandis* Boheman, and other insects.[8]

Results and Discussion

Preparation of the Bis(α,β-butenolides). The use of D-mannitol as starting material brings about the possibility of applying a bidirectional synthesis[9] with simultaneous homologation of both ends of the chain. We planned the synthesis of the C_2-symmetric bis(α,β-butenolides) **2** accordingly to this strategy (Scheme 2). The bis(epoxides) **3** were envisaged as suitable precursors to test a quite straightforward methodology that works efficiently to prepare simple α,β-butenolides. The procedure involves condensation of phenylselenoacetic acid dianion with an epoxide, followed by acid-catalyzed lactonization and then oxidation of the selenide with concomitant elimination to deliver the double bond.[10] We decided to investigate if this method could be applied to a bis(epoxide) to synthesize a bis(lactone) in a bidirec-

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SCHEME 3. Synthetic Sequence for the Preparation of C_2-symmetric Enantiopure Ethanotethered Bis(α,β-butenolides)

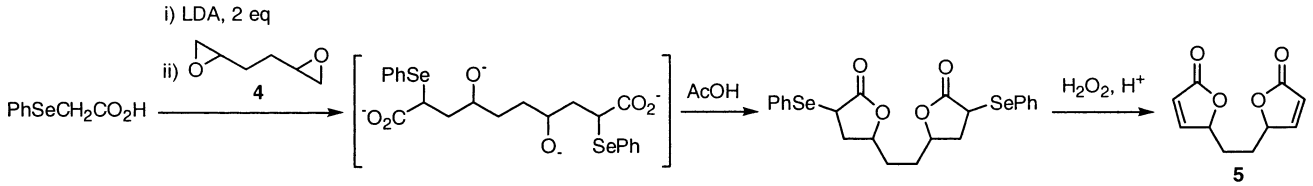
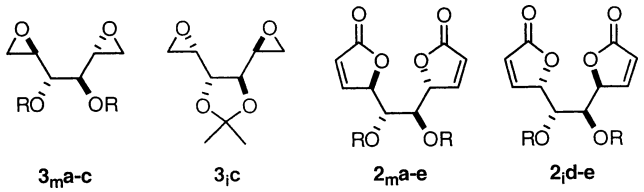


CHART 1[a]



[a] **a**, R = Et; **b**, R = $PhCH_2$; **c**, RR = CMe_2; **d**, R = H; **e**, R = TMS

tional process. Starting from commercial 1,2:5,6-diisopropylidene-D-mannitol, different protecting groups of the central diol can be introduced and, after removal of the isopropylidene moiety, the bis(epoxides) **3** can be formed either by displacement of the primary hydroxyl group by the secondary, with retention of configuration at C-2 and C-5, or the opposite way with inversion of configuration at these two equivalent carbon atoms, giving access respectively to two diastereoisomeric series, namely, D-mannitol (**3$_m$**) or L-iditol (**3$_i$**) derivatives from a common intermediate tetrol. Since the stereogenic center in the oxirane is retained in the final lactone, the D-mannitol derivatives **3$_m$** should give access to bis(butenolides) with *R*,*R* configuration at C-5/5′, while the L-iditol derivatives **3$_i$** would furnish the 5*S*,5′*S* diastereoisomeric bis(lactones).

The appropriate conditions for the bidirectional lactonization were investigated using the simple bis(epoxide) **4**[11] and could be conveniently adjusted to obtain the bis(lactone) **5** in 72% overall yield (Scheme 3). Then, (2*S*,5*S*)-**4** and the D-mannitol series of bis(epoxides) **3$_m$a**−**c** (Chart 1) were prepared following known methodologies,[12] although the synthetic sequences previously described for each particular bis(epoxide) were eventually modified (see Experimental Section). Following the bislactonization procedure, these enantiopure bis(epoxides) were converted into the corresponding enantiopure bis(butenolides) (5*S*,5′*S*)-**5** and **2$_m$a**−**c**, among which the isopropilydene derivative **2$_m$c** was obtained in the highest yield (75%). Hydrolysis of the acetonide **2$_m$c** afforded the unprotected analogue **2$_m$d**, which reacted with 1-(trimethylsilyl)imidazole (TMSIm) in THF at room temperature providing the disilyl derivative **2$_m$e**. Several trials to introduce the bulkier TBS group failed. Attempts to improve the synthesis of **2$_m$a**,**b** through alkylation of **2$_m$d** were also unsuccessful.

Next, the L-iditol type bis(epoxide) **3$_i$c** was prepared and its conversion into the corresponding isopropylidene bis(butenolide) was attempted. It was found that, under the selenide oxidation conditions, hydrolysis of the ketal occurs and the unprotected bis(butenolide) **2$_i$d**, diastereiosomer of **2$_m$d** with *S* configuration at C-5/5′, is directly isolated in 72% yield. From **2$_i$d**, the bis(trimethylsilyl) derivative **2$_i$e** was also prepared as above.[13]

Photoreactions of the Bis(α,β-butenolides) with ethylene. To study the influence of the diol protecting group, the (5*R*,5′*R*) bis(butenolides) **2$_m$a**−**e** were irradiated in a solution of acetone saturated with ethylene in a Pyrex vessel with a medium pressure 125 W mercury lamp at −78 °C, and the substrate conversion was monitored by ^{1}H NMR analysis of aliquot samples. A priori the cycloaddition can result in the formation of three isomeric bis(cyclobutanes) **6**−**8** (Chart 2), coming respectively from *anti*−*anti*, *anti*−*syn*, and *syn*−*syn* approaches of the ethylene to each carbon−carbon double bond of the excited lactone. The results of the photochemical reactions are collected in Table 1. The diethyl and dibenzyl bis(lactones) **2$_m$a** and **2$_m$b** gave complex crude reaction mixtures where, besides some expected bis(cyclobutane) adducts, other products formed through a competitive reaction pathway (vide infra) were also present in similar amounts. After irradiation of the acetonide derivative **2$_m$c** in the presence of ethylene, we isolated exclusively a mixture of the *anti*−*anti* and *anti*−*syn* bis(cyclobutanes) **6c** and **7c** in 3.6:1 ratio and 65% overall yield. This result reflects a 78% of facial discrimination, considering the overall percentage of anti and syn approach to each individual olefin. For the substrate with the free hydroxyl groups **2$_m$d**, the yield of the cycloaddition was even higher (90%) but the facial discrimination decreased, being the unique case leading to the formation of a significant amount of the *syn*−*syn* bis(cyclobutane) **8d**. The best result was found for the TMS derivative **2$_m$e**, which furnished cycloadducts **6e** and **7e** in 83% isolated yield and 98% facial discrimination.

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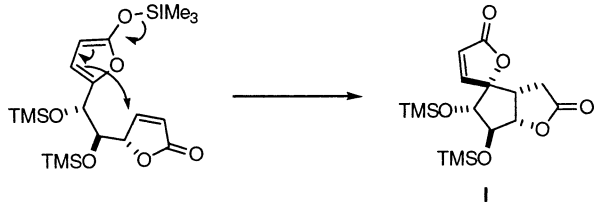
(13) Although the yield of the silylation reaction was usually high (98%), a byproduct was eventually formed, which could be isolated and characterized as **I** by X-ray analysis of a suitable crystal. An intramolecular conjugate addition of the trimethylsilyloxyfurane formed from one of the butenolide rings to the remaining unsaturated lactone may account for the formation of this compound:



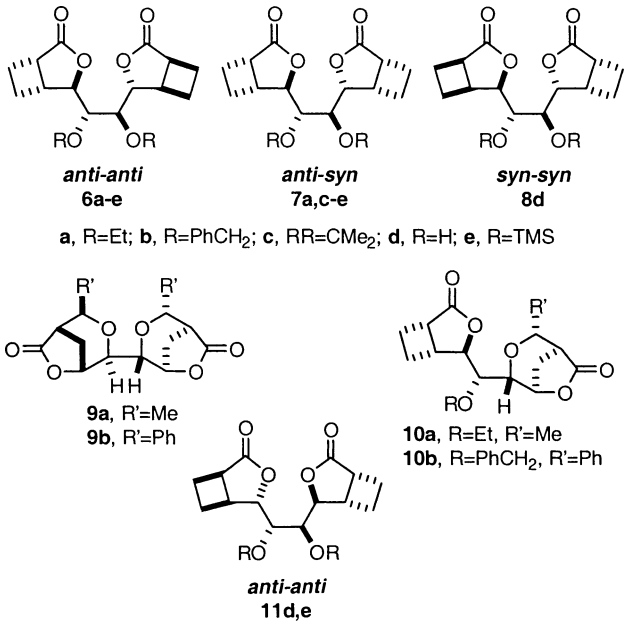
I

TABLE 1. Photochemical Reactions of the Bis(α,β-butenolides) 2_ma-e with Ethylene[a]

substrate	total yield[b]	**6** anti−anti	**7** anti−syn	**8** syn−syn	facial discrimination[c]	other products
$\mathbf{2_m a}$	80%	30%	10%			**9a** (10%), **10a** (30%)
$\mathbf{2_m b}$	75%	5%				**9b** (47%), **10b** (23%)
$\mathbf{2_m c}$	65%	51%	14%		78%	
$\mathbf{2_m d}$	90%	44%	38%	8%	40%	
$\mathbf{2_m e}$	85%	83%	2%		98%	

[a] Irradiations were performed in a solution of acetone saturated with ethylene in a Pyrex vessel with a medium pressure 125 W mercury lamp at −78 °C. The substrate conversion was monitored by ^{1}H NMR analysis of aliquot samples. [b] Yield of isolated products. [c] Facial diastereoselectivity considering the overall anti and syn approaches to each individual olefin.

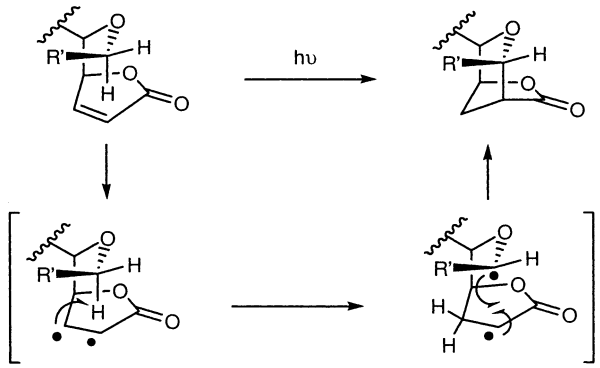
CHART 2



The structural and stereochemical assignment of the bis(cyclobutanes) was inferred from their NMR spectra, considering the double number of signals displayed by the *anti*−*syn* isomers, which lack the C_2-symmetry of the *anti*−*anti* or *syn-syn* bis(adducts), and the value of the coupling constant between the proton at the γ position of the lactone and its vicinal proton at the bridge junction, which is small (around 1.5 Hz) for a relative anti stereochemistry and larger (around 6.5 Hz) for a relative syn arrangement.[6m]

When the bis(lactones) $\mathbf{2_m a-e}$ were irradiated under identical conditions except for the absence of ethylene, substrates $\mathbf{2_m c-e}$ underwent only slow decomposition to unidentified products, but $\mathbf{2_m a}$ and $\mathbf{2_m b}$ cleanly converted into the corresponding bis(pyrans) **9a** and **9b** in very high yields. In previous studies with the monobutenolide analogue of the benzyl derivative, the photoinduced formation of a pyran had already been observed.[6m] A plausible mechanism for the formation of the pyran (Scheme 4) involves intramolecular abstraction of a hydrogen atom by the β carbon atom of the excited enone, followed by recombination of the diradical with formation of a new carbon−carbon σ bond. The isolation of **9a** provides evidence that this transformation may be extended to substituents other than benzyl, despite the lower stability of the intermediate radical presumably formed, but the presence of an alkyl chain with at least one hydrogen atom at the oxygen linked position is necessary. The stereochemistry of **9a** was established by X-ray analysis, demonstrating the stereoespecificity of

SCHEME 4. Mechanistic Proposal for the Photoactivated Formation of Pyrans



the cyclization. The isolation and characterization of the bis(pyrans) **9a**−**b** assisted the identification of the mixed cyclobutane-pyran adducts **10a**,**b** formed in the previous irradiations of $\mathbf{2_m a}$ and $\mathbf{2_m b}$ in the presence of ethylene.

Since the best photoactive substrate in the addition to ethylene within the (5*R*,5′*R*) series was the bis(trimethylsilyl) derivative $\mathbf{2_m e}$, the photoreaction of its (5*S*,5′*S*) diastereoisomer $\mathbf{2_i e}$ with ethylene was next studied. After 8 h of irradiation in the usual conditions, the only observed product was the *anti*−*anti* bis(cyclobutane) **11e**. This compound could not be purified because it is hydrolyzed rapidly, therefore the photoreaction crude was directly desilylated by treatment with Bu_4NF in THF and the corresponding diol **11d** was obtained in 83% overall yield.

Conformational Analysis and Diastereofacial Selectivity. The results of the photocycloadditions of ethylene to the bis(butenolides) $\mathbf{2_m c}$,**e** suggest a correlation between the facial discrimination and the size of the protecting groups of the central diol unit. In precedent thermal addition reactions to acyclic C_2-bis(allylic) disilylated diols, the control of the facial selectivity was attributed to the tendency of the bulky trialkylsilyloxy groups to adopt an antiperiplanar arrangement, generating an internal space hardly accessible to external reagents.[14] In the case of type **2** substrates, the alkoxy substituents are one position further away from the reacting carbon−carbon double bonds, but we believed that the remarkable antifacial selectivity experimentally observed for substrates $\mathbf{2_m e}$ and $\mathbf{2_i e}$ could probably be equally explained in terms of their conformational preference in solution. To support this hypothesis simple theoretical calculations for some of the photoreactive substrates were performed.[15] Molecular mechanics

(14) Saito, S.; Ishikawa, T.; Moriwake, T. *Synlett* **1994**, 279 and references therein.

(MMFF94 force field) was used to evaluate the conformational distribution and the equilibrium geometry of the global minimum and other significant local minima were then recalculated by semiempirical AM1 method.

The mechanism thoroughly accepted for the [2+2] photocycloaddition of an olefin to an enone involves the addition of the ground-state olefin to the triplet excited state $^3\pi\pi^*$ of the enone,[16] generating a diradical intermediate which determines the regioselectivity, and hence the stereoselectivity, of the process.[17] In general, the geometry of the triplet excited state of an enone may differ considerably from its ground state, since the conjugated carbonyl system evolves to a species consisting of an oxallyl radical adjacent to an alkyl radical. Nevertheless, the rigidity of the butenolide ring allowed us to anticipate that the pyramidalization of the β-carbonyl atom would not affect substantially the overall geometry of compounds of type **2**, as it was late confirmed by the calculation results.

Figure 1 shows the optimized geometry for the most representative conformers of the calculated compounds. The most stable conformer $\mathbf{G_me}$ found for compound $\mathbf{2_me}$ presents the bulky trimethylsilyloxy groups in gauche: the conformer keeps the C_2 molecular symmetry, and the syn approach to each individual lactone is extremely hindered. Since both additions of ethylene do not occur simultaneously, the two possible monocyclobutane intermediates anti-**12** and syn-**12** were also calculated. It was found that in their optimized geometries the TMS groups are also in gauche and that the approach to the syn face of the remaining unsaturated lactone is still very hampered. The calculations performed for the bis(ethyl) derivative $\mathbf{2_ma}$ delivered two energetically close conformers $\mathbf{G_ma}$ and $\mathbf{G'_ma}$, with the ethoxy substituents in gauche and in both of them the difference in accessibility to the anti and syn faces of the double bonds is clearly minor. For the rigid dioxolane derivative $\mathbf{2_mc}$, the calculated geometry of the most stable conformer is very similar to the solid-phase structure,[18] and as in the precedent case, for this substrate the approach to the syn face of the reacting olefin does not appear extremely encumbered. These theoretical results are in good agreement with the facial selectivity experimentally observed in the photocycloaddition of ethylene to these subtrates, which seem to correlate with their conformational behavior in the ground state. Analogous calculations were also performed for the 5*S*,5′*S* diastereoisomer of the bis(trimethylsilyloxy) derivative $\mathbf{2_ie}$, giving rise to two energetically very close conformers $\mathbf{G_ie}$ and $\mathbf{A_ie}$, with the bulky groups in gauche and anti relationship, respectively, both of them showing the syn face remarkably blocked.

Cleavage of the Bis(cycloadducts). Once the photocycloaddition study was completed and the best substrate and conditions had been established, the next step to validate the synthetic strategy depicted in Scheme 1 was the cleavage of the central carbon−carbon bond of the bis(cyclobutanes). Hydrolysis of the isopropylidene cycloadducts **6c** and **7c** or desilylation of **6e** and **7e** furnished the corresponding diols **6d** and **7d** in 90% and 97% yield,

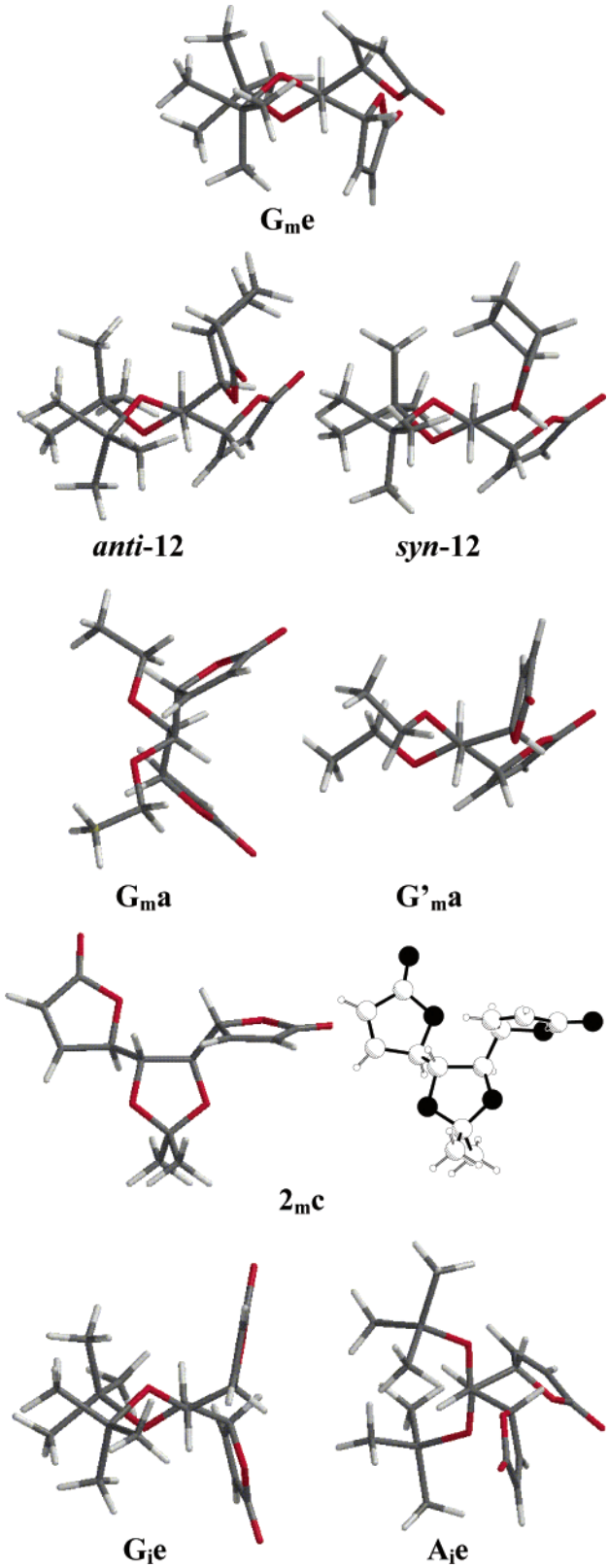


FIGURE 1. Optimized geometry for the most representative calculated conformers for compounds $\mathbf{2_ma}$, $\mathbf{2_mc}$, $\mathbf{2_me}$, and $\mathbf{2_ie}$ and the mono(cyclobutanic) derivatives ***anti*-12** and ***syn*-12**, and solid structure of $\mathbf{2_mc}$.

(15) Theoretical calculations were performed using the PC SPARTAN plus program of Wavefunction, Inc.

(16) Loufty, R. O.; De Mayo, P. *J. Am. Chem. Soc.* **1977**, *99*, 3559.

(17) Broecker, J. L.; Eksterowicz, J. E.; Belk, A. J.; Houk, K. N. *J. Am. Chem. Soc.*, **1995**, *117*, 1847 and references therein.

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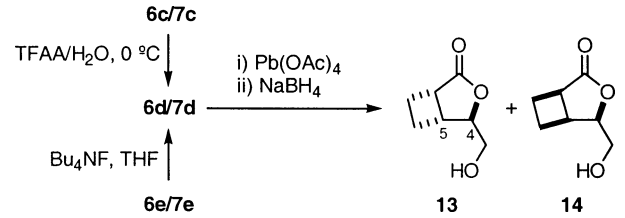
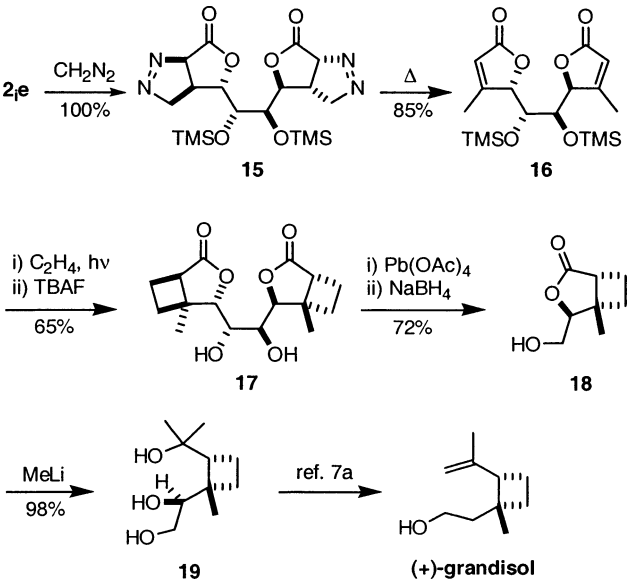
SCHEME 5. Cleavage of the Bis(cyclobutanic) Photoadducts



SCHEME 6. Synthesis of (+)-Grandisol



respectively (Scheme 5). Treatment of different mixtures of these diols with $Pb(OAc)_4$ followed by $NaBH_4$ reduction, provided the mono(lactones) (1*S*,4*R*,5*R*)-, and (1*R*,4*R*,5*S*)-4-hydroxymethyl-3-oxabicyclo[3.2.0]heptan-2-one, **13** and **14**, in 69% overall yield. The proportion of anti and syn mono(lactone) in the final mixture was in agreement with that of *anti-anti* and *anti-syn* bis(cyclobutanes) **6c**/**7c** or **6e**/**7e** in the starting mixture. Column chromatography allowed the isolation of the main component **13**, $[\alpha]_D$ = +49 (*c* 1.6, $CHCl_3$), in pure form and good yield, but the minor syn cyclobutane **14** was always contaminated by the major diastereoisomer, the anti stereochemistry of which was evidenced by the small value of the coupling constant $J_{4,5}$ = 1.5 Hz.[6m]

Formal Synthesis of (+)-Grandisol. Considering the above results, we undertook the synthesis of the target pheromone (Scheme 6). To this end, a methyl group was required at the β-carbonyl position of the unsaturated lactone. We knew from previous work[6j,m] that, in mono(butenolide) substrates, the incorporation of a β methyl group is quite detrimental to the facial selectivity of the photocycloaddition, probably due to its influence on the relative stability of the intermediate diradical species. Therefore, it was crucial to investigate the effect of this β-methyl group on the facial selectivity of the photoreaction in the case of the bis(lactones). The necessary substrate **16** was prepared from **2ie** in 85% yield by treatment with diazomethane, followed by pyrolysis of the corresponding bis(pyrazoline) **15** in refluxing 1,4-dioxane. The NMR spectra of **15** showed a single diastereoisomer of high symmetry, assigned as the *anti-anti*

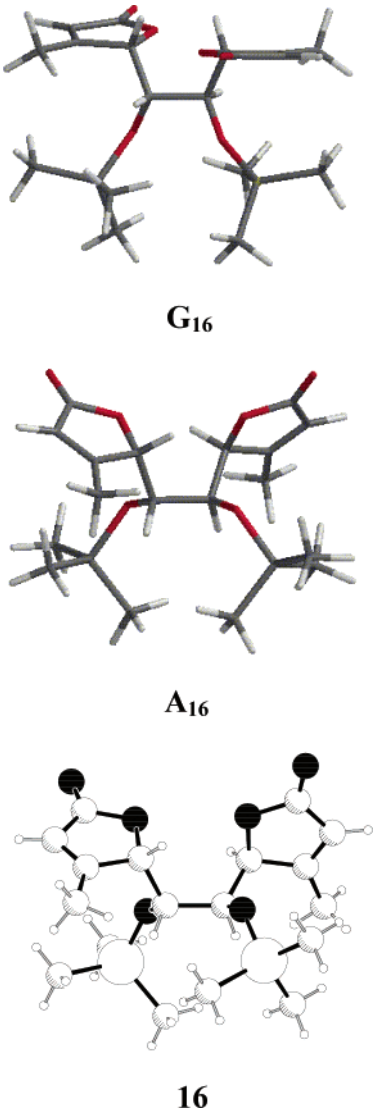


FIGURE 2. Optimized geometry for the most representative calculated conformers and solid structure of compound **16**.

on the basis of previous results,[6m] indicating that the diastereofacial selectivity of the dipolar cycloaddition of diazomethane is complete, although this fact is not relevant for our synthetic purpose.

Theoretical calculations analogous to those described above performed for the methylated bis(butenolide) **16** displayed two close minima $\mathbf{G_{16}}$ and $\mathbf{A_{16}}$ (Figure 2) similar to those found for **2ie**, with the trimethylsilyloxy groups in gauche and antiperiplanar relationship, respectively. In both conformers the approach to the syn face of the olefins is extremely encumbered. An X-ray analysis of **16** showed a structure very similar to the optimized geometry calculated for the conformer $\mathbf{A_{16}}$.[18]

Irradiation of the bis(butenolide) **16** in the presence of ethylene in the usual conditions furnished a crude reaction mixture, which ^1H and ^{13}C NMR spectra showed a main set of signals consistent with a highly symmetric bis(cyclobutane) adduct, along with traces of other products. Since all attempts to purify this material resulted in partial desilylation, the photoreaction crude was directly treated with tetra-*n*-butylammonium fluoride. The corresponding diol **17** could be purified by column

chromatography over silica and isolated in 65% yield for the two steps. Cleavage of the central bond of diol **17** by consecutive treatment with $Pb(OAc)_4$ and $NaBH_4$ in a one-pot procedure afforded the known hydroxylactone **18**[7a] in 72% yield. This correlation demonstrates the *anti-anti* stereochemistry of the precursor bis(cyclobutane). The syn diastereoisomer of **18**, coming from the opposite facial approach to the butenolide during the ethylene photocycloaddition, was not detected. The addition of an excess of methyllithium to lactone **18** yielded 98% of the triol **19**, which had been previously converted to (+)-grandisol.[7a] This new formal synthesis of (+)-grandisol, starting from 3,4-*O*-isopropylidene-D-mannitol, a compound easily available in large scale, has an overall yield of 11%, comparing favorably with previous syntheses.

Conclusions

In summary, a variety of enantiopure bis(α,*β*-butenolides) with C_2 symmetry have been readily prepared from D-mannitol through a bi-directional synthetic strategy, which allows the access to two complementary diasteoisomeric series. The efficiency of the central diol protection as asymmetric inductor in the photocycloaddition of ethylene to both equivalent carbon−carbon double bonds of the unsaturated lactones has been evaluated. Simple theoretical calculations showed a good correlation between the facial discrimination experimentally observed and the conformational preference of the irradiated substrates in the ground state, the bis(trimethylsilyloxy) derivatives displaying the highest diastereofacial selectivity. After the key addition step, cleavage of the central bond in the bis(adducts) renders formal derivatives of *γ*-hydroxymethyl-2(5*H*)-furanone. As an application of this study a new, highly stereoselective synthesis of (+)-grandisol has been completed, starting from 3,4-*O*-isopropylidene-D-mannitol, in 11% overall yield.

Experimental Section

Reaction mixtures were stirred magnetically. Reaction evolution was monitored by TLC with an appropriate solvent. The organic extracts were dried over anhydrous sodium sulfate. Reaction solutions were concentrated using a rotary evaporator at 5−10 Torr. Flash chromatography was performed using silica gel (230−400 mesh). Photochemical reactions were performed on a standard photochemical reactor for internal irradiation with a 125 W medium-pressure mercury lamp fitted in an immersion well, equipped with a Pyrex cooling jacket. ^{1}H NMR spectra were recorded at 250 MHz (unless otherwise stated) and ^{13}C NMR spectra at 62.5 MHz by Servei de Ressonància Magnètica Nuclear de la Universitat Autònoma de Barcelona. Microanalyses and MS were performed by Servei d'Anàlisi Química de la Universitat Autònoma de Barcelona. HRMS were performed by Servei de Masses del Centre d'Investigació i Desenvolupament de Barcelona (CSIC). Compound $\mathbf{3_m b}$ was prepared according to ref 12d.

1,5-Hexadiene Diepoxide (4). To a stirred solution of 1,2-epoxy-5-hexene (1.21 g, 12.4 mmol) in $CHCl_3$ (10 mL) was added a solution of dry *m*-chloroperbenzoic acid (prepared from 6.85 g of 55% by wt, 21.6 mmol) in $CHCl_3$ (30 mL) and the mixture was stirred at room temperature for 24 h. Then the solution was washed with 3M NaOH (2 × 50 mL), dried, filtered and concentrated to give 1.48 g of an oil, which distilled in a rotary oven (75−80 °C/30 Torr) furnished 1.34 g (87% yield) of **4**,[11] as a mixture of *meso*- and (*d*,*l*)-diastereoisomers.

(2*S*,5*S*)-4. (i) 1,2:5,6-Di-*O*-isopropylidene-D-mannitol-3,4-thionocarbonate (20). *N*,*N*′-Thiocarbonyldiimidazole (1.30 g 90% by wt, 7.3 mmol) was added to a solution of 1,2:5,6-di-*O*-isopropylidene-D-mannitol (941 mg, 3.6 mmol) in anhydrous THF (25 mL) under nitrogen, and the mixture was heated at 65 °C for 16 h. Then the solvent was removed and the residue purified by flash chromatography (EtOAc/hexane, 1/3) to give 907 mg (83% yield) of **20**,[19] $[\alpha]_D = -13.7$ (*c* 1.0, $CHCl_3$) [lit.[19a] $[\alpha]_D = -14$ (CH_2Cl_2)].

(ii) *trans*-3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-*threo*-hex-3-enitol (21). 1,3-Dimethyl-2-phenyl-1,3,2-diazaphospholidine (1.2 mL, 6.3 mmol) was added dropwise to **20** (638 mg, 2.1 mmol) under nitrogen and the mixture was stirred at 40 °C for 24 h. Purification of the cold mixture by flash chromatography (CH_2Cl_2/ether, 95/5) furnished 451 mg (94% yield) of **21**,[19a] $[\alpha]_D = +56$ (*c* 3.0, $CHCl_3$) [lit.[19a] $[\alpha]_D = +56.7$ (*c* 3.2, $CHCl_3$)].

(iii) (2*S*,3*E*,5*S*)-Hex-3-en-1,2,5,6-tetrol (22). Compound **22**[12b,20] was prepared from **21** following the procedure in ref 12b.

(iv) (2*S*,5*S*)-1,6-Di(*p*-toluensulfonyloxy)-2,5-dihydroxyhexane (23). Compound **23**[12b,21] was prepared from **22** according to ref 21.

(v) (2*S*,5*S*)-4. NaOH (4 N, 1 mL) was added dropwise to a solution of **23** (353 mg, 0.77 mmol) in THF (5 mL) at 0 °C, and the mixture was stirred at room temperature for 30 min. Then ether (50 mL) was added, and the organic phase was washed with water (30 mL). The organic extracts were dried and the solvent evaporated. The residue was distilled in the rotary oven (75−80 °C/30 Torr) to give 37 mg (42% yield) of (*2S*,*5S*)-4,[22] $[\alpha]_D = -20.1$ (*c* 0.7, $CHCl_3$) [lit.[22] $[\alpha]_D = -26.4$ (*c* 1.90, $CHCl_3$)].

1,2:5,6-Dianhydro-3,4-di-*O*-ethyl-D-mannitol (3_ma). To a mixture of 3,4-di-*O*-ethyl-D-mannitol[12c] (525 mg, 2.2 mmol) and Ph_3P (1.16 g, 4.4 mmol) were added a few drops of CH_2Cl_2 to get an homogeneous blend. Then diethyl azadicarboxylate (DEAD, 727 *μ*L, 4.4 mmol) was added dropwise, the solvent was removed at atmospheric pressure, and the solid residue was heated in a Kugelrohr at 110 °C/0.1 Torr for 3 h. Purification of the distillate by column chromatography (EtOAc/hexane, 1/7) gave 290 mg (65% yield) of $\mathbf{3_m a}$,[12c] $[\alpha]_D = -5.5$ (*c* 3.4, $CHCl_3$) [lit.[12c] $[\alpha]_D = -6.2$ (*c* 1.0, $CHCl_3$)].

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-D-mannitol (3_mc). To a mixture of 3,4-*O*-isopropylidene-D-mannitol[12e] (2.00 g, 9.0 mmol) and Ph_3P (4.75 g, 18.1 mmol) were added a few drops of CH_2Cl_2 to get an homogeneous blend. Then DEAD (3.0 mL, 18.1 mmol) was added dropwise, the solvent was removed at atmospheric pressure and the solid residue was heated in a Kugelrohr at 120 °C/0.1 Torr for 3 h. Purification of the distillate by column chromatography (EtOAc/hexane, 1/7) gave 1.10 g (68% yield) of $\mathbf{3_m c}$,[12e] $[\alpha]_D = -2.0$ (*c* 4.0, $CHCl_3$) [lit.[12c] $[\alpha]_D = -2.3$ (*c* 2.8, $CHCl_3$)].

1,2:5,6-Dianhydro-3,4-*O*-isopropylidene-L-iditol (3_iC). (i) 1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-di-*O*-isopropylidene-D-mannitol (24). To a stirred solution of 3,4-*O*-isoprolpylidene-D-mannitol[12e] (8.88 g, 40.0 mmol) in anhydrous DMF (40 mL) under nitrogen were added imidazole (10.88 g, 4.0 mmol) and *tert*-butyldimethylsilyl chloride (13.20 g, 87.6 mmol), and the mixture was stirred at room temperature for 1.25 h. Then it was diluted with ether (400 mL), and the resulting solution was washed twice with water (300 mL and 150 mL). The organic extracts were dried and the solvent evaporated to give 18.74 g of **24** as an oil, which was used in the next step without further purification; ^{1}H NMR ($CDCl_3$) *δ*

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3.90−3.60 (complex abs., 4H), 1.32 (s, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 109.2, 79.4, 73.1, 64.5, 26.9, 25.9, 18.4, −5.4.

(ii) 1,6-Bis(*tert*-butyldimethylsilyloxy)-2,5-dimethansulfonyloxy-3,4-di-*O*-isopropylidene-D-mannitol (25). Triethylamine (23 mL, 166 mmol) was added to a solution of the crude of **24** (18.73 g) in CH_2Cl_2 (50 mL), the mixture was cooled to 0 °C, MsCl (9.7 mL, 124.5 mmol) was added dropwise, and the mixture was stirred at 0 °C for 20 min. Then ether (500 mL) was added and the solution washed with water (2 × 200 mL). The organic extracts were dried and the solvent removed to give 24.6 g of an oily residue identified as **25** which was used in the next step without further purification; ^{1}H NMR ($CDCl_3$) δ 4.66 (m, 1H), 4.31 (m, 1H), 3.99 (dd, J = 11.7, 3.7 Hz, 1H), 3.81 (dd, J = 11.7, 6.6 Hz, 1H), 3.10 (s, 3H), 1.40 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 111.1, 82.6, 76.3, 62.5, 38.8, 27.0, 25.8, 18.3, −5.5.

(iii) 3_i**c**. To a solution of the crude of **25** (13.35 g) in anhydrous THF (100 mL) under nitrogen was added 1.1 M solution of Bu_4NF (120 mL, 132 mmol) in THF and the mixture was stirred at room temperature for 4.5 h. Water (200 mL) was poured into the reaction mixture, and it was extracted with EtOAc (1 × 400 mL plus 2 × 250 mL). The organic extracts were dried and the solvent evaporated to furnish an oily material which was redissolved in THF/MeOH (1/1) (300 mL). The solution was cooled to 0 °C and 40% aqueous NaOH (15 mL) was added dropwise. The mixture was stirred at the same temperature for 30 min and then diluted with water (300 mL) and extracted with ether (3 × 300 mL). The organic extracts were dried and concentrated, and purification of the solid residue by flash chromatography (EtOAc/CH_2Cl_2, 1/6) furnished 3.62 g (68% overall yield) of compound **3$_i$c**,[12e] $[\alpha]_D$ = −17.0 (*c* 1.0, CH_2Cl_2) [lit.[12e] $[\alpha]_D$ = −17.0 (*c* 2.0, CH_2Cl_2)].

5,5′-(Ethane-1,2-diyl)bis[2(5*H*)-furanone] (5): General Procedure for the Preparation of the Bis(butenolides). To a stirred solution of diisoproplylamine (3.0 mL, 21.8 mmol) in THF (25 mL) at 0 °C under nitrogen was added a 1.6 M solution of BuLi in hexane (13.6 mL, 21.8 mmol), and the mixture was stirred at 0 °C for 30 min. Then a solution of phenylselenoacetic acid (2.42 g, 11.3 mmol) in THF (10 mL) was added dropwise. A white precipitate was immediately formed. Next, a solution of diepoxide **4** (150 mg, 1.3 mmol) in THF (10 mL) was added dropwise, the cooling bath was removed, and the mixture was stirred at room temperature for 6 h. Then, the mixture was acidified with glacial AcOH and the resulting solution was heated at reflux overnight. After neutralization with saturated aqueous $NaHCO_3$, the mixture was extracted with Et_2O (3 × 25 mL).[23] The organic extracts were dried and concentrated to give 564 mg of an oily residue. To a stirred, cold solution of this material and AcOH (a few drops) in THF (5 mL) was added dropwise 30% H_2O_2 (3.0 mL, 26.4 mmol), keeping the temperature below 0 °C. The mixture was stirred at 0 °C for 45 min, then neutralized with saturated aqueous $NaHCO_3$ and extracted with ether (3 × 10 mL). The organic extracts were dried, the solvent evaporated and the oily residue purified by flash chromatography (EtOAc), affording 184 mg (72% yield) of **5**. An analytical sample was obtained by crystallization from EtOAc/hexane (1/9); mp 112−3 °C; IR (KBr) 3107, 2952, 2924, 2854, 1735, 1166, 1103, 1025 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 1H), 6.12 (m, 1H), 5.10 (m) and 5.03 (m) (1H), 2.14−1.97 (complex abs.) and 1.79−1.64 (complex abs.) (2H); ^{13}C NMR ($CDCl_3$) δ 172.5, 155.5, 122.0, 82.4 and 81.9, 28.9 and 28.3; MS *m*/*z* 194 (M^+, 42), 166 (18), 152 (100), 123 (47), 109 (46), 97 (44), 85 (50), 82 (91), 54 (63). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H 5.19. Found: C, 61.79; H, 5.14.

The same procedure starting from **(2*S*,5*S*)-4** furnished **(5*S*,5′*S*)-5**: mp 119−21 °C (EtOAc/hexane); IR (KBr) 3107, 2938, 1743, 1335, 1166, 1110, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.41 (dd, J = 5.7, 1.5 Hz, 1H), 6.11 (dd, J = 5.7, 1.8 Hz, 1H), 5.10 (m, 1H), 2.01 (m, 1H), 1.72 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.5, 155.5, 122.0, 81.9, 28.3; MS *m*/*z* 195 (M^++1, 1), 194 (M^+, 1) 166 (8), 148 (20), 98 (23), 83 (100), 55 (67). Anal. Calcd for $C_{10}H_{10}O_4$: C, 61.85; H 5.19. Found: C, 61.80; H, 5.06. $[\alpha]_D$ = +223 (*c* 0.8, $CHCl_3$).

(5*R*,5′*R*)-5,5′-[(1*R*,2*R*)-1,2-Diethoxyethane-1,2-diyl]bis[2(5*H*)-furanone] (2$_m$a). Following the general procedure for the preparation of the bis(butenolides), bis(epoxide) **3$_m$a** (45 mg, 0.2 mmol) afforded a crude material which purified by flash chromatography (EtOAc) furnished 34 mg (54% yield) of **2$_m$a**: mp 126−8 °C (EtOAc/hexane); IR (KBr) 3107, 2973, 2924, 1757, 1743, 1602, 1342, 1159, 1089, 1032 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (dd, J = 5.5, 1.5 Hz, 1H), 6.20 (dd, J = 5.5, 1.8 Hz, 1H), 5.15 (br d, J = 7.3 Hz, 1H), 3.67 (m, 2H), 3.50 (d, J = 7.3 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 172.0, 155.1, 122.3, 81.4, 81.1, 69.5, 15.5; MS *m*/*z* 199 (49), 171 (89) 125 (51), 116 (100), 113 (56), 97 (84); MS-(CI) *m*/*z* 300 (MNH_4^+, 100), 283 (MH^+, 10). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H 6.43. Found: C, 58.91; H, 6.41. $[\alpha]_D$ = +189 (*c* 1.0, $CHCl_3$).

(5*R*,5′*R*)-5,5′-[(1*R*,2*R*)-1,2-Dibenzyloxyethane-1,2-diyl]-bis[2(5*H*)-furanone] (2$_m$b). Following the general procedure for the preparation of the bis(butenolides), bis(epoxide) **3$_m$b** (89 mg, 0.3 mmol) afforded a crude material which purified by flash chromatography (EtOAc/hexane, 1/4) furnished 25 mg (23% yield) of **2$_m$b** as an amorphous solid: IR (KBr) 3107, 2917, 2882, 1757, 1342, 1166, 1082, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42 (dd, J = 5.8, 1.5 Hz, 1H), 7.32 (m, 5H), 6.10 (dd, J = 5.8, 1.8 Hz, 1H), 5.12 (br d, J = 7.3 Hz, 1H), 4.72 (d, J = 11.3 Hz, 1H), 4.58 (d, J = 11.3 Hz, 1H), 3.50 (d, J = 7.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 172.0, 155.1, 136.5, 128.7, 128.5, 128.3, 122.1, 81.7, 80.5, 75.5; MS *m*/*z* 315 (1), 91 (100); MS(CI) *m*/*z* 424 (MNH_4^+, 100), 407 (MH^+, 7). Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H 5.46. Found: C, 70.37; H, 5.65. $[\alpha]_D$ = +180 (*c* 1.2, $CHCl_3$).

(5*R*,5′*R*)-5,5′-[(1*R*,2*R*)-1,2-*O*-Isopropylidenedioxyethane-1,2-diyl]bis[2(5*H*)-furanone] (2$_m$c). Following the general procedure for the preparation of the bis(butenolides), bis-(epoxide) **3$_m$c** (150 mg, 0.8 mmol) afforded a crude material which purified by flash chromatography (EtOAc/hexane, 2/1) furnished 159 mg (75% yield) of **2$_m$c** as a white solid: mp 109−111 °C (EtOAc/hexane); IR (KBr) 3107, 2987, 2945, 1757, 1602, 1377, 1222, 1210, 1166, 1028 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (dd, J = 5.7, 1.3 Hz, 1H), 6.15 (dd, J = 5.7, 1.8 Hz, 1H), 5.08 (m, 1H), 3.98 (dd, J = 4.0, 1.5 Hz, 1H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 172.3, 153.8, 122.5, 112.0, 82.5, 77.7, 26.9; MS-(CI) *m*/*z* 284 (MNH_4^+, 100). Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.63; H 5.30. Found: C, 58.73; H, 5.37. $[\alpha]_D$ = +270 (*c* 1.0, $CHCl_3$).

(5*R*,5′*R*)-5,5′-[(1*R*,2*R*)-1,2-Dihydroxyethane-1,2-diyl]bis-[2(5*H*)-furanone] (2$_m$d). A solution of **2$_m$c** (1.00 g, 3.8 mmol) in TFAA/H_2O (9/1) (30 mL) was stirred at 0 °C for 4 h. The solvent was evaporated, EtOH/H_2O (1/1) (40 mL) was added to the oily residue and the solvent again removed, and EtOH (40 mL) was added and again evaporated. The overall process was repeated, and the solid residue was washed twice with EtOAc, giving 777 mg (92% yield) of **2$_m$c** as a white solid: mp 142−4 °C (EtOAc); IR (KBr) 3381 (br), 3114, 2924, 1750, 1412, 1320, 1173, 1082, 1039 cm^{-1}; ^{1}H NMR (D_2O) δ 7.75 (dd, J = 5.9, 1.5 Hz, 1H), 6.12 (dd, J = 5.9, 1.5 Hz, 1H), 5.18 (br d, J = 5.9 Hz, 1H), 3.90 (d, J = 5.9 Hz, 1H); ^{13}C NMR (d_4-MeOH) δ 175.3, 158.3, 122.4, 84.9, 73.1; MS *m*/*z* 227 (MH^+, 4), 190 (1), 143 (72), 125 (52), 97 (41), 84 (97), 83 (100), 55 (56). Anal. Calcd for $C_{10}H_{10}O_6$: C, 53.10; H 4.46. Found: C, 52.92; H, 4.48. $[\alpha]_D$ = +290 (*c* 0.5, MeOH).

(5*R*,5′*R*)-5,5′-[(1*R*,2*R*)-1,2-Bis(trimethylsilyloxy)ethane-1,2-diyl]bis[2(5*H*)-furanone] (2$_m$e). To a solution of **2$_m$d** (122 mg, 0.5 mmol) in anhydrous THF (10 mL) under nitrogen was added TMSIm (786 μL, 5.4 mmol), and the mixture was stirred at room temperature for 6 h. The reaction mixture was poured into water (10 mL) and extracted with ether (25 mL). The organic extracts were washed with water (10 mL) and dried,

(23) By acidification of the aqueous phase and extraction with ether, most excess of phenylselenoacetic acid (around 75%) can be recovered.

and the solvent was evaporated, affording 194 mg (97% yield) of **2$_m$e** as a white solid: mp 134−6 °C (EtOAc/hexane); IR (KBr) 3114, 2959, 2910, 1757, 1257, 1159, 1096, 906 cm^{-1}; ^{1}H NMR (d_6-acetone) δ 7.83 (dd, J = 5.9, 1.5 Hz, 1H), 6.22 (dd, J = 5.9, 1.8 Hz, 1H), 5.23 (m, 1H), 4.21(d, J = 4.4 Hz, 1H), 0.17 (s, 9H); ^{13}C NMR (d_6-acetone) δ 172.8, 156.6, 122.8, 84.0, 75.5, 0.5; MS (CI) m/z 388 (MNH_4^+, 100), 371 (MH^+, 27). Anal. Calcd for $C_{16}H_{26}Si_2O_6$: C, 51.86; H 7.07. Found: C, 52.13; H, 6.85. $[\alpha]_D$ = +200 (c 0.5, $CHCl_3$).

(5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-Dihydroxyethane-1,2-diyl]bis-[2(5*H*)-furanone] (2$_i$d). Following the general procedure for the preparation of the bis(butenolides), bis(epoxide) **3$_i$c** (668 mg, 3.6 mmol) afforded a crude material which, when purified by repeated washings with $CHCl_3$ and MeOH, furnished 583 mg (72% yield) of **2$_i$d**[1b] as a white solid.

(5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-Bis(trimethylsilyloxy)ethane-1,2-diyl]bis[2(5*H*)-furanone] (2$_i$e). To a solution of **2$_i$d** (200 mg, 0.9 mmol) in anhydrous THF (10 mL) under nitrogen was added TMSIm (1.3 mL, 8.9 mmol), and the mixture was stirred at room temperature for 4 h. The reaction mixture was diluted with ether (60 mL) and washed with water (3 × 60 mL). The organic phase was dried and the solvent evaporated, affording 321 mg (98% yield) of **2$_i$e**[1b] as an oil, which can be crystallized in EtOAc/hexane (1/9).

(3a*R*,4*R*,5*S*,6*R*,6a*S*)-5,6-Bis(trimethylsilyloxy)-3a,5,6,-6a-tetrahydrospiro[cyclopenta[b]furo-4(5*H*),2′(5′*H*)-furan]-2(3*H*),5′-dione (I). Compound **I** was eventually detected as a byproduct of the former reaction. An analytical sample of **I** could be isolated by flash chromatography (EtOAc/hexane, 2/1) of a 1:1 mixture of **2$_i$e** and **I**, followed by crystallization. **I**: mp 215−7 °C (EtOAc/hexane); IR (KBr) 3535, 3350, 3100, 2938, 1792, 1750, 1187, 1110, 1039 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.18 (d, J = 5.5 Hz, 1H), 6.17 (d, J = 5.5 Hz, 1H), 4.66 (dd, J = 8.8, 2.9 Hz, 1H), 4.25 (dd, J = 6.4, 2.9 Hz, 1H), 3.97 (d, J = 6.4 Hz, 1H), 3.13 (ddd, J = 9.8, 8.8, 3.5 Hz, 1H), 2.51 (dd, J = 18.5, 9.8 Hz, 1H), 2.37 (dd, J = 18.5, 3.5 Hz, 1H), 0.17 (s, 9H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.8, 170.8, 153.9, 123.5, 92.5, 86.1, 81.6, 79.7, 39.9, 27.9, 0.1, −0.1; MS m/z 370 (M^+, 1), 215 (20), 129 (42), 73 (100). Anal. Calcd for $C_{16}H_{26}Si_2O_6$: C, 51.86; H 7.07. Found: C, 52.04; H, 6.70. $[\alpha]_D$ = −20 (c 0.7, THF).

Photocycloaddition of Ethylene to 2$_m$c: General Procedure for the Irradiation of the Bis(butenolides) in the Presence of Ethylene. A solution of **2$_m$c** (96 mg, 0.36 mmol) in freshly distilled acetone (60 mL) was placed in a photochemical reactor. The reactor was immersed in a cooling bath at −78 °C, and a stream of MeOH at −20 °C was circulated throughout the refrigeration jacket. The solution was saturated with ethylene by bubbling it through and then the reactor was connected to a gas buret filled with ethylene. The reaction mixture was irradiated, following the reaction progress by ^{1}H NMR analysis of aliquot samples. After a 4 h irradiation, the solvent was removed and the residue was purified by flash chromatography ($CHCl_3$/hexane, 2/1), giving 75 mg (65% yield) of a white solid identified as a 77/23 mixture of (1*S*,1′*S*,4*R*,4′*R*,5*R*,5′*R*)-, **6c**, and (1*S*,1′*R*,4*R*,4′*R*,5*R*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-di-*O*-isoprolylidendioxyethane-1,2-diyl]bis(3-oxabicyclo[3.2.0]-heptan-2-one), **7c**. **6c** + **7c**: IR (KBr) 2987, 2938, 1771, 1384, 1321, 1236, 1166, 1103, 1068 cm^{-1}; MS m/z 307 (15), 211 (28), 111 (100), 55 (30); MS (CI) m/z 340 (MNH_4^+, 100), 323 (MH^+, 44). Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H 6.88. Found: C, 63.22; H, 6.86. **6c** (data extracted from an enriched sample): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 (m, 1H), 3.78 (dd, J = 3.4, 1.5 Hz, 1H), 3.09 (complex abs., 2H), 2.59−2.00 (complex abs., 4H), 1.33 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 179.6, 110.8, 85.0, 78.7, 38.4, 35.5, 26.8, 24.6, 23.6. **7c** (data extracted from an enriched sample): ^{1}H NMR (400 MHz, $CDCl_3$, observable signals) δ 4.58 (br d, J = 2.4 Hz, 1H), 4.34 (dd, J = 9.1, 6.1 Hz, 1H), 4.27 (dd, J = 6.7, 2.4 Hz, 1H), 3.30 (m, 1H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, observable signals) δ 84.0, 81.7, 81.2, 74.0, 39.4, 39.3, 37.2, 34.7, 23.7, 23.2, 19.5.

Photocycloaddition of Ethylene to 2$_m$a. Following the general procedure, a solution of **2$_m$a** (80 mg, 0.28 mmol) in acetone was irradiated in the presence of ethylene for 6 h. Purification of the reaction crude by flash chromatography (EtOAc/hexane, 1/3) afforded 79 mg of a white solid which analyzed by ^{1}H NMR and GC-MS (Cross-linked 5% PH ME Siloxane, 12 m × 0.2 mm × 0.22 μm, T_1 = 100 °C, t_1 = 1 min, T_2 = 240 °C, rate = 10 °C/min) showed a 1/3/3/1 mixture of (1*S*,1′*S*,2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-4,4′-bis[2-methyl-3,6-dioxabicyclo-[3.2.1]octan-7-one], **9a**, (1*S*,2*R*,4*S*,5*R*)-4-{(1*R*)−(ethoxy)-[(1*S*,4*R*,5*R*)-2-oxo-3-oxabicyclo[3.2.0]hept-4-yl]methyl}-2-methyl-3,6-dioxabicyclo[3.2.1]octan-7-one, **10a**, (1*S*,1′*S*,4*R*,4′*R*,5*R*,5′*R*)-, **6a**, and (1*S*,1′*R*,4*R*,4′*R*,5*R*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-diethoxyethane-1,2-diyl]bis(3-oxabicyclo[3.2.0]heptan-2-one), **7a**. **6a**: MS (CI) m/z 356 (MNH_4^+, 100), 339 (MH^+, 17); (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 1H), 3.66 (dq, J = 8.8, 7.3 Hz, 1H), 3.53 (dq, J = 8.8, 7.3 Hz, 1H), 3.44 (s, 1H), 3.09 (complex abs., 2H), 2.57−2.00 (complex abs., 4H), 1.11 (t, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 180.1, 84.8, 80.6, 69.2, 39.2, 35.2, 24.7, 23.7, 15.6. **7a**: MS (CI) m/z 356 (MNH_4^+, 100), 339 (MH^+, 7); (data extracted from an enriched sample): ^{1}H NMR ($CDCl_3$, observable signals) δ 4.39 (dd, J = 9.5, 5.8 Hz, 1H). **9a**: see below. **10a**: MS (CI) m/z 328 (MNH_4^+, 100), 311 (MH^+, 2); (data extracted from an enriched sample): ^{1}H NMR ($CDCl_3$, observable signals) δ 4.67 (d, J = 5.1 Hz, 1H), 4.49 (m, 1H), 3.95 (q, J = 6.6 Hz, 1H), 3.85 (d, J = 3.6 Hz, 1H).

Photocycloaddition of Ethylene to 2$_m$b. Following the general procedure, a solution of **2$_m$b** (152 mg, 0.37 mmol) in acetone was irradiated in the presence of ethylene for 6 h. Purification of the reaction crude by flash chromatography (EtOAc/hexane, 1/4) afforded 120 mg of a white solid which analyzed by ^{1}H NMR showed a 1/10/5 mixture of (1*S*,1′*S*,4*R*,4′*R*,5*R*,5′*R*)-4,4′-[(1*R*,2*R*)-1,2-dibenzyloxyethane-1,2-diyl]bis(3-oxabicyclo[3.2.0]heptan-2-one), **6b**, (1*S*,1′*S*,2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-4,4′-bis[2-phenyl-3,6-dioxabicyclo[3.2.1]octan-7-one], **9b**, and (1*S*,2*R*,4*S*,5*R*)-4-{(1*R*)−(benzyloxy)-[(1*S*,4*R*,5*R*)-2-oxo-3-oxabicyclo[3.2.0]hept-4-yl]methyl}-2-phenyl-3,6-dioxabicyclo[3.2.1]-octan-7-one, **10b**. **6b**: (data extracted from an enriched sample): ^{1}H NMR ($CDCl_3$, observable signals) δ 4.40 (s, 1H), 3.70 (s, 1H). **9b**: see below. **10b**: (data extracted from an enriched sample): ^{1}H NMR ($CDCl_3$, observable signals) δ 4.70−4.50 (complex abs., 4H), 4.05 (d, J = 4.1 Hz, 1H), 3.77 (t, J = 4.1 Hz, 1H).

Photocycloaddition of Ethylene to 2$_m$d. Following the general procedure, a solution of **2$_m$d** (86 mg, 0.38 mmol) in acetone was irradiated in the presence of ethylene for 7 h. Purification of the reaction crude by flash chromatography (EtOAc) afforded 95 mg (90% yield) of a white solid which analyzed by ^{1}H NMR showed a 49/42/9 mixture of (1*S*,1′*S*,4*R*,4′*R*,5*R*,5′*R*)-, **6d**, (1*S*,1′*R*,4*R*,4′*R*,5*R*,5′*S*)-, **7d**, and (1*R*,1′*R*,4*R*,4′*R*,5*S*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-dihydroxyethane-1,2-diyl]bis(3-oxabicyclo[3.2.0]heptan-2-one), **8d**. **6d** + **7d** + **8d**: IR (KBr) 3360, 2952, 2860, 1778, 1764, 1335, 1166, 1068 cm^{-1}; MS m/z 283 (MH^+, 4), 111 (100), 83 (38), 55 (33). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H 6.43. Found: C, 59.30; H, 6.47. **6d**: (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$, observable signals) δ 4.35 (d, J = 6.6 Hz, 1H), 3.61 (d, J = 6.6 Hz, 1H), 3.25 (m, 1H), 3.12 (m, 1H), 2.68 (d, J = 7.3 Hz, 1H), 2.56−2.13 (complex abs., 4H); ^{13}C NMR (d_6-DMSO) δ 183.0, 87.3, 71.9, 40.0, 37.1. 25.7, 24.5. **7d**: (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$, observable signals) δ 4.47−4.37 (complex abs., 2H), 3.86 (dd, J = 10.4, 1.8 Hz, 1H), 3.70 (dd, J = 7.0, 1.8 Hz, 1H); ^{13}C NMR (d_6-DMSO, observable signals) δ 87.2, 80.0, 72.5, 69.0, 41.4, 40.0, 38.4, 23.9, 20.5. **8d**: (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$, observable signals) δ 4.50 (dd, J = 9.7, 6.2 Hz, 1H), 4.00 (d, J = 9.7 Hz, 1H).

Photocycloaddition of Ethylene to 2$_m$e. Following the general procedure, a solution of **2$_m$e** (196 mg, 0.53 mmol) in acetone was irradiated in the presence of ethylene for 6 h. Purification of the reaction crude by flash chromatography

(EtOAc) afforded 190 mg (85% yield) of a colorless oil which solidifies on standing and analyzed by ^{1}H NMR showed a 97/3 mixture of (1*S*,1′*S*,4*R*,4′*R*,5*R*,5′*R*)-, **6e**, and (1*S*,1′*R*,4*R*,4′*R*,5*R*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-bis(trimethylsilyloxy)ethane-1,2-diyl]-bis(3-oxabicyclo[3.2.0]heptan-2-one), **7e**. Anal. Calcd for $C_{20}H_{34}Si_2O_6$: C, 56.30; H 8.03. Found: C, 56.52; H, 8.11. Repeated flash chromatography furnished an analytical sample of pure **6e**: IR (KBr) 2959, 2868, 1778, 1257, 1166, 1110, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.52 (s, 1H), 3.79 (s, 1H), 3.00 (m, 1H), 2.77 (m, 1H), 2.54−2.07 (complex abs., 4H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 180.0, 84.5, 74.7, 39.5, 35.0, 24.4, 23.5, 0.10; MS *m*/*z* 212 (17), 142 (100), 111(20), 73 (87); MS (CI) *m*/*z* 444 (MNH_4^+, 18), 427 (MH^+, 13), 279 (100). On standing, compound **6e** suffers partial hydrolysis rapidly. **7e**: (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$, observable signals) δ 4.32 (br d, J = 6.9 Hz, 1H), 4.25 (dd, J = 8.8, 5.1 Hz, 1H), 3.94 (dd, J = 8.8, 2.5 Hz, 1H), 3.70 (dd, J = 6.9, 2.5 Hz, 1H), 0.14 (s, 9H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$, observable signals) δ 85.9, 79.9, 71.5, 25.6, 23.2, 21.0.

(1*S*,1′*S*,2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-4,4′-Bis[2-methyl-3,6-dioxabicyclo[3.2.1]octan-7-one] (9a): General Procedure for the Irradiation of the Bis(butenolides) in the Absence of Ethylene. A solution of $\mathbf{2_m a}$ (70 mg, 0.25 mmol) in freshly distilled acetone (60 mL) was placed in a photochemical reactor. The reactor was immersed in a cooling bath at −78 °C, and a stream of MeOH at −20 °C was circulated throughout the refrigeration jacket. Then the solution was irradiated, following the reaction progress by ^{1}H NMR analysis of aliquot samples. After a 6 h irradiation, the solvent was removed and the residue was purified by flash chromatography (EtOAc/hexane, 1/9), giving 55 mg (79% yield) of a colorless solid identified as **9a**: mp 193−5 °C (EtOAc/hexane); IR (KBr) 2987, 2868, 1785, 1454, 1395, 1314, 1264, 1152, 1053, 1018 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.71 (d, J = 5.1 Hz, 1H), 3.99 (q, J = 6.6 Hz, 1H), 3.84 (s, 1H), 2.45 (d, J = 11.7 Hz, 1H), 2.34 (d, J = 4.4 Hz, 1H), 2.25 (ddd, J = 11.7, 5.1, 4.4 Hz, 1H), 1.29 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 178.6, 79.6, 77.8, 69.6, 43.7, 26.2, 22.4; MS *m*/*z* 283 (MH^+, 4), 282 (M^+, 5), 141 (100), 97 (41), 69 (52), 55 (96), 41 (66). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H 6.43. Found: C, 59.66; H, 6.54. $[\alpha]_D$ = −5.8 (*c* 0.7, $CHCl_3$).

(1*S*,1′*S*,2*R*,2′*R*,4*S*,4′*S*,5*R*,5′*R*)-4,4′-Bis[2-phenyl-3,6-dioxabicyclo[3.2.1]octan-7-one] (9b). Following the general procedure, a solution of $\mathbf{2_m b}$ (123 mg, 0.30 mmol) in acetone was irradiated in the presence of ethylene for 4 h. Purification of the reaction crude by flash chromatography (EtOAc/hexane, 1/4) afforded 94 mg (76% yield) of a white solid identified as **9b**: mp 180−1 °C (EtOAc/hexane); IR (KBr) 3022, 2959, 2882, 1785, 1454, 1363, 1314, 1187, 1138, 1046 cm^{-1}; ^{1}H NMR (400 MHz, d_6-benzene) δ 7.22−7.13 (complex abs., 5H), 4.77 (s, 1H), 4.26 (d, J = 4.7 Hz, 1H), 3.41 (s, 1H), 2.34 (d, J = 11.5 Hz, 1H), 2.33 (d, J = 4.7 Hz, 1H), 1.57 (dt, J = 11.5, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 178.0, 141.3, 128.9, 128.4, 125.1, 79.5, 78.8, 74.9, 45.6, 26.3; MS *m*/*z* 279 (20), 167 (45), 149 (100), 71 (23), 57 (31); MS (CI) *m*/*z* 424 (MNH_4^+, 34), 279 (100). Anal. Calcd for $C_{24}H_{22}O_6$: C, 70.92; H 5.46. Found: C, 70.89; H, 5.54. $[\alpha]_D$ = +64 (*c* 1.7, $CHCl_3$).

(1*R*,1′*R*,4*S*,4′*S*,5*S*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-Dihydroxyethane-1,2-diyl]bis(3-oxabicyclo[3.2.0]heptan-2-one) (11d). Following the general procedure, a solution of $\mathbf{2_i e}$ (143 mg, 0.39 mmol) in acetone was irradiated in the presence of ethylene for 8 h. The reaction crude was filtered through a short path of silica gel (EtOAc) and the solvent removed affording 144 mg of a yellowish oil. This residue was solved in THF (25 mL), 2.0 mL of 1 M Bu_4NF in THF was added and the solution was stirred at room temperature for 20 h. Then the reaction mixture was concentrated to dryness and purification of the reaction crude by flash chromatography (EtOAc) furnished 91 mg (83% yield of a white solid identified as **11d**: mp 179−80 °C (EtOAc/hexane); IR (KBr) 3393, 3094, 1748, 1184, 1133, 1104 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.50 (s, 1H), 3.69 (s, 1H), 3.37 (br s, 1H), 3.16 (m, 1H), 2.61−2.00 (complex abs., 4H); ^{13}C NMR (d_6-DMSO) δ 181.3, 84.8, 73.3, 39.3, 37.2, 24.8, 23.8; MS (CI) *m*/*z* 301 (MNH_5^+, 100), 300 (MNH_4^+, 100). Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H 6.43. Found: C, 59.37; H, 6.41. $[\alpha]_D$ = + 10 (*c* 0.8, $CHCl_3$).

Hydrolysis of 6c/7c. A 77/23 mixture of the bis(cycloadducts) **6c** and **7c** (35 mg, 0.11 mmol) were solved in 9/1 TFAA/H_2O (0.9 mL) at 0 °C and stirred at this temperature for 4h. Then the solvent was removed, and the remaining TFAA was eliminated by sequential addition/evaporation of 1/1 EtOH/H_2O (4 mL) and EtOH (twice, 4 mL). Finally, 29 mg (90% yield) of a white solid identified as a 77/23 mixture of **6d** and **7d** were obtained.

Desilylation of 6e/7e. To a solution of a 97/3 mixture of **6e** and **7e** (47 mg, 0.11 mmol) in anhydrous THF (5 mL) under nitrogen was added 1.1 M Bu_4NF in THF (0.6 mL, 0.66 mmol), and the mixture was stirred at room temperature for 5 h. Removal of the solvent and purification of the residue by flash chromatography (EtOAc) furnished 30 mg (97% yield) of a white solid identified as a 97/3 mixture of **6d** and **7d**.

Cleavage of 6d/7d. To a solution of a 3/1 mixture of **6d** and **7d** (100 mg, 0.35 mmol) in EtOAc (20 mL), 95% $Pb(OAc)_4$ (414 mg, 0.89 mmol) was added and the resulting suspension was stirred at room temperature for 2 h. Then, $NaBH_4$ (49 mg, 1.2 mmol) was added and the mixture was stirred at room temperature for 2 h. The reaction mixture was poured into H_2O (25 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic extracts were dried and concentrated and the oily residue was purified by distillation in a Kugelrohr (125−30 °C/0.1 Torr), providing 69 mg (69% yield) of a 7/1 mixture of (1*S*,4*R*,5*R*)-, **13**, and (1*R*,4*R*,5*S*)-4-hydroxymethyl-3-oxabicyclo-[3.2.1]heptan-2-one, **14**, which could not be separated and only a sample of the major isomer **13** could be obtained in pure form. **13**: IR (film) 3437 (br), 2945, 2875, 1757, 1454, 1349, 1293, 1166, 1082, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.43 (ddd, J = 4.5, 2.9, 1.5 Hz, 1H), 3.77 (ddd, J = 12.1, 5.8, 2.9 Hz, 1H), 3.55 (dt, J = 12.1, 4.5 Hz, 1H), 3.13 (m, 1H), 3.01 (m, 1H), 2.62−2.31 (complex abs., 3H), 2.21−2.08 (complex abs., 2H); ^{13}C NMR ($CDCl_3$) δ 181.1, 86.3, 64.1, 39.3, 36.2, 24.7, 23.8; MS *m*/*z* 143 (MH^+, 5), 125 (5), 111 (100), 83 (51), 55 (53); HRMS clcd for $C_7H_{10}O_3$ = 142.0630, found 142.0628. $[\alpha]_D$ = + 49 (*c* 1.6, $CHCl_3$). **14**: (data extracted from an enriched sample) ^{1}H NMR ($CDCl_3$, observable signals) δ 4.55 (ddd, J = 7.6, 5.8, 4.4 Hz, 1H), 3.96 (m, 1H), 3.72 (m, 1H), 3.27−3.11 (complex abs., 2H), 2.59−2−02 (complex abs., 4H), 1.81 (m, 1H).

(3a*S*,3a′*S*,4*S*,4′*S*,6a*R*,6a′*R*)-4,4′-[(1*R*,2*R*)-1,2-Bis(trimethylsilyloxy)ethane-1,2-diyl]bis[3a,4,6,6a-tetrahydro-3*H*-furo-[3,4-*c*]pyrazol-6-one] (15). An ethereal solution of diazomethane (ca. 7.6 mmol) prepared in situ from Diazald (2.18 g, 10.2 mmol) was slowly distilled over a solution of $\mathbf{2_i e}$ (321 mg, 0.9 mmol) in THF (5 mL) at 0 °C, and the mixture was kept in the dark at room temperature for 2 days. Removal of the solvent furnished 393 mg (100% yield) of **15**[1b] as a white solid.

(5*S*,5′*S*)-5,5′-[(1*R*,2*R*)-1,2-Bis(trimethylsilyloxy)ethane-1,2-diyl]bis[4-methyl-2(5*H*)-furanone] (16). A solution of **15** (393 mg, 0.90 mmol) in freshly distilled 1,4-dioxane (40 mL) was heated at the reflux temperature for 7 days. The solvent was evaporated and purification of the residue by flash chromatography (EtOAc/hexane, 1/1) afforded 293 mg (85% yield) of **16**[1b] as a white solid.

(1*R*,1′*R*,4*S*,4′*S*,5*S*,5′*S*)-4,4′-[(1*R*,2*R*)-1,2-Dihydroxyethane-1,2-diyl]bis[5-methyl-3-oxabicyclo[3.2.0]heptan-2-one] (17). Following the general procedure, a solution of **16** (100 mg, 0.25 mmol) in acetone was irradiated in the presence of ethylene for 5 h. Evaporation of the solvent furnished 143 mg of a yellowish oil, identified as the *anti-anti* bis(cycloadduct): ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 1H), 3.74 (s, 1H), 2.48 (complex abs., 3H), 2.04 (m, 1H), 1.77 (m, 1H), 1.29 (s, 3H), 0.12 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 180.8, 82.6, 72.5, 44.1, 43.7, 32.1, 22.0, 18.4, 1.1; MS (CI) *m*/*z* 455 (MH^+, 7), 156 (100). This oil was dissolved in THF (25 mL) and treated with 1 M Bu_4NF in THF (650 μL, 0.65 mmol), and the mixture was stirred at room temperature

for 16 h. The solvent was removed, and the residue was purified by flash chromatography (EtOAc), affording 50 mg (65% yield) of **17**.[1b]

(1*R*,4*S*,5*S*)-4-Hydroxymethyl-5-methyl-3-oxabicyclo-[3.2.0]heptan-2-one (18). To solution of **17** (80 mg, 0.26 mmol) in EtOAc (20 mL) was added 95% $Pb(OAc)_4$ (300 mg, 0.64 mmol), and the mixture was stirred at room temperature for 2 h. Then, $NaBH_4$ (50 mg, 1.3 mmol) was added and stirring was continued for 2.5 h. The reaction mixture was poured into water (25 mL) and extracted with $CHCl_3$ (3 × 50 mL). The organic extracts were dried and evaporated to dryness. The remaining oil was purified by flash chromatography (EtOAc/hexane, 1/1) furnishing 59 mg (74% yield) of **18**.[7a]

(1*S*)-1-[(1*S*,2*R*)-2-(1-hydroxy-1-methylethyl)-1-(methyl)-cyclobutyl]ethane-1,2-diol (19). To a solution of **18** (50 mg, 0.32 mmol) in anhydrous THF (10 mL) at −78 °C was added MeLi 1.6 M in ether (1.2 mL, 1.9 mmol) dropwise, and the mixture was stirred at −78 °C for 1 h and at room temperature for 2 h. Then, saturated solution of NH_4Cl (4 mL) was slowly added, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and EtOAc (3 × 10 mL). The organic extracts were washed with brine, dried, and the solvents removed. Purification of the residue by flash chromatography (EtOAc) furnished 59 mg (98% yield) of **19**[7a] as a white solid.

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Supporting Information Available: Crystal data of compounds **I** and **9a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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