Tandem Cycloadditions of Functionalized Bis-Dienes. An Orthogonal Route to New Dipseudoglycals

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A direct and stereocontrolled access to a new class of conjugated bis-dienes is presented that relies on a double conjugated−elimination reaction induced by the action of strong bases such as *n*-BuLi or KHMDS on bis-α,*β*-unsaturated acetals. These bis-dienes undergo double [4 + 2] cycloadditions with activated dienophiles under thermal conditions. With methyl acrylate, the reaction is totally endo and regiocontrolled with respect to both dienes and exhibits up to 60% inter-ring diastereocontrol when performed under high pressure. Mixed adducts can also be obtained by adding successively two different dienophiles. Again, the endo and regiocontrols are total while the ring-to-ring diastereocontrol depends on reaction conditions but remain, most of the time, relatively low. Double hetero-Diels−Alder reactions have also been performed, yielding bicyclic skeletons of novel 4↔4′ disaccharidic structures. Finally, the corresponding nonconjugated bis-dienes have also been evaluated in cycloadditions. They react at room temperature with NMM or diethyl ketomalonate to provide highly functionalized polycyclic structures in high yields.

Introduction

Because of current fast-growing environmental and energy conservation concerns, highly convergent processes are not considered only for their synthetic elegance but also for the key roles they may be given in modern organic chemistry. Several fruitful new concepts have emerged around these ideas, from the atom economy[1] to the "think simple" chemistry[2], the (quasi-)symmetrical chain growth first proposed by Schreiber,[3,4] or the tandem, domino, cascade, and other serial-primer reactions.[5,6] The combination of these with the tremendous potential of cycloadditions, the scope of which has been progressively extended to the [*m* + *n*] order,[7] adds up complementary interests and renders certain polyenes, particularly bis-dienes, very desirable targets. There are not many examples of acyclic bis-dienes in the literature,[8] albeit original applications to the steroid[9] or the taxoid[10] skeletons have appeared lately. To our knowledge, only two examples of dienes tethered by a heteroatomic link have been reported to date, the first one by Luh and coworkers[11] and the second one by us.[12] We thought compounds such as **3** could be regarded as synthons well-suited to tandem Diels−Alder reactions provided the two sequential cyclizations would be efficient and highly endo, chemo-, regio-, and stereocontrolled (to secure the local control of the four asymmetric centers borne by each new ring). In addition, one should keep in mind that the two independent cyclization steps can occur on the same or opposite sides of the formal symmetry plane of the double diene (Figure 1). The former "syn" process provides a meso adduct while the "anti" one affords its diasteroisomer presenting a C_2-axis. Therefore, this syn vs anti selectivity secures the relative control of the asymmetric centers of one ring with respect to the other. Last, not least, the kinetic of these two successive reactions should, ideally, be sufficiently different to allow the selective

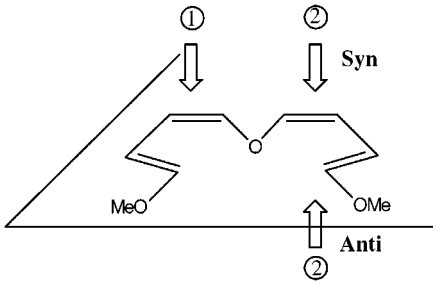

Figure 1. Syn and anti additions with respect to the formal symmetry plane of bis-dienes **3**.

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(1) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1472. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.
(2) (a) Wender, P. *Chem. Rev.* **1996**, *96*, 1−2. (b) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30.
(3) Poss, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17.
(4) In addition to examples in ref 3, see for recent applications of this strategy: (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989−5995. (b) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996−6000.
(5) Reviews: (a) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Eng.* **1993**, *32*, 131−163. (b) Radl, S. *Aldrichim. Acta* **1997**, *30*, 97−100.
(6) For a spectacular example of a naturally occurring cascade sequence, see: Laschat, S. *Angew. Chem., Int. Ed. Eng.* **1996**, *35*, 289−291.
(7) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.
(8) (a) Kraus, G.; Taschner, M. *J. Am. Chem. Soc.* **1980**, *102*, 1974−1977. (b) Goldberg, D.; Hansen, J.; Giguere, R. *Tetrahedron Lett.* **1993**, *34*, 8003−8006. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176. (d) Aime, S.; Oulyadi, H.; Maddaluno, J.; Venturello, P. *Org. Lett.* **1999**, *1*, 1631−1634.
(9) Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844−851.
(10) Winkler, J. D.; Kim, H. S. *Tetrahedron Lett.* **1995**, *36*, 687−690.
(11) Chen, R. M.; Weng, W. W.; Luh, T. Y. *J. Org. Chem.* **1995**, *60*, 3272−3273.
(12) (a) Guillam, A.; Maddaluno, J.; Duhamel, L. *J. Chem. Soc. Chem. Commun.* **1996**, 1295−1296. (b) Martin, C.; Maddaluno, J.; Duhamel, L. *Tetrahedron Lett.* **1996**, *37*, 8169−8172. (c) Guillam, A. Ph.D. Thesis, Université de Rouen, 1997.

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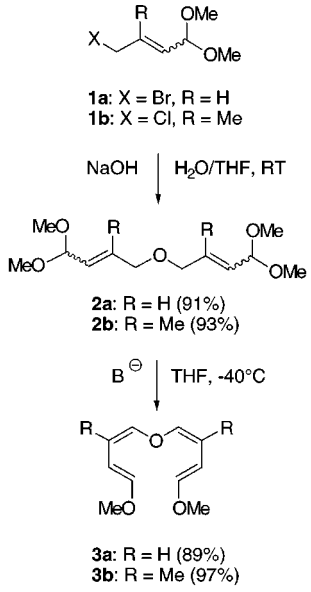
addition of two different dienophiles. The results presented here tend to evaluate the reactivity and various types of selectivities that bis-dienes of type **3** can afford.

Results and Discussion

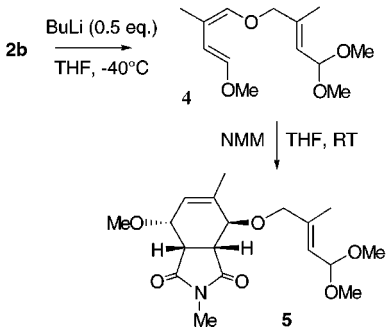
Access to Starting Materials. Treatment of α,β-unsaturated haloacetals **1**[13] in THF as an heterogeneous mixture with aqueous sodium hydroxide at room temperature provides bis-acetal **2** in very good yields (eq 1).[12a]



(1)

The configuration of **2a** is 2*E*,2′*E*, while that of **2b** roughly follows the statistical combination of the 75:25 *E*/*Z* **1b** mixture (2*E*,2′*E*/2*E*,2′*Z* ≈ 60:40), the 2*Z*,2′*Z* isomer being hardly detected. Treatment of these acetals by 2.5 equiv of *n*-BuLi at −40 °C in THF triggers a double deprotonation−conjugated elimination process that leads, in an almost quantitative single step, to bis-dienes **3** (eq 1).[12a,14] A KHMDS solution can also be used in the case of **2a**. The stereochemical outcome of the elimination step does not depend on the homogeneity of the precursor, the (1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E*) ratio being 90:10 and 92:8 for **3a** and **3b**, respectively.[15] Despite bearing four enol ether moieties, bis-dienes **3** are reasonably stable entities. Their sensitivity to moisture and dioxygen prevents chromatography or storage when concentrated. The best chemical yields have been obtained by putting **3** directly into reaction with various activated dienophiles, in the presence of a little hydroquinone.[16]

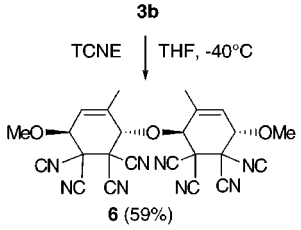
A single deprotonation of bis-acetal **2b** has also been attempted; using only 1 equiv *n*-butyllithium at −40 °C leads to a mixture of starting material, mono-acetal and bis-diene. By contrast, decreasing the amount of base to 0.5 equiv provides, at the same temperature, a 60:40 mixture of starting bis-acetal and mono-diene **4** (eq 2).



(2)

Interestingly, the stereochemical ratio changed from 2*E*,2′*E*/ 2*E*,2′*Z* ≈ 60:40 in starting acetal **2b** to 100% 2*E*,2′*E* in the recovered one. This result suggests that *n*-butyllithium deprotonates slightly more rapidly the 2*E*,2′*Z* isomer of **2b** and that this reaction takes place first on the *Z*-side of the molecule, providing a single 1*Z*,3*E*,2′*E* trienic structure, **4**.[17]

Cycloadditions and Selectivities. Most of our (2 × [4 + 2]) studies have been conducted with bis-diene **3b** because of the easy access to its precursor. It has been first reacted with the very reactive tetracyanoethylene (TCNE) to avoid the endo and regio-selectivity problems. The double addition on **3b** in THF at −40 °C for 15 min provides adduct **6**, as a single diastereoisomer, in fair yields (eq 3).[18] The ^{1}H and ^{13}C NMR spectra of **6** feature



(3)

signals corresponding to a single cyclohexenic system due to the presence of a C_2 molecular axis, as unraveled by an X-ray crystallographic analysis (Figure 2). The ORTEP plot shows that both cyclohexenes adopt a half-chair

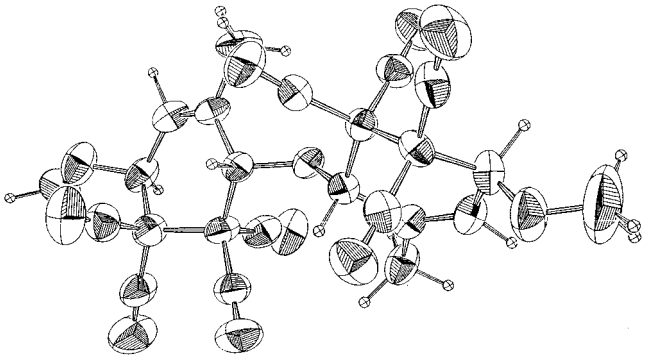


Figure 2. ORTEP plot for bis-adduct **6**.

(13) Bromoacetal **1a** is prepared in two steps from crotonaldehyde (Gaonac′h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, *56*, 4045−4048) while chloroacetal **1b** is an industrial intermediate. Both can also be also conveniently prepared from acetoxybutadiene and acetoxyisoprene; see: Deagostino, A.; Balma Tivola, P.; Prandi, C.; Venturello, P. *Synlett* **1999**, 1841−1843.

(14) Previous examples of elimination-based diene synthesis: (a) Mioskowski, C.; Manna, S.; Falck, J. R. *Tetrahedron Lett.* **1984**, *25*, 519−522. (b) Fujiwara, S.; Katsumura, S.; Isoe, S. *Tetrahedron Lett.* **1990**, *31*, 691−694. (c) Venturello, P. *J. Chem. Soc. Chem. Commun.* **1992**, 1032−1033. (d) Mason, P. H.; Emslie, N. D. *Tetrahedron*, **1995**, *51*, 2673−2678. (e) Maddaluno, J.; Gaonac′h, O.; Marcual, A.; Toupet, L.; Giessner-Prettre, C. *J. Org. Chem.* **1996**, *61*, 5290−5306.

(15) The double bond configurations of these compounds have been deduced from NMR coupling constant measurements and NOE experiments and the isomer ratios confirmed by GC and GC/MS analysis.

(16) Broekhuis, A. A.; Scheeren, J. W.; Nivard, R. J. F. *Rec. Trav. Chim. Pays-Bas* **1980**, *99*, 6−12.

(17) For a detailled theoretical analysis of a comparable deprotonation step, see: Fossey, J.; Ghigo, G.; Tonachini, G.; Venturello, P. *Tetrahedron* **1997**, *53*, 7937−7946.

(18) Together with small amounts (≈8% from ^{1}H NMR integration) of the adduct derived from *EZE′E′* isomer **3**.

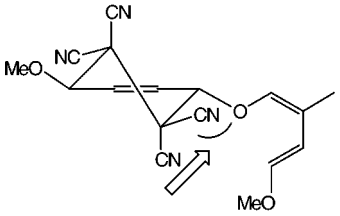
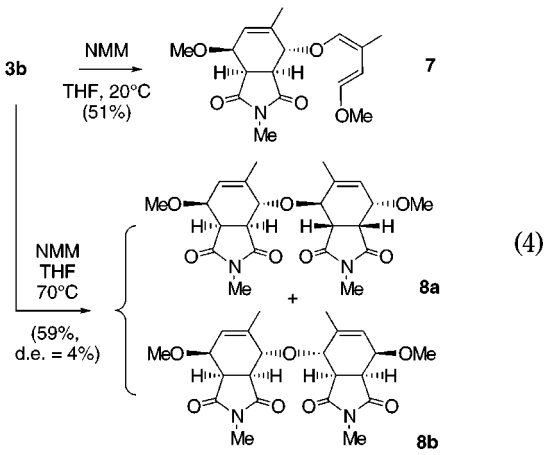


Figure 3. Possible origin of the diastereodifferenciation during the second cycloaddition step leading to bis-adduct **6**.

conformation with all alkoxy groups in pseudoequatorial positions. The total diastereoselectivity observed in this case can tentatively be ascribed to one of the equatorial cyano groups on the intermediate monoadduct that would prevent the syn approach of a second TCNE molecule along the pro-meso face of the remaining dienic moiety under its s-cis conformation (Figure 3).[19] We have no proof about the system's preference for such a conformation; however, molecular models indicate that, on steric grounds, this is one of the very rare s-cis arrangement possible for the diene.

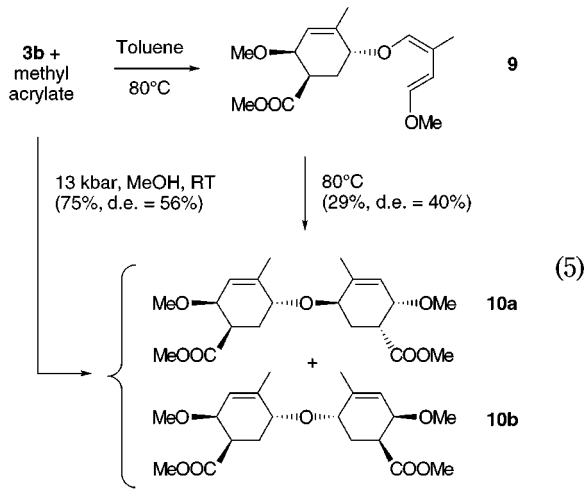
We then turned our hands to more standard dienophiles such as NMM. In THF, the tandem addition on **3b** can be run in one or two steps, depending on the temperature. At reflux in THF, both cycloadditions take place and the double adduct **8** is recovered in 59% yield after 48 h, but in 4% de only (eq 4). A small amount



(4)

(13%) of a third diastereosiomer **8c**, derived from the 1*Z*,3*E*,1′*E*,3′*E* starting bis-diene, has also been isolated and characterized in one case. The NMR spectra show that, for both **8a** and **8b**, each bicyclic unit derives from an endo approach and adopts a convex boat conformation, a result fitting those obtained for adducts derived from 1,4-dialkoxydienes.[20] Thus, the lack of control necessarily stems from the syn/anti relative approaches of the two NMM molecules and may be due to the convex boat topology of intermediate adduct **7**, which would poorly differentiate the remaining diene's faces. Actually, **7** can be prepared selectively using only 1 equiv of NMM at 20 °C; it can be isolated by flash chromatography on silica gel in 51% yield[21] (eq 4) and its NMR spectrum is indeed consistent with a convex-boat conformation. Advantage can be taken from this easy access to **7** to involve a different dienophile in the second cycloaddition step, as presented below.

Methyl acrylate certainly constitutes a synthetically more attractive partner in these reactions. However, at least three new problems arise with this reagent: (i) its reactivity is significantly lower than that of TCNE or NMM, (ii) the regioselectivity becomes difficult to predict,[20] and (iii) the endoselectivity is also difficult to predict.[22] Heating **3b** at 80 °C in a 1:1 mixture of toluene and methyl acrylate leads to the relatively rapid consumption of the bis-diene, yielding monoadduct **9**, which, in turn, slowly adds to a second methyl acrylate molecule to provide double-adducts **10** (eq 5). After 10 days, 45%



(5)

9 still remains in the medium and **10** is isolated as a 70:30 diastereoisomeric mixture, in a mediocre 29% yield after flash chromatography. This lack of reactivity could be circumvented by resorting to high pressure: under 13 kbar, **3** reacts at room temperature in a 1:1 mixture of methanol and methyl acrylate, yielding **10** in 75% yield after 72 h. The selectivity is marginaly improved (78:22) and remains in favor of the same isomer. The NMR performed on each isomer clearly shows that they are fully symmetrical, the endo and regiocontrols associated with the two successive addition steps being therefore identical and total.

The major isomer crystallizes out of the oily mixture after 3 days at −20 °C. The minor isomer crystallizes in turn from the enriched oil at the same temperature after a few days. Both isomers can then be recrystallized from a 70:30 mixture of petroleum ether and ethyl acetate. The X-ray performed on both isomers provided the ORTEP plots of Figure 4, which indicate that the terminal (*E*) methoxy group behaves as the directing group, a result in line with our own observations on (*E*,*Z*)-1,4-dialkoxydienes.[20] The ORTEP plots also confirm the endoselections deduced from the NMR data and show that the main isomer **10a** is C_2 symmetrical (Figure 4A) while **10b** is meso (Figure 4B). Worthy of note is the half-chair conformation of the two cyclohexenes of both isomers, which places the methoxy and the linking oxygen in pseudoaxial orientations, while the ester remains equatorial. Such a conformation is in excellent agreement with the NMR data for intermediate **9**.

(19) For a comparable discussion see: Lubineau, A.; Queneau, Y. *J. Org. Chem.* **1987**, *52*, 1001−1007.

(20) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.*, **1998**, *63*, 5110−5122.

(21) This modest yield is probably due to partial hydrolysis of the dienol diether moiety on silica; adding 1% NEt_3 to the eluant induces a quantitative aromatization of **7** into phthalimide.

(22) Mellor, J. M.; Webb, C. F. *J. Chem. Soc., Perkin Trans. 2* **1974**, 17−22.

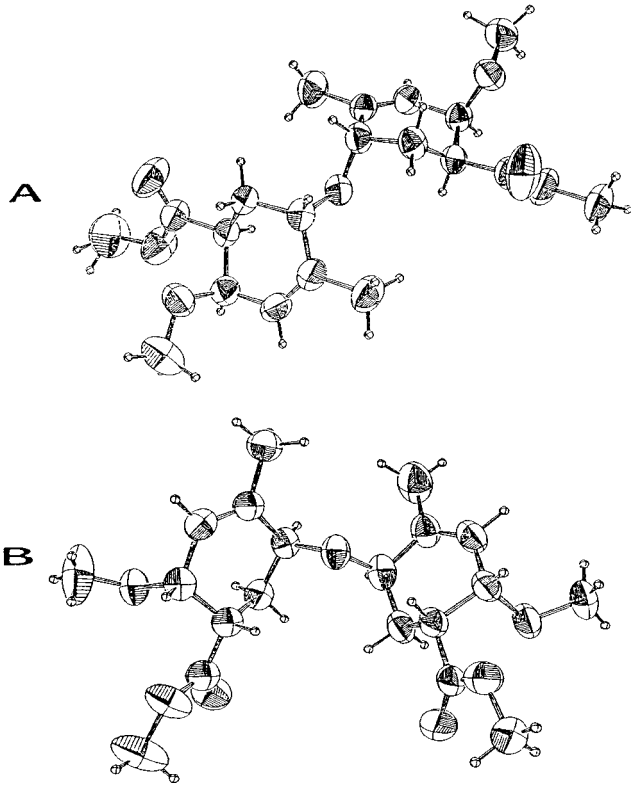


Figure 4. ORTEP plots for bis-adducts **10a** (A) and **10b** (B).

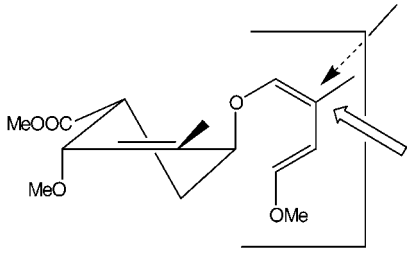


Figure 5. Possible origin of the diastereodifferenciation during the **9** → **10** step.

The diastereoselectivity in favor of **10a** can be accounted for considering that the sterically demanding neighborhood in **9** leaves little liberty for the diene to adopt a s-cis conformation. A likely threshold form is depicted in Figure 5, in which the diene (linked through a pseudoaxial oxygen) seems easier to approach from the double bond (flat) side of the half-chair. Actually, **9** can be obtained selectively (in 55% yield after chromatography) by placing **3b** with 1 equiv of methyl acrylate under the above hyperbaric conditions for 2 days. Here again, the ease with which the reaction can be quenched at its first stage prompted us to prepare mixed adducts from **9**, as described below.

It was tempting at first to consider the addition of two different dienophiles through a sequential diene synthesis−cycloaddition approach. The results of eq 2 put into evidence the practical limits of this strategy: if the monoelimination and the first cycloaddition both take place and provide stereoselectively the expected adduct **5**, the yields are low and decrease the scheme's overall efficiency. We therefore decided to concentrate on the possibilities offered by the difference between successive reactivities of **3b** dienes, an approach that proved more rewarding.

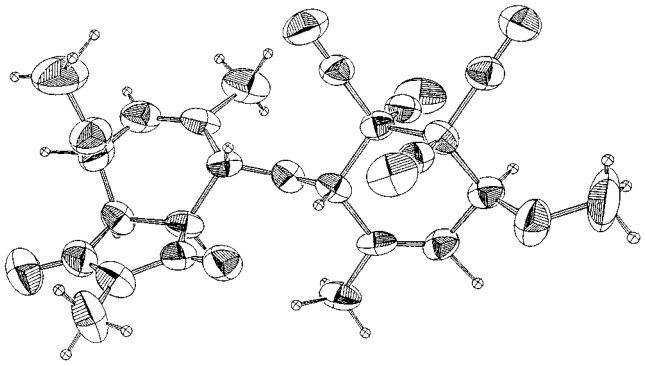
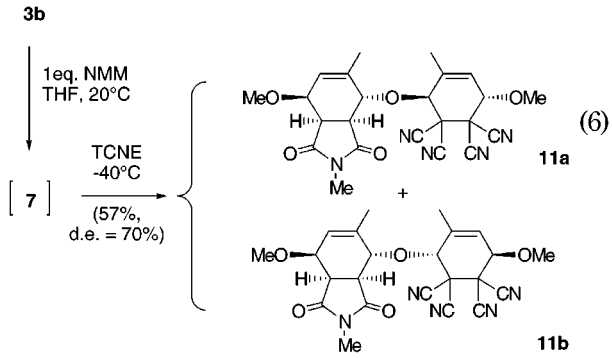


Figure 6. ORTEP plot for mixed adduct **11**.

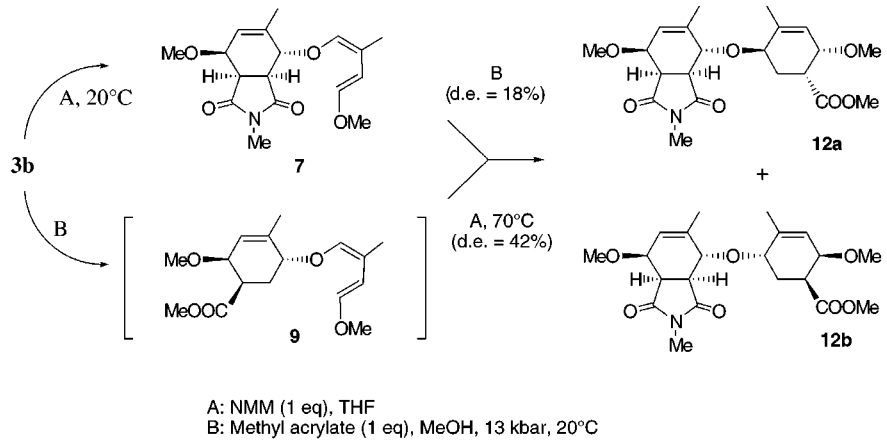
Our first dienophile-scrambling experiment was performed with monoadduct **7**. TCNE reacts with **7** at −40 °C, in a one-pot procedure, leading, after 15 min, to a mixed double-adduct **11** in 57% yield after purification and 85:15 selectivity (eq 6). As above, the main isomer



(6)

of **11** crystallized out of the oily mixture after 1 week at −20 °C and was then submitted to an X-ray single-crystal analysis. The ORTEP plot (Figure 6) as well as the NMR data show that the fused-bicyclic part of the molecule adopts a convex-boat conformation (with an axial methoxy group) derived from an endo approach comparable to that above, while the cyclohexene keeps the half-chair arrangement that puts both the methoxy and the connecting oxygen in pseudoequatorial positions. The diastereoselectivity we report indicates that even the NMM-derived convex-boat arrangement can act as a fair inducer, provided the second addition takes place at low temperature.

In a second set of experiments, **7** was reacted with methyl acrylate. To take into account the lesser reactivity of this second dienophile, the reaction was performed under 13 kbar conditions (eq 7). After 3 days, the expected mixed adducts **12** are obtained in 53% yield and 59:41 selectivity. Those can be easily separated by flash chromatography, both leading to white crystalline compounds. From a conformational point of view, NMR suggests that **12** combine the endo convex-boat bicyclic moiety described above and the half-chair cyclohexene associated with acrylate adducts in which both oxygenated groups are axial. This can be proposed on the basis of the comparison between chemical shifts and coupling constants in **12** and those obtained for corresponding adducts derived from comparable mono-dienes.[20] Thus, the maleimide-derived fragment of **12** compares nicely to a related bicyclic adduct (see compound **18b** in ref 20). The acrylate-derived cyclohexene has been characterized through its coupling constants: the anomeric proton H^4



(7)

(δ = 3.97 ppm in **12a**, 3.96 ppm in **12b**) is coupled to the ethylenic H^3 (^2J = 4.7/4.5 Hz), indicating that H^4 is pseudoequatorial, and therefore the methoxy group is pseudoaxial (eq 7). On the other hand, H^5 (δ = 2.89 ppm in **12a**, 2.91 ppm in **12b**) also couples with H^4 (^2J = 4.6 Hz in **12a**, not measured in **12b**) and axial H^6 (^2J = 12.8 Hz in **12a**, not measured in **12b**), figures supporting an axial arrangement for H^5 and therefore an equatorial one for the ester group. Finally, both axial (δ = 2.03 in **12a**, 2.00 in **12b**) and equatorial (δ = 2.20 in **12a**, 2.31 in **12b**) H^6 are coupled to H^1 (^2J = 3.3/4.0 Hz for H^6 ax., ^2J = 2.6/? Hz for H^6 eq.), all constants in fair agreement with a pseudoequatorial position for H^1 and therefore a pseudoaxial one for the bridging oxygen.

Actually, **12** can also be prepared the other way around, starting from acrylate intermediate monoadduct **9**. The NMM addition on **9** is complete at reflux of THF in 3 days, leading to **12** in 56% yield and as a 71:29 mixture, still in favor of the same isomer (eq 7). We did not run X-ray crystallography on these samples, but in light of the above results, it is reasonable to assume that the C_2-type isomer **12a** is the major one, the selectivity being driven either poorly by the convex-boat structure (**7** → **12**) or more efficiently by the half-chair cyclohexene (**9** → **12**).

We then considered the application of these bis-dienes to heterocycloadditions, in an attempt to widen their synthetic scope. Such a double [4 + 2] assembling can indeed provide new grounds to approach disaccharidic skeletons, following a disconnection orthogonal to the usual sugar−sugar coupling strategy (Figure 7). The hetero-Diels−Alder route to mono-saccharides has been thoroughly explored, both in its direct[23] or inverse-demand[24] versions, but never, to our knowledge, has a tandem version been considered.[25]

Ethyl glyoxylate was likely to constitute a fine hetero-dienophile when combined with **3b** since the preliminary studies performed on simple (*E*,*Z*)-1,4-dialkoxydienes had

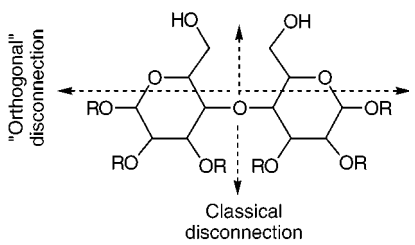
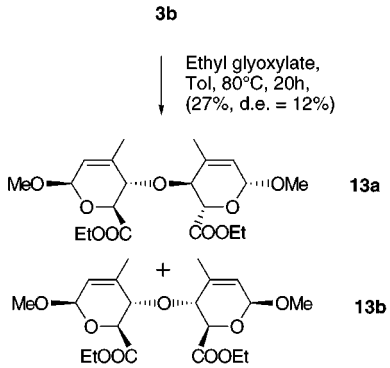


Figure 7. Principle of an "orthogonal" route to disaccharidic structures.

shown that the regioselectivity is total with this ester, the carboxy function being found ortho to the group borne by the original *E* bond, while the endo-to-exo ratios measured on the resulting dihydropyrans remained high enough to be of synthetic interest.[12c] The double cycloaddition has been performed by heating a commercial solution of ethyl glyoxylate (8 equiv) in toluene with **3b** at 80 °C for 20 h (eq 8). A mixture of diastereoisomers is



(8)

recovered in 27% yield of adducts **13** (in a 56:44 ratio) after flash chromatography. They easily separate from the other isomers (probably including adducts derived from endo/exo and exo/exo double additions) but could not be separated from the each other. However, the NMR spectrum of the mixture is easy to analyze since the most important signals for **13a** and **13b** are resolved. Both

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(24) See inter alia: (a) Schmidt, R. R. *Pure Appl. Chem.* **1987**, *59*, 415−424. (b) Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem., Int. Ed. Eng.* **1994**, *33*, 980−982. (c) Dondoni, A.; Kniezo, L.; Martinkova, M. *J. Chem. Soc. Chem. Commun.* **1994**, 1963−1964. (d) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1996**, *37*, 4007−4010.

(25) Several di- and trisaccharides have been prepared through a single heterocycloaddition step involving sugar-bound dienes: (a) David, S.; Eustache, J.; Lubineau, A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2274−2278. (b) David, S.; Lubineau, A.; Thieffry, A. *Tetrahedron* **1978**, *34*, 299−304. (c) David, S.; Lubineau, A.; Vatèle, J. *J. Chem. Soc. Chem. Commun.* **1978**, 535−537. (d) David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230−2234. (e) Larsen, D. E.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1841−1852.

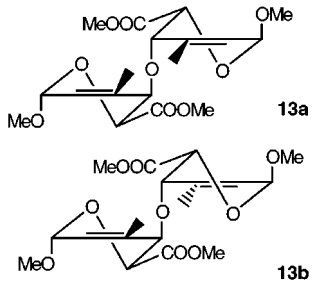
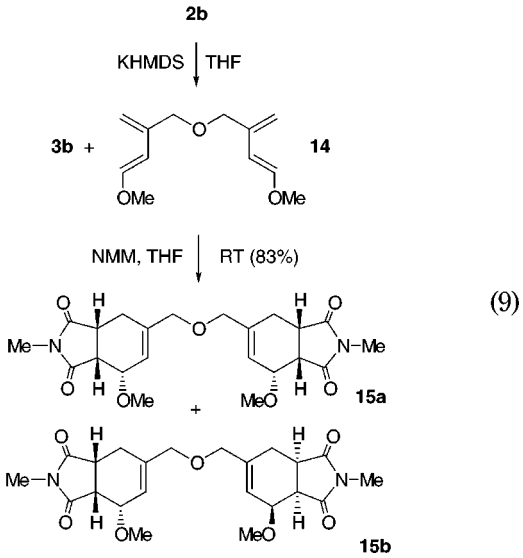


Figure 8. Possible conformations of bis-adducts **13**.

isomers are fully symmetrical and thus result from two cyclization steps presenting identical stereochemical characteristics. A set of irradiations and coupling constant measurements indicates that both isomers result from the same endo and regiocontrolled approach of ethyl glyoxylate. Therefore, the topological difference seems once more to be due to the meso vs C_2 symmetry problem (Figure 8). As expected from above experiments, the terminal methoxy group directs the regiocontrol and leads to a dipseudoglycal, precursor of an unknown family of 4↔4′ "disaccharides".[26]

Conformationally, the two isomers consist of two half-chairs with all pseudoaxial substituents (Figure 8). The combination of the anomeric effect with the allylic $A^{1,2}$ strain induced by the vinylic methyl group can account for this axial preference. Comparable observations have been reported previously for monocyclic[27] or disaccharidic[28] dihydropyrans.

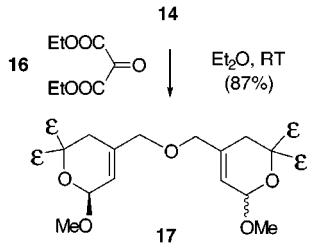
Finally, we also tried to evaluate the reactivity of allylic bis-dienes **14**. A bulkier base such as KHMDS induces a competitive deprotonation on the vinylic methyl group of bis-acetal **2** and leads to (*E*,*E*′) **14**, as a 50:50 mixture with **3b**, in 95% global yield (eq 9). A silica gel chromatography of the mixture provides selectively **14** in 37% yield, **3b** being totally hydrolyzed on the column. Compound **14** being more stable than **3**, it keeps overnight in solution at −20 °C in the presence of hydroquinone.



(9)

Tetraene **14** was first reacted with 2.0 equiv of NMM in THF at rt. After 15 min the expected double-adduct **15** is recovered in 83% yield as an (apparent) 59:41 mixture of diastereoisomers (eq 9). No intermediate monoadduct could be observed in this case, both additions being equally rapid. The two isomers could not be separated by flash chromatography, but comparison of the NMR data of their mixture with above compounds clearly indicates that both bicycles of both isomers derive from an endo approach and adopt the same convex-boat conformation found in **7**, **8**, and **12**. It is therefore very likely that, as described above, the syn vs anti approach of both dienophile molecules with respect to **14** leads to a meso vs C_2 symmetry difference. The modest diastereoselectivity observed did not prompt us into further investigations to assign topologies to isomers of **15**. Danishefsky's diene type pattern of **14** probably explains the excellent reactivity of this compound in which (i) the conjugation of the methoxy group with the dienic system is not counterbalanced any more by another electron-donor group in the 4-position but rather reinforced by the alkoxymethyl group influence in the 3-position and (ii) this substitution in the 3-position contibutes to stabilize the s-cis conformation of each diene.

We also thought advantage could be taken of the excellent reactivity of **14** in heterocycloadditions under mild conditions. It was condensed onto 2 equiv of diethyl ketomalonate **16** in ether at rt. After 3 days, the double adduct **17** is obtained as an unseparated 50:50 mixture[29] of two diastereoisomers in 87% yield after flash chromatography (eq 10). There again, the NMR experiments



(10)

performed on the mixture lead to the conclusion that the stereoheterogeneity in these fully symmetrical compounds comes from the meso/C_2 difference. As expected, the regioselectivity is controlled by the terminal methoxy group and leads to a dipseudoglycal structure. The NMR data suggest that, for both isomers, **17** conformation consists of two half-chairs with pseudoaxial methoxy groups (Figure 9). The measurement of the coupling constants[30] between the acetalic proton H^1 ($\delta = 5.08$ ppm) and the ethylenic one H^2 ($\delta = 5.66$ ppm, $^3J = 2.4$ Hz) and between H^1 and the remote equatorial H^4 ($\delta = 2.24$ ppm, $^5J = 2.0$ Hz) indeed suggests that H^1 is pseudo-equatorial, therefore placing the anomeric methoxy group in a pseudoaxial position. This is supported by a NOESY

(26) In absence of any anomeric linkage, the compounds derived from **12a**/**12b** cannot be considered as disaccharides.

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(29) This 50:50 ratio has been deduced from the splitting of one single peak (tertiary ethylenic carbon at 119.5/119.7 ppm) in the ^{13}C NMR spectrum of **17**. The diastereoselectivity of this step is therefore to be considered as uncertain.

(30) These measures of relatively small coupling constants have to be done while decoupling the vinylic methyl group to simplify the signals of interest. The values obtained for these constants are in agreement with published data on comparable systems; see for instance: (a) Achmatowicz, O.; Bukowski, P. *Rocz. Chem.* **1973**, *47*, 99−113. (b) Dawe, R. D.; Fraser-Reid, B. *J. Org. Chem.* **1984**, *49*, 522−528. (c) Takeda, K.; Nakamura, H.; Ayabe, A.; Akiyama, A.; Harigaya, Y.; Mizuno, Y. *Tetrahedron Lett.* **1994**, *35*, 125−128.

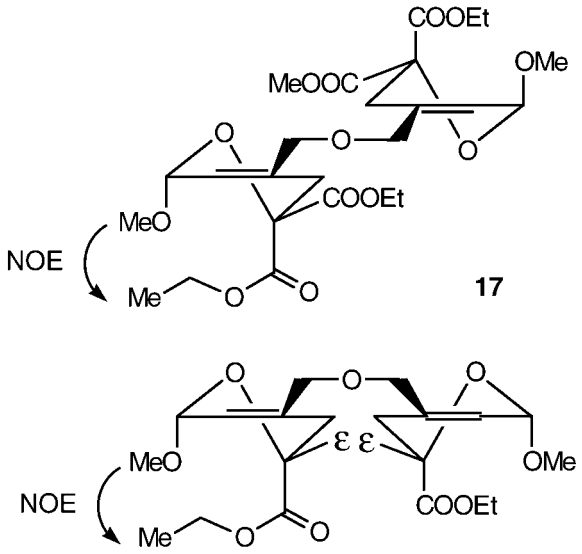

Figure 9. Possible conformation of bis-adduct **17**.

experiment displaying a strong correlation between the methoxy group and the terminal methyl fragment of the close axial ethyl ester (Figure 9).

The reactivity of **14** is noteworthy: this bis-diene adds twice and in high yields onto ketone **16** in the absence of any catalytic, thermal, or hyperbaric activation and provides access to precursors of an unknown family of pseudodisaccharides presenting a 3↔3′ coupling pattern.

Concluding Remarks

The bis-dienes we describe can be considered as multifunctional synthons, obtained in one step from simple precursors and that give access to fairly complex molecular structures in a small number of steps. They behave as fine partners in tandem ($2 \times [4 + 2]$) cycloadditions, yielding polycyclic adducts thanks to their good thermal reactivity, associated with generally high endo, chemo-, and regioselectivities. Depending on dienophile and addition conditions, the diastereofacial selectivity steming from the syn/anti approach of the two dienophiles onto the double diene average plane can also be controlled to some extent. For the conjugated bis-dienes, the difference of reactivity between the two dienic moieties is large enough to allow two successive single additions involving two dienophiles which can be the same or different. The extension of these results to hetero-Diels−Alder cycloadditions affords, in modest yields and selectivities, dipseudoglycals that can be regarded as direct precursors to unknown disaccharides. Therefore, this approach provides an orthogonal route to new families of carbohydrate-related compounds[31,32] and new oligosaccharides[33] the importance of which has been underlined lately. The application of these bis-dienes to an hetero-Diels−Alder/Diels−Alder sequence of reaction would also set the stage for an easy approach to pseudodisaccharides, that we are currently exploring.

Experimental Section

General Aspects. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz; chemical shift (δ) are given in parts per million (ppm) and the coupling constants (J), in hertz. The solvent was deuteriochloroform or deuteriobenzene. IR spectra were realized by transmission. Gas chromatography analyses were performed on a high-resolution DB-1 type column (30 m, 0.25 mm i.d., 0.25 μm coating). GC/MS analyses were performed on an instrument equipped with the same column. The mass spectra under electron impact conditions (EI) were recorded at 70 eV ionizing potential; methane (CH_4), isobutane (t-BuH), or ammonia (NH_3) were used for chemical ionization (CI). The silica gel used for flash chromatography was 230−400 mesh. All reagents were of reagent grade and were used as such or distilled prior to use.

Bis-[1,1′]-(4,4-dimethoxy)but-2-enyl Ether 2a. To a solution of 2-*E*-bromoacetal **1a** (3.0 g, 15.4 mmol) in 10 mL of THF were added 10 mL of 4.6 M NaOH (46.0 mmol, 3 equiv) and 100 mg of tetrabutylammonium iodide. The resulting heterogeneous mixture was stirred for 15 min at 20 °C. After separation, the aqueous phase was washed twice with ethyl acetate (20 mL). The combined organic phases were then dried ($MgSO_4$) and evaporated under reduced pressure. The 2*E*,2′*E* bisacetal **2a** was obtained as an orange oil (1.72 g, yield = 91%). IR (neat) 1449, 1356, 1194 cm^{-1}; EIMS (70 eV) *m*/*z* 215 ($M^{+\bullet}$ − 31, 6), 182 ($M^{+\bullet}$ − 62, 3), 153 (12), 115 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.26 (12H, s), 4.00 (4H, d, J = 5), 4.76 (2H, d, J = 4.5), 5.66 (2H, dd, J = 6.4, 4.5), 5.88 (2H, dt, J = 16.4, 5.0). Anal. Calcd: C, 58.54; H, 8,94. Found: C, 58.70; H, 8.76.

Bis-[1,1′]-(4,4-dimethoxy-2-methyl)but-2-enyl Ether 2b. To a solution of chloroacetal **1b** (5.05 g, 30.7 mmol) [2*E*/2*Z* = 75:25] in 10 mL of THF were added 10 mL of 9 N NaOH (90 mmol, 2.9 equiv) and 100 mg of tetrabutylammonium iodide. The resulting heterogeneous mixture was stirred for 24 h at 70 °C. The same workup as above provided bisacetal **2b** (7.82 g, yield = 93%) as an orange oil [2*E*,2′*E*/2*E*,2′*Z* = 60:40]. IR (neat) 1674, 1444, 1380 cm^{-1}; CIMS (NH_3) *m*/*z* 292 (M + 18, 3), 260 (13), 243 (100), 228 (38), 211 (59); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) *2E*,*2′E* isomer, 1.65 (6H, s), 3.20 (12H, s), 3.75 (4H, s), 4.99 (2H, d, J = 6.3), 5.46 (2H, d, J = 6.3); *2E*,*2′Z* isomer, 1.65 (3H, s), 1.75 (3H, s), 3.20 (12H, s), 3.75 (2H, s), 3.94 (2H, s), 4.99 (2H, d, J = 6.3), 5.35 (1H, d, J = 6.3), 5.46 (1H, d, J = 6.3); ^{1}H (200 MHz, C_6D_6) *2E*,*2′E* isomer, 1.64 (6H, s), 3.18 (12H, s), 3.66 (4H, s), 5.08 (2H, d, J = 6.3), 5.72 (2H, d, J = 6.3); *2E*,*2′Z* isomer, 1.64 (3H, s), 1.75 (3H, s), 3.18 (12H, s), 3.66 (2H, s), 3.95 (2H, s), 5.08 (1H, d, J = 6.3), 5.12 (1H, d, J = 6.3), 5.53 (1H, d, J = 6.3), 5.72 (1H, d, J = 6.3); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) *2E*,*2′E* isomer, 13.8, 51.2, 74.1, 99.6, 123.9, 137.9; *2E*,*2′Z* isomer, 13.3, 20.4, 52.0, 72.7, 74.8, 99.0, 99.6, 124.4, 125.7, 137.4, 138.1. Anal. Calcd: C, 69.29; H, 9.55. Found: C, 69.4; H, 9.16.

Bis-[1,1′]-(4-methoxy)buta-1,3-dienyl Ether 3a. To a solution of bisacetal **2a** (1.00 g, 4.06 mmol) was added 17 mL of 0.7 M KHMDS in THF (11.9 mmol, 3.0 equiv) at room temperature. After 12 h, the medium was quenched by 2 mL of distilled water. After separation, the aqueous phase was washed twice with ether (3 mL). The combined organic phases were then dried ($MgSO_4$) and evaporated under reduced pressure. Bisdiene **3a** (658 mg, yield = 89%) [68% 1*Z*,3*E*,1′*Z*,3′*E*] was obtained as a rapidly darkening oil. NMR (200 MHz, $CDCl_3$) δ (ppm) 3.14 (6H, s), 5.02 (2H, dd, J = 11.6, 6.4), 5.83 (2H, d, J = 6.4), 6.13 (2H, dd, J = 12.8, 11.6), 6.54 (2H, d, J = 12.8).

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Bis-[1,1′]-(4-methoxy-2-methyl)buta-1,3-dienyl Ether 3b. To a solution of bisacetal **2b** (1.00 g, 3.65 mmol) [2*E*,2′*E*/2*E*,2′*Z* = 60:40] in 10 mL of THF was added 4.6 mL of 2 M *n*-butyllithium in hexane (9.2 mmol, 2.5 equiv) at −40 °C. After 15 min, the medium was quenched by 2 mL of distilled water. The temperature was then raised to rt and the workup was identical to that above, leading to bis-diene **3b** (743 mg, yield = 97%) [1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E* = 92:8] as a rapidly darkening oil. CIMS (*i*-BuH) *m*/*z* 267 (M + 57, 13), 235 (22), 211 (M + 1, 49), 179 (87), 113 (90), 85 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1*Z*,3*E*,1′*Z*,3′*E* isomer, 1.57 (6H, s), 3.56 (6H, s), 5.92 (2H, s), 6.00 (2H, d, *J* = 13.8), 6.48 (2H, d, *J* = 13.8); ^{1}H (200 MHz, C_6D_6) δ (ppm) 1*Z*,3*E*,1′*E*,3′*E* isomer, 1.53 (3H, s), 1.56 (3H, s), 3.25 (6H, s), 5.55 (1H, d, *J* = 12.5), 5.75 (1H, s), 6.08 (1H, s), 6.41 (1H, d, *J* = 12.5), 6.64 (1H, d, *J* = 12.5), 6.83 (1H, d, *J* = 12.5); 1*Z*,3*E*,1′*Z*,3′*E* isomer, 1.53 (6H, s), 3.25 (6H, s), 5.82 (2H, s), 6.40 (2H, d, *J* = 12.5), 6.62 (2H, d, *J* = 12.5). A NOE experiment has been performed on the 1*Z*,3*E*,1′*Z*,3′*E* isomer, irradiation at 1.55 ppm induces an enhancement at 5.82 ppm (3%) and at 6.60 ppm (1%). ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 1*Z*,3*E*,1′*E*,3′*E* isomer, 13.9, 14.1, 51.3, 55.2, 100.0, 100.9, 113.2, 138.1, 138.4, 147.6, 147.8; 1*Z*,3*E*,1′*Z*,3′*E* isomer, 14.0, 55.2, 100.9, 113.2, 138.1, 147.6.

Ether of [1,1′]-(4,4-Dimethoxy-2-methyl)but-2-enyl and (4-Methoxy-2-methyl)buta-1,3-dienyl 4. To a solution of bisacetal **2b** (1.00 g, 3.65 mmol) [2*E*,2′*E*/2*E*,2′*Z* = 60:40] in 8 mL of THF was added 0.9 mL of 2 M *n*-butyllithium in hexane (1.8 mmol, 0.5 equiv) at −40 °C. After 15 min, the above workup led to 950 mg of a 60:40 mixture of bis-acetal **2b** (2*E*,2′*E*) and diene **4** [1*Z*,3*E*,7*E*] as a redish oil. Those were neither separated nore purified. ^{1}H NMR for **4** (200 MHz, C_6D_6) δ (ppm) 1.55 (3H, s), 1.65 (3H, s), 3.20 (6H, s), 3.27 (3H, s), 3.89 (2H, s), 5.07 (1H, d, *J* = 6.3), 5.66 (1H, s), 5.73 (1H, d, *J* = 6.3), 6.40 (1H, d, *J* = 12.5), 6.63 (1H, d, *J* = 12.5).

***N*-Methyl-2-(4,4-dimethoxy-2-methyl)but-2-enoxy-7,9-dioxo-5-methoxy-3-methyl-8-azabicyclo[4.3.0]non-3-ene 5.** To 950 mg of a 60:40 mixture of bisacetal **2b** and acetal **4** (348 mg, 1.44 mmol of this latter) dissolved in 7 mL of THF were added *N*-methylmaleimide (192 mg, 1.73 mmol, 1.2 equiv) and 100 mg of hydroquinone in 3 mL of THF. After 2 days of stirring at 20 °C, evaporation of the solvents, and flash chromatography, adduct **5** was isolated as a colorless oil (325 mg, yield = 26%, 64% with respect to **4**). IR (neat) 1709, 1684, 1512, 1444, 1284, 1217 cm^{-1}; CIMS (NH_3) *m*/*z* 371 (M + 18, 3), 325 (100), 322 (43), 307 (65); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.75 (3H, s), 1.85 (3H, s), 2.93 (3H, s), 3.15 (2H, m), 3.25 (3H, s), 3.27 (3H, s), 4.10 (2H, q_{AB}, *J* = 12.5), 4.20 (1H, m), 4.25 (1H, m), 5.05 (1H, d, *J* = 6.3), 5.55 (1H, d, *J* = 6.3), 5.77 (1H, d, *J* = 2.0); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.1, 20.5, 24.5, 42.6, 45.9, 52.1, 56.5, 71.9, 73.6, 74.4, 99.7, 123.3, 124.2, 138.1, 141.1, 171.1, 177.9.

Bis-[1,1′]-(4-methoxy-2-methyl-5,5,6,6-tetracyano)cyclohex-2-enyl Ether 6. To a solution of bis-diene **3b** (340 mg, 1.62 mmol) [1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E* = 92:8] in 5 mL of THF was added a mixture of tetracyanoethylene (456 mg, 3.56 mmol, 2.2 equiv) and hydroquinone (50 mg) in 10 mL of THF, at −40 °C and under argon. The dark blue color of this latter solution faded away instantaneously upon addition. After 15 min of stirring at −40 °C and evaporation of the solvents, the crude reaction mixture was flash chromatographed on silica gel, eluting with a petroleum ether/ethyl acetate = 80:20 mixture. It yielded a dark solid, recrystallized in dichloromethane (408 mg, yield = 54%, 59% with respect to 1*Z*,3*E*,1′*Z*,3′*E* isomer). Mp = 180−182 °C; IR (neat) 2253 cm^{-1}; CIMS (CH_4) *m*/*z* 467 (M + 1, 19), 143 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 2.18 (6H, s), 3.73 (6H, s), 4.57 (2H, d, *J* = 1.8), 5.42 (2H, s), 5.86 (2H, d, *J* = 1.8); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.4, 44.3, 44.6, 60.0, 76.9, 80.1, 107.1, 107.9, 109.6, 110.1, 124.5, 133.2. The adduct presumably derived from the 1*Z*,3*E*,1′*E*,3′*E* isomer has been observed in the NMR spectrum of the crude mixture but has not been isolated. Anal. Calcd for $C_{24}H_{18}N_8O_3$: C, 61.80; H, 3.89; N, 24.02. Found: C, 61.49; H, 3.85; N, 24.06.

***N*-Methyl-7,9-dioxo-5-methoxy-2-(4-methoxy-2-methylbuta-1,3-dienoxy)-3-methyl-8-azabicyclo[4.3.0]non-3-ene 7.** To a solution of bis-diene **3b** (1.49 g, 7.08 mmol) in 20 mL of THF [1*Z*,3*E*,1′*Z*,3′*E* / 1*Z*,3*E*,1′*E*,3′*E* = 92:8] were added *N*-methylmaleimide (786 mg, 1.0 equiv) and 200 mg of hydroquinone. The mixture was stirred for 2 days at 20 °C and the reaction monitored by NMR and TLC. After chromatography on silica gel, eluting with petroleum ether/ethyl acetate (70:30), **7** was obtained as a colorless oil (977 mg, yield = 47%, 51% with respect to the 1*Z*,3*E*,1′*Z*,3′*E* bis-diene). CIMS (i-BuH) *m*/*z* 322 (M + 1, 100); ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1.64 (3H, s), 1.75 (3H, s), 2.52 (1H, dd, *J* = 10.2, 4.8), 2.71 (1H, dd, *J* = 10.2, 4.4), 2.74 (3H, s), 2.90 (3H, s), 3.31 (3H, s), 3.89 (1H, t, *J* = 4.8), 4.67 (1H, m), 5.44 (1H, m), 6.27 (1H, s), 6.37 (1H, d, *J* = 13.6), 6.60 (1H, d, *J* = 13.6).

Bis-[2,2′]-*N*-methyl-(7,9-dioxo-5-methoxy-3-methyl)-8-azabicyclo[4.3.0]non-3-enyl Ethers 8. To a solution of bis-diene **3b** (420 mg, 2.0 mmol) [1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E* = 92:8] in 20 mL of THF was added *N*-methylmaleimide (533 mg, 2.4 equiv) and 100 mg of hydroquinone. The mixture was refluxed for 2 days. The transitory formation of **7** was monitored by TLC and NMR. The two double adducts **8a,b** were finally obtained in a 52:48 ratio (from ^{1}H NMR) and purified together by flash chromatography to provide 467 mg of a colorless oil (yield = 54%, 59% with respect to the 1*Z*,3*E*,1′*Z*,3′*E* bis-diene). Adduct **8a** precipitated after 3 days at −20 °C. The supernatant, enriched in **8b**, crystallized out in turn after 1 week at this same temperature. Both were recrystallized separately using a petroleum ether/ethyl acetate = 70:30 mixture, yielding two white solids. In addition, about 60 mg of isomer **8c**, derived from the 1*Z*,3*E*,1′*E*,3′*E* isomer of **3b**, could be isolated from the above flash chromatography. It crystallized in a few days at −20 °C and was recrystallized as above. The stereochemical identity of this isomer could be determined by comparison with the spectroscopical data of an authentic sample obtained by cycloaddition of a bis-diene **3b** mixture enriched in the 1*Z*,3*E*,1′*E*,3′*E* isomer on NMM.

8a: Mp = 182−184 °C; IR (neat) 1704, 1438, 1384, 1282 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 433 (M + 1, 100); ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1.80 (6H, s), 2.67 (6H, s), 2.95 (2H, dd, *J* = 10.0, 5.2), 3.12 (6H, s), 3.28 (2H, dd, *J* = 10.0, 4.5), 4.15 (2H, t, *J* = 5.2), 4.90 (2H, d, *J* = 4.5), 5.55 (2H, d, *J* = 5.2). Three NOE experiments have been performed: irradiation at 1.80 ppm induces an enhancement at 4.90 ppm (2%) and at 5.57 ppm (2%); irradiation at 3.12 ppm induces an enhancement at 4.15 ppm (2%) and at 4.90 ppm (1%); and irradiation at 4.90 ppm, induces an enhancement at 1.80 ppm (3%). ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 20.7, 24.4, 43.5, 44.5, 56.4, 72.5, 73.4, 125.4, 141.8, 175.4, 178.2. Anal. Calcd for $C_{22}H_{28}N_2O_7$: C, 61.10; H, 6.53; N, 6.48. Found: C, 61.14; H, 6.47; N, 6.28.

8b: Mp = 197−199 °C; IR (neat) 1704, 1438, 1384, 1282 cm^{-1}; CIMS (*t*-BuH) *m*/*z* 433 (M + 1, 100); ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1.98 (6H, s), 2.62 (2H, dd, *J* = 10.0, 4.0), 2.67 (6H, s), 2.80 (2H, dd, *J* = 10.0, 5.8), 3.05 (6H, s), 4.10 (2H, t, *J* = 4.0), 5.37 (2H, d, *J* = 5.8), 5.57 (2H, d, *J* = 4.0). Five NOE experiments have been performed: irradiation at 1.98 ppm induces an enhancement at 2.80 ppm (2%), at 5.37 ppm (2%) and at 5.57 ppm (6%); irradiation at 3.05 ppm induces an enhancement at 4.10 ppm (2%) and at 5.37 ppm (1%); irradiation at 4.10 ppm induces an enhancement at 3.05 ppm (3%); irradiation at 5.37 ppm induces an enhancement at 1.98 ppm (3%); and irradiation at 5.57 ppm induces an enhancement at 1.98 ppm (3%).^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 20.4, 24.4, 44.9, 46.8, 55.8, 71.7, 75.8, 121.7, 145.1, 175.4, 178.2. Anal. Calcd for $C_{22}H_{28}N_2O_7$: C, 61.10; H, 6.53; N, 6.48. Found: C, 61.14; H, 6.51; N, 6.28.

8c: Mp = 199−200 °C; IR (neat) 1705, 1442, 1267 cm^{-1}; CIMS (CH_4) *m*/*z* 461 (M + 29, 14), 433 (M + 1, 10), 401 (16), 226 (40), 194 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.77 (3H, s), 2.00 (3H, s), 2.92, 2.95 (6H, 2s), 3.07 (2H, m), 3.20 (3H, s), 3.43 (1H, dd, *J* = 8.8, 6.9), 3.50 (3H, s), 3.67 (1H, dd, *J* = 8.8, 6.3), 4.03 (1H, m), 4.20 (1H, t, *J* = 4.4), 4.71−4.58 (2H, m), 5.64 (1H, quint, *J* = 1.2), 5.84 (H, d, *J* = 4.4); ^{1}H (200 MHz, C_6D_6) δ (ppm) 1.80 (3H, s), 2.20 (3H, s), 2.26 (1H, dd, *J* = 9.5, 4.2), 2.55 (1H, dd, *J* = 9.5, 3.9), 2.66 (3H, s), 2.77 (3H, s), 2.92 (3H, s), 2.97 (1H, dd, *J* = 8.8, 7.0), 3.27 (1H, dd, *J* = 8.8, 5.2), 3.35 (3H, s), 3.86−4.03 (2H, mm), 4.60 (1H, m),

4.78 (1H, m), 5.53 (1H, m), 5.66 (1H, m); ^{13}C (50 MHz, C_6D_6) δ (ppm) 18.8, 20.2, 24.5, 41.5, 42.2, 43.6, 46.3, 56.2, 57.5, 71.0, 71.4, 71.9, 73.4, 123.0, 123.5, 139.1, 142.6, 175.0, 175.3, 176.3 Anal. Calcd for $C_{22}H_{28}N_2O_7$: C, 61.10; H, 6.53; N, 6.48. Found: C, 60.57; H, 6.34; N, 6.61.

3-Methoxycarbonyl-6-(4-methoxy-2-methyl)buta-1,3-dienoxy-1-methylcyclohex-1-ene 9. Bis-diene **3b** (500 mg, 2.38 mmol) [1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E* = 92:8], 200 mg hydroquinone, and methyl acrylate (205 mg, 2.38 mmol, 1.0 equiv) in 4 mL of anhydrous methanol were put under 13 kbar at 20 °C for 2 days. After pressure release, flash chromatography on silica gel, using petroleum ether/ethyl acetate (80:20) as eluant, provided **9** as a colorless oil (359 mg, yield = 51%, 55% with respect to 1*Z*,3*E*,1′*Z*,3′*E* **3b** isomer). This compound kept for a few hours in the freezer. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.59 (3H, s), 1.81 (3H, s), 2.01 (1H, td, J = 14.6, 4.0), 2.12 (1H, m), 2.88 (1H, dt, J = 11.7, 4.0), 3.33 (3H, s), 3.55 (3H, s), 3.70 (3H, s), 3.93 (1H, m), 3.97 (1H, t, J = 5.1), 5.80 (1H, s), 5.87 (1H, dd, J = 5.1, 1.5), 5.88 (1H, d, J = 12.4), 6.43 (1H, d, J = 12.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 14.5, 21.0, 23.1, 39.7, 51.4, 56.1, 57.1, 72.1, 76.8, 101.2, 105.5, 123.4, 137.3, 139.7, 146.9, 173.0.

Bis-[1,1′]-(4-methoxy-5-methoxycarbonyl-2-methyl)cyclohex-2-ene Ethers 10. Thermal Activation. Bis-diene **3b** (500 mg, 2.38 mmol) [1*Z*,3*E*,1′*Z*,3′*E*/1*Z*,3*E*,1′*E*,3′*E* = 92:8] was dissolved, with 200 mg hydroquinone, in 20 mL toluene/methyl acrylate (1:1) and warmed to 80 °C under argon. A NMR monitoring showed the transitory formation of **9** and its slow convertion into the two adducts **10a**,**b**. After 10 days, all **3b** had been consumed and the crude reaction medium contained a 45:55 mixture of **9** and **10** (70:30). Flash chromatography, after adsorption of the polymers on silica gel, using a petroleum ether/ethyl acetate mixture (75:25) as eluant yielded adduct **9** as a colorless oil (70 mg, yield ≈ 10%) and adducts **10a**,**b** as a clear oily mixture (232 mg, yield = 27%, 29% with respect to 1*Z*,3*E*,1′*Z*,3′*E* **3b** isomer).

Hyperbaric Activation. The same reaction was performed placing bis-diene **3b** (1.00 g, 4.76 mmol) and 200 mg of hydroquinone under 13 kbar at 20 °C in 8 mL of methyl acrylate/methanol (1:1) for 72 h. A mixture of adducts **10a**,**b** (78:22) was directly obtained that could be isolated as above in 69% yield (75% with respect to 1*Z*,3*E*,1′*Z*,3′*E* **3b** isomer). The major adduct **10a** precipitated after 3 days at −20 °C. The supernatant, enriched in **10b**, crystallized in turn after 2 days at −20 °C. Both compounds were recrystallized separatly in a 70:30 petroleum ether/ethyl acetate mixture to provide two white solids.

10a: Mp = 148−150 °C; IR (neat) 1738, 1437, 1287 cm^{-1}; CIMS (CH_4) m/z 383 (M + 1, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.75 (6H, s), 1.95 (2H, td, J = 14.6, 4.0), 2.16 (2H, dt, J = 14.6, 2.5), 2.86 (2H, dt, J = 13.1, 3.3), 3.32 (6H, s), 3.70 (8H, s), 3.94 (2H, t, J = 4.0), 5.83 (2H, dd, J = 5.1, 1.5); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.9, 23.9, 39.6, 51.5, 57.1, 72.2, 72.6, 123.3, 137.7, 173.2. Anal. Calcd: C, 62.81; H, 7.91. Found: C, 62.66; H, 7.98.

10b: Mp = 138−140 °C; IR (neat) 1738, 1435, 1288 cm^{-1}; CIMS (CH_4) m/z 383 (M + 1, 100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.83 (6H, s), 2.02 (4H, m), 2.86 (2H, td, J = 7.5, 4.7), 3.31 (6H, s), 3.70 (3H, s), 3.79 (2H, t, J = 3.3), 3.91 (2H, t, J = 4.7), 5.76 (2H, dd, J = 5.1, 1.5); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 21.5, 26.1, 39.6, 51.4, 57.1, 72.6, 75.4, 122.6, 138.4, 173.2.

Ethers of [1,2′]-(4-Methoxy-2-methyl-5,5,6,6-tetracyano)cyclohex-2-enyl and *N*-Methyl-(7,9-dioxo-5-methoxy-3-methyl)-8-azabicyclo[4.3.0]non-3-enyl 11. The two steps were run in one pot. To crude **6**, prepared by reacting bis-diene **3b** (700 mg, 3.33 mmol) [1*Z*,3*E*,1′*Z*,3′*E* / 1*Z*,3*E*,1′*E*,3′*E* = 92:8] with *N*-methylmaleimide (445 mg, 4.00 mmol, 1.2 equiv) as described above, was added dropwise a dark-blue solution of tetracyanoethylene (426 mg, 1.0 equiv) and hydroquinone (100 mg) in 10 mL of THF at −40 °C. The color faded away instantaneously upon stirring and the consumption of **7** was monitored by TLC. After 15 min at −40 °C, THF was evaporated and the crude mixture analyzed by NMR. The spectrum displayed signals accounting for adducts **11a**,**b** in a 85:15 ratio. Those were purified together by flash chromatography on silica gel, using a 55:45 petroleum ether/ethyl acetate mixture as eluant, yielding a dark oil (785 mg, yield = 52%, 57% with respect to 1*Z*,3*E*,1′*Z*,3′*E* **3b** isomer). Isomer **11a** crystallized out after 1 week at −20 °C and was recrystallized in dichloromethane to provide brown crystals.

11a: Mp = 192−193 °C; IR (neat) 2362, 1693, 1516, 1440, 1213 cm^{-1}; CIMS (CH_4) m/z 450 (M + 1, 100); ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1.64 (3H, s), 2.06 (3H, s), 2.40 (1H, dd, J = 10.0, 3.5), 2.54 (1H, dd, J = 10.0, 6.0), 2.60 (3H, s), 2.75, 2.90 (6H, 2s), 3.82 (1H, dd, J = 5.0, 3.5), 4.29 (1H, m), 5.05 (1H, q, J = 1.5), 5.17 (1H, d, J = 6.0), 5.37 (1H, d, J = 5.0), 6.48 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 19.3, 19.5, 24.1, 42.9, 44.7, 45.0, 46.5, 55.1, 58.6, 70.4, 77.2, 78.0, 78.3, 108.1, 109.6, 111.0, 123.4, 124.3, 135.8, 141.7, 175.0, 178.8. Anal. Calcd: C, 61.46; H, 5.16; N, 15.58. Found: C, 61.73; H, 4.88; N, 15.77.

11b: ^{1}H NMR (200 MHz, C_6D_6) δ (ppm) 1.70, 1.78 (6H, s), 2.50 (1H, m), 2.54 (1H, m), 2.60 (3H, s), 2.70, 2.85 (6H, 2s), 3.97, 4.22 (3H, 2m), 4.92 (1H, m), 5.49 (1H, m), 6.24 (1H, s); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 19.3, 19.5, 24.1, 42.9, 43.8, 45.0, 45.6, 55.8, 57.5, 71.6, 75.3, 76.5, 74.8, 108.1, 109.6, 111.0, 121.2, 123.5, 135.8, 141.7, 175.0, 178.8.

Ethers of [1,2′]-(4-Methoxy-5-methoxycarbonyl-2-methyl)-cyclohex-2-enyl and *N*-Methyl-(7,9-dioxo-5-methoxy-3-methyl)-8-azabicyclo[4.3.0]non-3-enyl 12. Cycloaddition of 7 with Methyl Acrylate. Purified **7** (900 mg, 2.80 mmol) in 8 mL of methyl acrylate/methanol (1:1) was mixed with 200 mg of hydroquinone and put under 13 kbar at 20 °C for 72 h. After release of the pressure and evaporation of solvents, a NMR spectrum of the crude medium displayed signals corresponding to a 59:41 mixture of diastereomers **12**. These could be separated by flash chromatography on silica gel, using petroleum ether/ethyl acetate (70:30) as eluant, yielding two white solids (672 mg total, yield = 53%). Both were recrystallized from petroleum ether/ethyl acetate (70:30).

Cycloaddition of 9 with *N*-Methylmaleimide. Purified **9** (350 mg, 1.18 mmol, 1.0 equiv) in 10 mL of THF was mixed with *N*-methylmaleimide (157 mg, 1.2 equiv) and 100 mg of hydroquinone and the mixture warmed to reflux for 3 days. The NMR analysis of the crude mixture accounted for a 71:29 mixture of adducts **12a**,**b**. These were purified as above in 56% yield.

12a: Mp = 163−165 °C; IR (neat) 1739, 1703, 1437, 1287 cm^{-1}; CIMS (CH_4) m/z 408 (M + 1, 90), 376 (65), 344 (18), 208 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.78 (3H, s), 1.81 (3H, s), 2.03 (1H, td, J = 15.0, 3.3), 2.20 (1H, dt, J = 15.0, 2.6), 2.89 (1H, dt, J = 12.8, 4.6), 2.95 (3H, s), 3.12 (2H, m), 3.20 (3H, s), 3.34 (3H, s), 3.72 (3H, s), 3.97 (1H, t, J = 4.7), 4.15 (1H, t, J = 4.0), 4.32 (1H, m), 4.41 (1H, m), 5.80 (1H, dt, J = 4.7, 1.5), 5.86 (1H, dd, J = 5.5, 1.3); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.4, 21.0 24.0, 24.5, 39.8, 43.3, 46.7, 51.5, 56.3, 57.1, 71.4, 72.0, 72.6, 73.1, 123.1, 123.7, 138.0, 141.8, 173.3, 176.2, 178.3. Anal. Calcd: C, 61.92; H, 7.12; N, 3.44. Found: C, 61.83; H, 7.40; N, 3.46.

12b: Mp = 136−137 °C; CIMS (*t*-BuH) m/z 408 (M + 1, 18), 376 (7), 344 (3), 226 (86), 208 (37), 159 (100); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.79 (3H, s), 1.82 (3H, s), 2.00 (1H, td, J = 13.6, 4.0), 2.31 (1H, dt, J = 13.6, 4.0), 2.91 (1H, m), 2.91 (3H, s), 3.17 (1H, dd, J = 8.8, 3.6), 3.31 (1H, dd, J = 8.8, 6.8), 3.33 (3H, s), 3.41 (3H, s), 3.74 (3H, s), 3.91 (1H, m), 3.96 (1H, t, J = 4.5), 4.37 (1H, m), 4.54 (1H, d, J = 3.6), 5.78 (1H, m), 5.85 (1H, d, J = 5.2); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 21.4, 22.0, 23.5, 24.5, 39.6, 41.4, 46.1, 51.4, 57.0, 72.5, 72.6, 73.0, 73.1, 123.5, 126.7, 138.0, 138.7, 173.3, 175.3, 176.7.

Bis-[3,3′]-(2-ethoxycarbonyl-6-methoxy-4-methyl)-1-oxacyclohex-4-enyl Ethers 13. A solution of ethyl glyoxylate at 50% in toluene (10 mL, 5.25 g of glyoxylate, 51.5 mmol) was warmed to reflux for 1 h. After cooling to 40 °C, a solution of **3b** (1.4 g, 6.67 mmol, 1.0 equiv) [1*Z*,3*E*,1′*Z*,3′*E* / 1*Z*,3*E*,1′*E*,3′*E* = 92:8] and hydroquinone (400 mg) in toluene was added dropwise under argon before warming up to 80 °C for 20 h. The solvents were then evaporated, and a NMR spectrum of the crude medium showed a mixture of diastereoisomeric adducts. Adducts **13a**,**b** (56:44) were purified by flash chro-

matography on silica gel, using petroleum ether/ethyl acetate (80:20) as eluant. A colorless oil (690 mg, yield = 25%, 27% with respect to 1*Z*,3*E*,1′*Z*,3′*E* **3b** isomer) was recovered. IR (neat) 1732, 1450, 1371, 1297, 1211 cm^{-1}. Anal. Calcd: for $C_{18}H_{26}O_9$: C, 57.96; H, 7.29. Found: C, 58.16; H, 7.54.

Diastereoisomer 1 (**13a** or **13b**): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.23 (6H, t, J = 6.9), 1.88 (6H, s), 3.42 (6H, s), 3.99 (2H, d, J = 1.3), 4.12 (4H, m), 4.49 (2H, d, J = 1.3), 4.89 (2H, m), 5.59 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.7, 20.3, 55.8, 61.1, 70.3, 71.6, 95.4, 123.0, 133.7, 170.3.

Diastereoisomer 2 (**13b** or **13a**): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.31 (6H, t, J = 6.9), 1.91 (6H, s), 3.41 (6H, s), 4.12 (4H, m), 4.20 (2H, d, J = 1.3), 4.42 (2H, d, J = 1.3), 4.89 (2H, m), 5.55 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.7, 20.7, 55.7, 61.1, 71.9, 72.8, 95.4, 122.9, 134.6, 170.1.

Bis-[3,3′]-(1-methoxybuta-1,3-dienyl)methyl Ether 14. To bis-acetal **2b** [2*E*,2′*E*/2*E*,2′*Z* = 60:40] (1.00 g, 3.65 mmol) was added 15.6 mL of 0.7 M KHMDS in THF (10.92 mmol, 3.0 equiv) and the reaction remained at rt for 4 h under dry argon. After above workup using diethyl ether for extractions, 728 mg of a 50:50 mixture of **3b** and **14** was obtained. Flash chromatography using petroleum ether/ethyl acetate/triethylamine (85:14:1) as eluant provided pure **14** (284 mg, 1.35 mmol, yield = 37%) as a colorless oil [100% 1*E*,1′*E*]. IR (neat) 1640, 1452, 1338, 1208 cm^{-1}; EIMS (70 eV) *m*/*z* 210 ($M^{+\bullet}$, 0.4), 178 (5), 163 (2), 113 (51), 83 (100); ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.57 (6H, s), 4.05 (4H, s), 4.96 (2H, s), 4.90 (2H, s), 5.52 (2H, d, J = 13.5), 6.81 (2H, d, J = 13.5); ^{1}H (200 MHz, C_6D_6) 3.20 (6H, s), 4.03 (4H, s), 5.01 (2H, s), 4.95 (2H, s), 5.55 (2H, d, J = 12.5), 6.92 (2H, d, J = 12.5); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 55.3, 70.4, 104.9, 111.8,140.5, 149.5.

Bis-[3,3′]-(*N*-methyl-(7,9-dioxo-5-methoxy)-8-azabicyclo-[4.3.0]non-3-enyl)methyl Ethers 15. A 5 mL THF solution containing *N*-methylmaleimide (275 mg, 2.48 mmol, 2.0 equiv) and 100 mg of hydroquinone was added atop bis-diene **14** (260 mg, 1.24 mmol) in solution in the same solvent. The mixture was stirred at 20 °C for 15 min. TLC showed an almost instantaneous consumption of **14**. Silica gel chromatography provided a white solid corresponding to a 59:41 mixture (as determined from quantitative ^{13}C NMR measurements) of diastereomers **15a**,**b** (445 mg, yield = 83%). Mp = 124−126 °C; IR (neat) 1698, 1434, 1382, 1280 cm^{-1}; CIMS (CH_4) *m*/*z* 461 (M + 29, 51), 435 (39), 401 (37), 369 (100); Anal. Calcd: C, 61.10; H, 6.53; N, 6.48. Found: C, 61.35; H, 6.82; N, 6.12.

Diastereoisomer 1 (**15a** or **15b**): ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 2.16 (2H, dd, J = 11.0, 8.7), 2.36 (2H, dt, J = 8.8, 6.3), 2.46 (2H, dd, J = 9.6, 5.1), 2.53 (2H, tm, J_{app} = 7.1), 2.70_6 (6H, s), 3.00 (6H, s), 3.50 (2H, s), 3.92 (2H, t, J = 4.9), 5.79 (2H, dq, J = 4.9, 1.6); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 23.4, 24.0, 37.0, 44.6, 55.9, 72.0, 72.2, 123.5, 140.3, 175.3, 178.7.

Diastereoisomer 2 (**15b** or **15a**): ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 2.12 (2H, dd, J = 11.0, 8.7), 2.36 (2H, dt, J = 8.8, 6.3), 2.48 (2H, dd, J = 9.6, 5.1), 2.57 (2H, tm, J_{app} = 7.1), 2.71_0 (6H, s), 3.00 (6H, s), 3.50 (2H, s), 3.91 (2H, t, J = 4.9), 5.77 (2H, dq, J = 4.9, 1.6); ^{13}C NMR (50 MHz, C_6D_6) δ (ppm) 23.4, 24.0, 37.0, 44.6, 55.9, 72.0, 72.2, 123.2, 140.3, 175.3, 178.7.

Bis-[4,4′]-(6,6-diethoxycarbonyl-2-methoxy)-1-oxacyclohex-3-enyl Ethers 17. Purified bis-diene 1*E*,1′*E*-**14** (125 mg, 0.59 mmol) was added to a 5 mL THF solution of diethyl ketomalonate (207 mg, 1 mmol, 1.7 equiv) and 50 mg of hydroquinone. The mixture was stirred for 3 days at 20 °C. A set of TLC and NMR showed the progressive appearance of two diastereoisomers. These adducts were purified together by flash chromatography on silica gel, eluting with petroleum ether/ethyl acetate (70:30), yielding 289 mg of adducts **17** as a colorless oil (yield = 87%). The **17a**/**b** ratio was 50:50 from quantitative ^{13}C NMR. IR (neat) 1746, 1460, 1440, 1370, 1275, 1250, 1212 cm^{-1}; EIMS (70 eV) *m*/*z* 558 ($M^{+\bullet}$, 100). Anal. Calcd: C, 55.91; H, 6.86. Found: C, 55.53; H, 6.58.

Isomer 1 (**17a** or **17b**): ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.22 (12H, t, J = 7.2), 2.24 (2H, dd, J = 17.5, 2.0), 2.81 (2H, d, J = 17.5), 3.44 (6H, s), 3.93, 3.97 (2H, $2d_{AB}$, J = 13.6), 3.90−4.35 (8H, m), 5.08 (2H, t, J = 2.4), 5.66 (2H, d, J = 2.4); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.6, 13.8, 28.9, 56.0, 61.5, 61.8, 71.7, 96.2, 119.5, 135.1, 168.0, 168.3.

Isomer 2 (**17b** or **17a**): ^{1}H NMR (200 MHz, $CDCl_3$) same spectrum as isomer **1**. ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.6, 13.8, 28.9, 56.0, 61.5, 61.8, 71.7, 96.2, 119.7, 135.1, 168.0, 168.3.

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Supporting Information Available: Copies of the ^{1}H NMR spectra for compounds **2b**, **3**, **4**, **5**, **7**, **8a**, **9**, **10**, **12**, **13**, **14**, **17** and ^{13}C NMR spectra for compounds **8c**, **13**, **15**, **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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