JOC Article

Thermal/Hyperbaric Heterocycloaddition of 1,4-Dialkoxy-1,3-dienes: The *de novo* (*E*,*Z*) Way to Sugars

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1-(*Z*)-Alkoxy-4-(*E*)-methoxybutadiene derivatives have been reacted with ethylgyoxylate and diethyl ketomalonate under thermal or hyperbaric conditions. They provide, with a total regioselectivity and fair to total endoselectivities, the expected dihydropyranic cycloadducts. Three of those pseudoglycals have been converted in a few classical steps (deprotection, reduction, and dihydroxylation) into (racemic) allose, mannose, and gullose derivatives. The order of these three steps has a direct influence on the efficiency of the transformation and determines the stereochemistry of the final sugar.

Introduction

The biological potential of rare and modified saccharides, carba and pseudosugars, disaccharide mimics, ... explains the renewed interest of the organic chemist's community into new routes to highly functionalized tetrahydropyran skeletons, in particular asymmetric (catalytic) ones.[1] The so-called *de novo* approach of sugars sometimes offers an interesting short-cut toward these targets and can thus favorably compare to the classical methods of glycochemistry. In particular, the convergent [4+2] cycloaddition strategies, under their direct (diene + heterodienophile)[2] or inverse (heterodiene + dienophile)[3] demand versions, have been widely explored and both have led to convincing results. The very convergent approach proposed by Danishefsky and colleagues,[4] which relies on 1,4-dialkoxy-2-silyloxy dienes, is especially worth underlining since it takes double advantage of the silyloxy moiety that acts both as a convenient hydroxy precursor and as a polarizing group increasing the reactivity of the diene. By contrast, Scheeren et al.[5] have shown that the gem-disubstituted 1,1,4-trimethoxybutadiene also adds to glyoxylates, while providing a complex mixture of [2+2] adducts. Interestingly, one of the simplest routes to these heterocycles, viz. the addition of 1,4-dialkoxydienes on glyoxylates (Scheme 1), has been relatively neglected.[2b,c,h,j,6] Early reports about the poor reactivity of these types of dienes (assigned to the competing polarizations induced by the 1,4-disubstitution pattern)[2c] and the relative paucity of simple synthetic routes to 1,4-difunctionalized dienes are probably responsible for this partial void in the literature.

We have previously described a one-step stereoselective access to (1*Z*,3*E*)-1,4-dialkoxydienes **2**,[7] from α,β-unsaturated acetals such as **1**.[8] Despite their (1*Z*,3*E*) configuration, the [4+2] cycloadditions involving these dienes turned out to be chemically efficient and highly regio-

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(1) Very convincing recent exemples: (a) Dosseter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398−2400. (b) Yao, S.; Roberson, M.; Reichel, F.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1999**, *64*, 6677−6687. (c) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491. (d) Lillelund, V. H.; Jensen, H. H.; Liang, X.; Bols, M. *Chem. Rev.* **2002**, *102*, 515.

(2) See inter alia: (a) Banaszek, A. *Bull. Acad. Pol. Sci. Ser. Sci. Chim.* **1974**, *22*, 1045. (b) Angerbauer, R.; Schmidt, R. R. *Carbohydr. Res.* **1981**, *89*, 193. (c) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250. (d) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (e) Bauer, T.; Kozak, J.; Chapuis, C.; Jurczak, J. *J. Chem. Soc., Chem. Commun.* **1990**, 1178. (f) Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* **1991**, *32*, 935. (g) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741. (h) Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1380. (i) Kleindl, P. J.; Donaldson, W. A. *J. Org. Chem.* **1997**, *62*, 4176. (j) Seeberger, P. H.; Bilodeau, M. T.; Danishefsky, S. J. *Aldrichim. Acta* **1997**, *30*, 75.

(3) See inter alia: (a) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065. (b) Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 980. (c) Dondoni, A.; Kniezo, L.; Martinkova, M. *J. Chem. Soc., Chem. Commun.* **1994**, 1963. (d) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1996**, *37*, 4007. (e) Dujardin, G.; Martel, A.; Brown, E. *Tetrahedron Lett.* **1998**, *39*, 8647. (f) Dujardin, G.; Leconte, S.; Coutable, L.; Brown, E. *Tetrahedron Lett.* **2001**, *42*, 8849.

(4) (a) Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 7761. (b) Danishefsky, S. J.; Barbachyn, M. R. *J. Am. Chem. Soc.* **1985**, *107*, 7762. (c) Danishefsky, S. J.; Hungate, R.; Shulte, G. *J. Am. Chem. Soc.* **1988**, *110*, 7434.

(5) Van Balen, H. C. J. G; Broekhuis, A. A.; Scheeren, J. W.; Nivard, R. J. F. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 36.

(6) (a) Schmidt, R. R.; Angerbauer, R. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 783. (b) David, S.; Eustache, J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2230. See also in relation: (c) Schmidt, R. R.; Wagner, A. *Tetrahedron Lett.* **1983**, *24*, 4661.

(7) (a) Maddaluno, J.; Gaonac'h, O.; Le Gallic, Y.; Duhamel, L. *Tetrahedron Lett.* **1995**, *36*, 8591. (b) Guillam, A.; Maddaluno, J.; Duhamel, L. *J. Chem. Soc., Chem. Commun.* **1996**, 1295. (c) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1998**, *63*, 5110. (d) Guillam, A.; Toupet, L.; Maddaluno, J. *J. Org. Chem.* **1999**, *64*, 9348−9357.

(8) These acetals were easily prepared from either 1-acetoxyisoprene (for **1a**,**b**) or 1-acetoxybutadiene (for **1c**,**d**) following the very convenient procedure described in: Deagostino, A.; Balma Tivola, P.; Prandi, C.; Venturello, P. *Synlett* **1999**, *11*, 1841.

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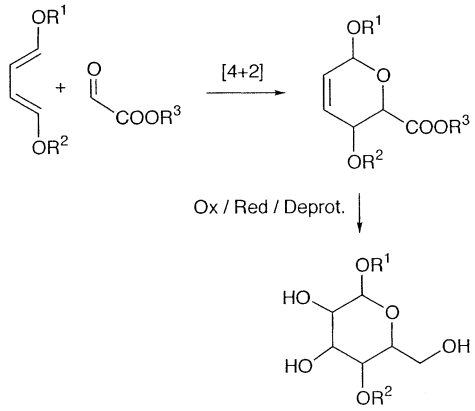
TABLE 1. Heterocycloaddition of 2 with Ethylglyoxylate in Toluene under Various Conditions

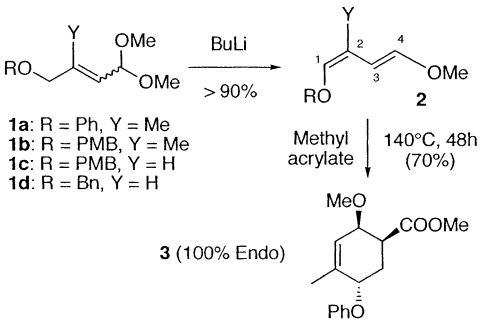
entry	diene	R	Y	*T* °C	*P* (kbar)	*t* (h)	adduct	yield[a] (%)	endo/exo[b]
1	**2a**	Ph	Me	80	1×10^{-3}	12	**4a**	73	85:15
2	**2b**	PMB	Me	80	1×10^{-3}	12	**4b**	58	75:25
3	**2b**	PMB	Me	20	12	48	**4b**	58	91:9
4	**2b**	PMB	Me	50	12	48	**4b**	69	>99:1
5	**2c**	PMB	H	50	12	24	**4c**	40	>99:1

[a] Calculated on the mixture or endo + exo isomers with respect to (1*Z*,3*E*) dienes **2**. [b] Based on the NMR integrations for the adducts derived from the (1*Z*,3*E*) dienes **2**.

SCHEME 1. Direct Demand *de novo* Access to Sugars



and endoselective, providing, for instance, cyclohexene **3** as a single (racemic) isomer in good yield under thermal activation (eq 1).[7c] We now present the extension of this reaction to the heterocycloaddition of these dienes with activated carbonyl species, under both thermal and hyperbaric conditions.

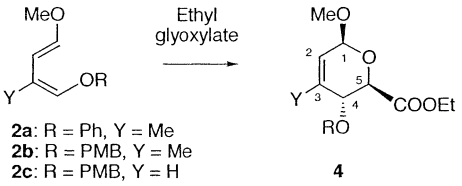


(1)

Results and Discussion

As described previously,[7] the treatment of α,*β*-unsaturated acetals **1a** by 2.5 equiv of *n*-BuLi at −45 °C in THF triggers a deprotonation−conjugated elimination sequence leading, in an almost quantitative step, to diene **2a** (eq 1). This reaction also applies to acetals **1b**,**c**, in which the phenyl group is replaced by a cleavable *p*-methoxybenzyl (PMB) one, using a lesser quantity of a stronger base (1.2 equiv of *t*-BuLi). The yields remain in the 90−95% range. Acetal **1d** could also be deprotonated using 1.6 equiv of KHMDS in THF at room temperature in 78% yield. As previously described for **2a**,[7c] these compounds were obtained mainly under their (1Z,3*E*) configuration (1*Z*,3*E*/1*E*,3*E* = 90:10 for **2b** and 100:0 for **2c**,**d**) and were pure enough to be used as such. These relatively fragile enol ethers are otherwise difficult to chromatograph.

Cycloadditions and Selectivities. Three dienes **2** were then reacted with commercial ethyl glyoxylate under thermal or hyperbaric conditions (eq 2). This heterodienophile is available as a 50% solution in toluene and was first depolymerized by refluxing the solution for 1 h. The results gathered in Table 1 are relative to adducts **4** obtained from the major (>90%) (1*Z*,3*E*) isomers of dienes **2**. All adducts **4** obtained show that the regioselectivity is totally controlled by the *E*-borne alkoxy group, as previously observed in classical Diels−Alder cycloadditions,[7c] probably because of the better conjugation of this substituent with the *π*-system of the diene. Entries 1 and 2 indicate that a simple thermal activation (80 °C) leads, in good yields for both **2a** and **2b**, to the expected heteroadducts but with relatively low diastereoselectivities (de = 50 to 70%). Resorting to high pressure (entry 3) increases the selectivity,[9] as expected in favor of the endo isomer **4b** (de > 80%). Finally, a slight warming of the pressurized medium improves both the yield and/or the selectivity, entries 4 and 5 exhibiting a total endo preference under the 12 kbar/50 °C conditions for dienes **2b**,**c**. The adducts stemming from the (1*E*,3*E*) dienes **2** have been separated but their endo/exo ratio was found insignificant (ca. 50:50 for **4b** as obtained under 12 kbar at 50 °C). The full regio- and endoselectivities obtained with the (1*Z*,3*E*) dienes **2** demonstrate the superiority, in a strategy relying on a heterocycloaddition key step, of these isomers over the (1*E*,3*E*) ones.[2c]

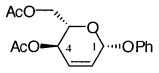
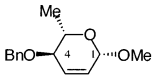


(2)

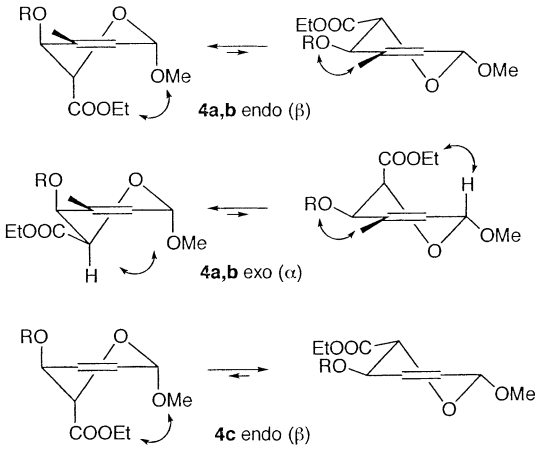
The regio- and endoselectivities reported above have been determined by high-field NMR analysis. The determination of the regioselectivity of this reaction was first carried out on **4a**. The close values of the chemical shifts for the acetalic proton H^1 and that for H^4 made the assignment of the signals difficult. We thus compared our data to that described in the literature for related dihydropyranes[10] (Table 2). The presence of a phenoxy group at the anomeric center is indeed known to shift the corresponding H^1 at low field. This is not observed for **4a** isomers, indicating that the methoxy moiety occupies the anomeric position. This same orientation was easily checked for **4b**,**c**, the chemical shifts for the acetalic proton H^1 and that for H^4 being very different

(9) Jenner, G. *Tetrahedron* **1997**, *53*, 2669.
(10) (a) Brakta, M.; Lhoste, P.; Sinou, D. *J. Org. Chem.* **1989**, *54*, 1890. (b) Brescia, M. R.; Shimshock, Y. C.; DeShong, P. *J. Org. Chem.* **1997**, *62*, 1257.

TABLE 2. Comparison of the Chemical Shifts of Dihydropyranes 4a,b with Literature Data

Entry	Structure	δ H^1 (ppm)	δ H^4 (ppm)	Ref
1	**4a** endo	5.02	4.99	This work
2	**4a** exo	5.11	4.75	This work
3	**4b** endo	4.95	4.16	This work
4	**4b** exo	4.96	?	This work
5	**4c** endo	4.96	4.27	This work
6	**4c** exo	5.12	?	This work
7		5.80	?	10a
8		5.10	?	10b

SCHEME 2. Conformational Equilibria for Dihydropyrans 4



this time. This regiodirection is expected from the polarization of diene **2a**, as deduced from our previous observations on classical Diels−Alder cycloadditions.[7c]

While the anti relationship between the methoxy and 4-alkoxy groups is secured by the (1*Z*,3*E*) configuration of **2** the determination of the syn/anti relationship between the methoxy and the ester apendages, i.e. the endo/exo selectivity, on the basis of the simple NMR data is not straightforward. Two half-chair conformations have to be considered for the both the endo and the exo isomers (Scheme 2). In the **4a**,**b** (endo) cases, the conformation on the left puts all substituents in an axial position, which of course gives rise to unfavorable 1,3-diaxial interactions between the methoxy and ester groups. Twisting to the other threshold half-chair (to the right) puts all the substituents in an equatorial arrangement, which, in turn, is unfavorable to the anomeric methoxy and generates a $A^{1,2}$ allylic strain[11] between the methyl and the phenoxy/PMBO groups. A comparable reasoning can be applied to the exo-adducts **4a**,**b** (Scheme 2, middle). This equilibrated situation could result in a balanced mixture between both conformers.[12] In the case discussed here, we have measured[13] the critical coupling constants in **4**. The comparison between J_{1-2} and values from the literature[6a,14] in similar situations tends to

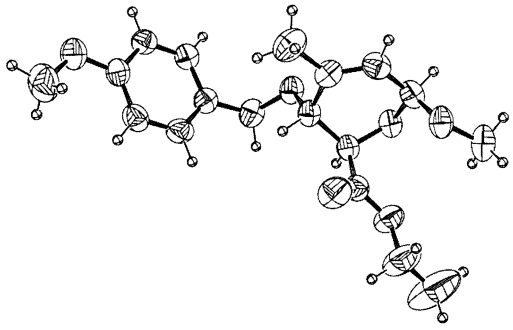
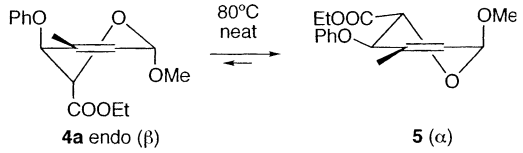


FIGURE 1. ORTEP representation of heterocycloadduct **4b**.

indicate that the anomeric H^1 proton is pseudoequatorial, in both **4a** and **4b**. This suggests that the methoxy and the phenoxy/PMBO groups adopt pseudoaxial orientations, while the ester moiety is either in an axial (endo isomers) or an equatorial (exo isomers) position (Scheme 2, left). The J_{4-5} values measured are also consistent with pseudoequatorial/equatorial and pseudoequatorial/axial situations in **4a** and **4b**.

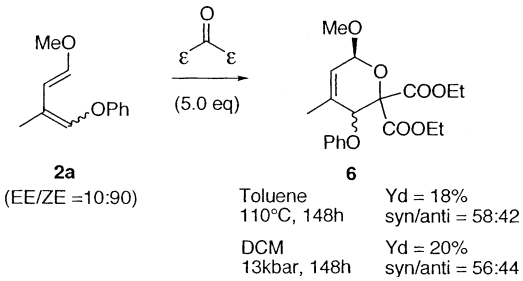
These structural hypotheses have been supported by a single-crystal X-ray analysis on **4b**(endo) that shows the all-axial orientation of the methoxy, PMBO, and COOEt appendages (Figure 1). Upon thermal treatment, these all-axial adducts tend to epimerize. This has been checked on **4a**(endo) (80 °C, 12 h, neat), which partially converts (70%) into its isomer **5** in which the anomeric methoxy remains axial but both the phenoxy and ethyl carboxylate groups have swapped to an equatorial orientation (eq 3).



(3)

The case of adduct **4c**(endo) deserves separate comments since the absence of a vinylic methyl group in this compound affects its conformation in solution (Scheme 2). The disappearance of the $A^{1,2}$ allylic strain displaces the balance on the all-equatorial side (Scheme 2, bottom right) at the expense of the anomeric effect. The coupling constants are in agreement with the endo-adduct substituents relationships.

A cycloaddition between **2a** and the highly activated diethyl ketomalonate has also been performed in refluxing toluene (eq 4). Following this slow reaction by TLC



(4)

(11) Johnson, F. *Chem. Rev.* **1968**, *68*, 375−412.

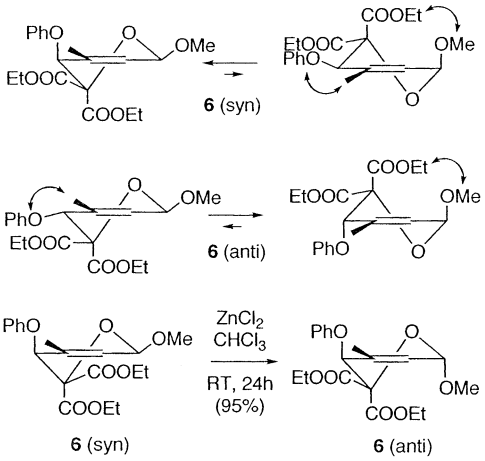
(12) See for instance ref 8a and: Achmatowicz, O.; Bukowski, P. *Rocz. Chem.* **1973**, *47*, 99.

(13) The precise measurement of these coupling constants requires a simultaneous homodecoupling on the allylic methyl group.

(14) Ferrier, R. J.; Prasad, N.; Sankey, G. H. *J. Chem. Soc.* **1969**, 587.

and GC showed that the (1*E*,3*E*) isomer converted, relatively rapidly and quasiquantitatively, into the corresponding syn-adduct **6**, while its (1*Z*,3*E*) analogue was sluggish and decomposed progressively during the prolonged warming. Finally a 58:42 mixture of **6**(syn), derived from (1*E*,3*E*) **2a**, and **6**(anti), derived from the (1*Z*,3*E*) **2a** isomer, is recovered in a mediocre 18% total yield. The same result was obtained under 12 kbar, in dichloromethane, and at room temperature.

As above, and for both **6**(syn) and **6**(anti), the $A^{1,2}$ strain arising between the phenoxy and vinylic methyl groups (eq 5) explains the preference for an axial PhO and



(5)

equatorial MeO in **6**(syn), as well as the diaxial PhO and MeO in **6**(anti). Comparable results have been reported in the literature.[2b,15] The equatorial anomeric methoxy group in **6**(syn) can be epimerized almost quantitatively into its diaxial (anti) isomer after a mild Lewis acid treatment. After 24 h at room temperature in a $ZnCl_2$ presaturated chloroform solution, 95% epimerization was observed (eq 5). These NMR results were confirmed on **5**(anti) by single-crystal X-ray diffraction. The corresponding ORTEP (Figure 2) clearly shows the axial orientation of the two allylic substituents.

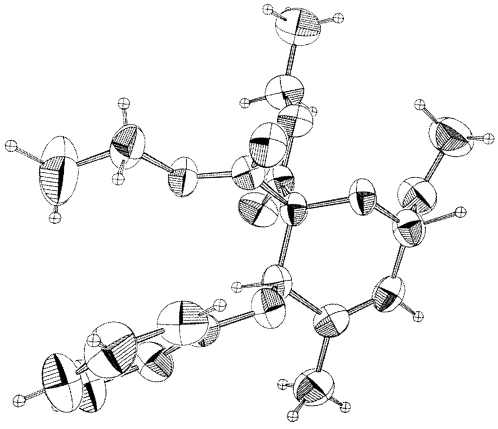
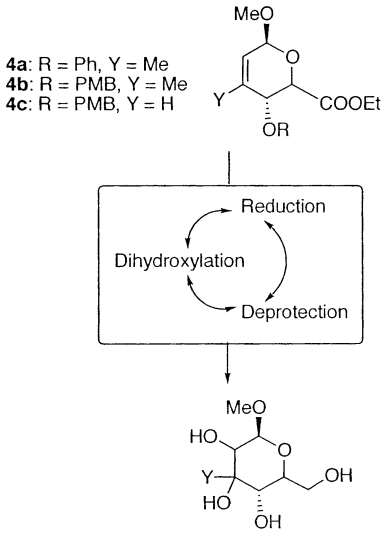


FIGURE 2. ORTEP representation of heterocycloadduct **6** (anti).

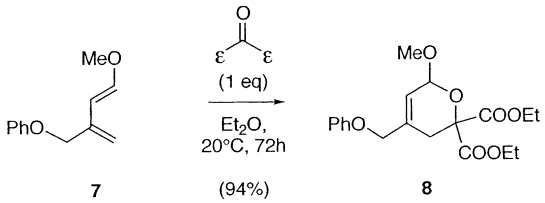
Finally, it was tempting to probe the reactivity of this same dienophile with the allylic diene **7**,[7c] prepared from

(15) Achmatowicz, O.; Grynkiewicz, G.; Szechner, B. *Tetrahedron* **1976**, *32*, 1051.

SCHEME 3. From Dihydropyrans to Sugars



the acetalic precursor **1a** following Gassman's conditions.[16] The heterocycloaddition is actually much more efficient when performed with **7**. The reaction takes place at room temperature in diethyl ether and the corresponding dihydropyrane **8** is obtained this time in 94% yield (eq 6).



(6)

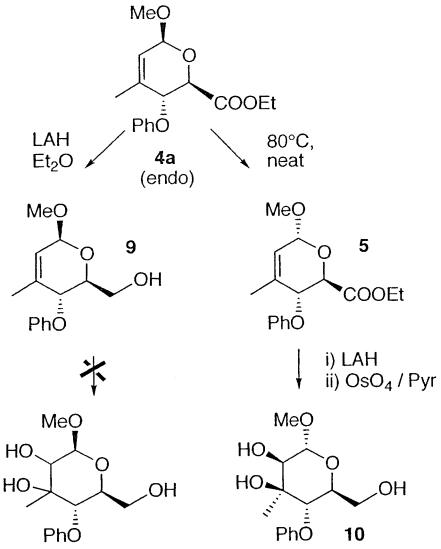
Functionalization of Adducts. The validity of this [4+2] strategy for the *de novo* approach of carbohydrates was then dependent on the efficiency of the following functionalization steps. Basically, the conversion of dihydropyranes **4** in the corresponding sugars required three operations, viz. a deprotection, a dihydroxylation, and a reduction step (Scheme 3). Because it was likely to have an impact on the stereochemistry of the final sugar, the order of these transformations had to be studied in detail.

We have first examined the reduction/dihydroxylation/deprotection sequence on the model adduct **4a**(endo). This compound was reacted with LAH in diethyl ether, providing the corresponding alcohol **9** in 82% yield (eq 7). Unfortunately, all further attempts to dihydroxylate this dihydropyrane resorting to classical catalytic or stoichiometric osmium tetroxide methods[17] turned out to be in vain.

Interestingly, this sequence worked, albeit poorly, in the case of **5**, the anomer of **4a**(endo). The LAH reduction was quantitative (99%) while the OsO_4 dihydroxylation in pyridine provided the mannose skeleton **10** diastereo-

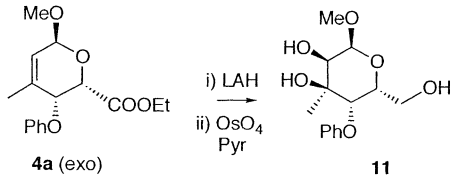
(16) Gassman, P. G.; Burns, S. J.; Pfister, K. B. *J. Org. Chem.* **1993**, *58*, 1449.

(17) Stoichiometric: ref 6a. Catalytic: (a) Ray, M.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449. (b) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247. (c) Burdisso, M.; Gandolfi, R. *Tetrahedron Lett.* **1991**, *32*, 2634. (d) Carless, H. A. J.; Busia, K.; Dove, Y.; Malik, S. S. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2505.



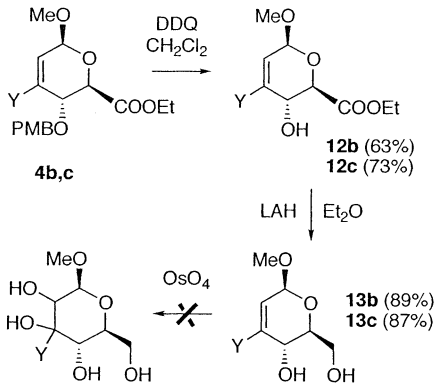
(7)

selectively but in very low yield (27%, eq 7). This same sequence became efficient (65% for the two steps) when applied to the small amounts of epimer **4a**(exo) available and led to triol **11**, a gulose derivative (eq 8). These two results suggest that the dihydroxylation step requires the methoxy and CH_2OH groups to be anti one to the other. The final conversion of **11** into the corresponding sugar was not attempted in this case since the deprotection of the phenoxy group was expected to require conditions too harsh to be compatible with this delicate substrate.



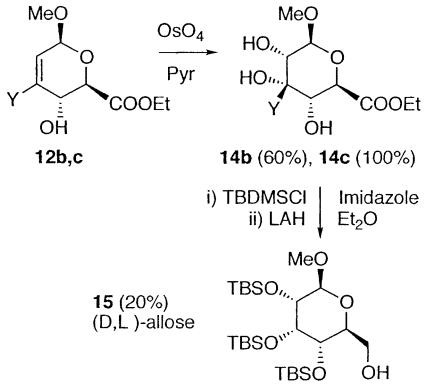
(8)

We thus next considered the deprotection/reduction/dihydroxylation sequence applied to substrates **4b**,**c** bearing an easy to remove PMB protecting group (eq 9). This latter was indeed cleanly cleaved under the action of dichlorodicyanoquinone (DDQ) in a methylene chloride/water mixture at room temperature.[18] The reduction was still performed with LAH and provided efficiently the diols **13**. However, these proved inert toward OsO_4 in pyridine or mixtures of *t*-BuOH and pyridine, up to 50 °C, even using stoichiometric quantities of osmium tetroxide. Note that, in this case again, the methoxy and CH_2OH appendages are in a syn relationship.



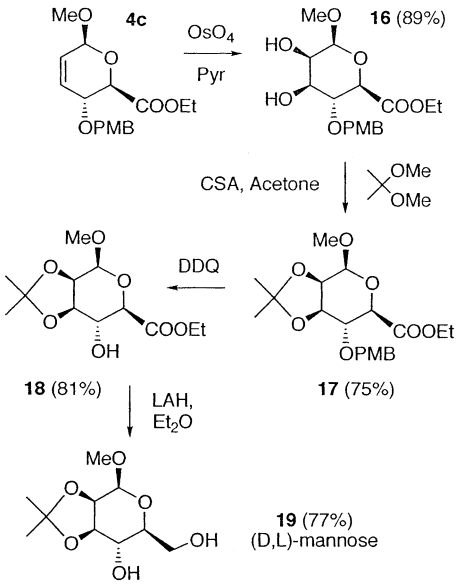
(9)

To avoid this structural feature and elude from the possible chelation of the osmium nucleus by the two alcohols borne by **13**, we decided to evaluate the deprotection/dihydroxylation/reduction sequence on compounds **12b**,**c**, obtained as above from **4b**,**c**. Their dihydroxylation by 1.1 equiv of OsO_4 in pyridine at room temperature afforded the expected triols **14** in high yields this time. A total α-diastereoselectivity was also observed, probably due to the anchimeric assistance of the allylic 4-hydroxyl group oriented along the α-face (eq 10). Unfortunately, we have been unable to turn this stoichiometric dihydroxylation into its catalytic version. The following steps have then been restricted to **14c**, a natural sugar precursor. A preliminary silylation of the three hydroxyl groups has been performed before the reduction.[19] The intermediate tris(*tert*-butyldimethylsilyl) ether was not isolated and directly engaged in the LAH reduction step that provided alcohol **15** in a low (nonoptimized) 20% yield for the two steps. The NMR characteristics indicated **15** to be a protected form of (D,L)-allose, thus confirming the dihydroxylation selectivity.



(10)

The dihydroxylation/deprotection/reduction sequence has finally been investigated on adduct **4c**. The same dihydroxylation conditions as above provide diol **16** in good yield and total diastereoselectivity but along the *β*-face this time (eq 11). This underlines the importance



(11)

of the allylic hydroxyl group in the orientation of the

dihydroxylation of such substrates. The following steps rely on classical carbohydrate chemistry. The diol in protected ethyl mannuronate **16** was transformed into its acetonide **17** by 2,2-dimethoxypropane in catalytic acidic conditions and the PMB group removed by DDQ. The alcohol **18** was then reduced by LAH in ether, affording diol **19**, a protected form of (D,L)-mannose, as checked by comparison to literature data, in good yield. The overall yield for the conversion of **4c** into **19** is about 42% in 4 steps.

Concluding Remarks

The results presented here show that (1*Z*,3*E*)-1,4-dialkoxydienes are efficient partners in hetero-Diels−Alder reactions with simple heterodienophiles such as ethyl glyoxylate, giving a totally regio- and endocontrolled access to the corresponding dihydropyranes. These characteristics seem to be closely related to the polarization induced by the configuration of the diene, the (1*E*,3*E*) isomers leading to poorly controlled cycloadditions. We then investigated the transformation of such adducts into carbohydrates. Four of the six possible different permutation sequences of the deprotection/reduction/dihydroxylation steps to be performed have been considered. Three have provided a diastereoselective access to various derivatives of three different (racemic) natural sugars (gulose, allose, and mannose). In conclusion, the use of (1*Z*,3*E*)-1,4-dialkoxydienes allows the interest in *de novo* strategies in the synthesis of rare or modified sugars (such as those based on branched diene **2b** that have not been exploited yet) to be restored. Further developments will be presented in due time.

Experimental Section

General Aspects. ^{1}H NMR spectra were recorded at 200 or 300 MHz and ^{13}C NMR spectra at 50 or 75 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 recorded 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), and 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.

4-(4-Methoxybenzyloxy)-3-methylbut-2-enal Dimethyl Acetal (1b). A solution of *p*-methoxybenzyl alcohol (7.95 g, 57.4 mmol) in THF (30 mL) was added to a dispersion of KH (2.52 g, 63.1 mmol) in THF (70 mL). After dihydrogen bubbling ended, a solution of 4-bromo-3-methylbut-2-enal dimethyl acetal E/Z:70/30 (12,0 g, 57.4 mmol) in THF (50 mL) was added at 0 °C. The reaction mixture was stirred for 30 min at room temperature, then water was poured slowly after returning to 0 °C. The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the resulting organic solution was dried ($MgSO_4$) and concentrated under vacuum to give the crude product **1b**. Flash chromatography on silica gel (eluent: ethyl acetate/heptane 30:70) afforded 13.02 g (48.9 mmol, 86%) of **1b** E/Z:70/30 as a colorless oil.

IR ν_{max} (film)[1] 2934, 1612, 820 cm^{-1}. *E* isomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.75 (3H, d, J = 1.1 Hz), 3.32 (6H, s), 3.79 (3H, s), 3.90 (2H, s), 4.40 (2H, s), 5.08 (1H, d, J = 6.4 Hz), 5.55 (1H, dq, J = 1.1, 6.4 Hz), 6.87 (2H, dd, J = 1.9, 8.7 Hz), 7.26 (2H, dd, J = 1.9, 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.9, 52.7, 55.7, 71.9, 75.0, 100.4, 114.2, 124.1, 129.7, 130.7, 139.0, 159.6. *Z* isomer ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.84 (3H, d, J = 1.1 Hz), 3.27 (6H, s), 3.79 (3H, s), 4.04 (2H, s), 4.40 (2H, s), 5.02 (1H, d, J = 6.4 Hz), 5.44 (1H, dq, J = 1.1, 6.4 Hz), 6.87 (2H, dd, J = 1.9, 8.7 Hz), 7.26 (2H, dd, J = 1.9, 8.7 Hz). δ_C (75 MHz) 21.6, 52.7, 55.7, 68.7, 72.0, 99.8, 114.3, 126.1, 129.7, 130.7, 139.3, 159.6. EIMS (70 eV) *m*/*z* 266 ($M^{+\cdot}$, 0.3), 234 (M^+ − MeOH, 0.7), 121 (100). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.56; H, 8.34.

***E*-4-(4-Methoxybenzyloxy)but-2-enal Dimethyl Acetal (1c).** This compound was prepared as above deprotonating *p*-methoxybenzylic alcohol (8.15 g, 59.0 mmol) by KH (7.50 g, 65.5 mmol) and reacting the alcoholate with *E*-4-bromobut-2-enal dimethyl acetal (11.50 g, 59.0 mmol). **1c** (12.20 g) was thus obtained (48.4 mmol, 82%) as a pale yellow oil and as a pure *E* isomer.

IR ν_{max} (film) 2934, 2834, 1690, 1514, 820 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.32 (6H, s), 3.79 (3H, s), 4.02 (2H, d, J = 5.3 Hz), 4.44 (2H, s), 4.79 (1H, d, J = 4.8 Hz), 5.70 (1H, ddt, J = 1.5, 4.8, 15.8 Hz), 5.95 (1H, ddt, J = 0.8, 5.3, 15.7 Hz), 6.87 (2H, d, J = 8.5 Hz), 7.26 (2H, d, J = 8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 53.1, 55.6, 69.7, 72.3, 102.9, 114.2, 129.1, 129.7, 130.6, 131.8, 159.6.

***E*-4-Benzyloxybut-2-enal Dimethyl Acetal (1d).** This compound was prepared as above deprotonating benzylic alcohol (2.53 g, 23.4 mmol) by NaH (1.44 g, 60.0 mmol) and reacting the alcoholate with *E*-4-bromobut-2-enal dimethyl acetal (4.07 g, 20.9 mmol). **1c** (3.80 g) was thus obtained (17.1 mmol, 82%) as a colorless oil and as a pure *E* isomer.

IR ν_{max} (film) 2934, 2830, 1454, 1128, 1052 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.30 (6H, s), 4.05 (2H, d, J = 5.7 Hz), 4.55 (2H, s), 4.80 (1H, d, J = 5.2 Hz), 5.45 (1H, dd, J = 5.2, 16.8 Hz), 5.95 (1H, dd, J = 5.7, 16.8 Hz), 7.35 (s, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 52.6, 69.4, 72.1, 102.3, 126.8, 127.6, 128.3, 128.6, 131.0, 141.2. EIMS (70 eV) *m*/*z* 221 (M − H, 32), 205 (19), 190 (99), 173 (100), 91 (60).

1*Z*,3*E*-1-(4-Methoxybenzyloxy)-3-methyl-4-methoxybuta-1,3-diene (2b). This diene has been prepared from acetal **1b** in 93% yield following a procedure similar to that described for **2a** in ref 7c (method A) and was recovered as a colorless oil and as a mixture of (1*Z*,3*E*) and (1*E*,3*E*) isomers (90:10). Crude spectral data: IR ν_{max} (film) 2930, 2830, 1614, 1514, 1426, 820 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) for (1*Z*,3*E*) isomer: δ (ppm) 1.57 (3H, s), 3.57 (3H, s), 3.78 (3H, s), 4.70 (2H, s), 5.82 (1H, s), 6.00 (1H, d, J = 13.1 Hz), 6.48 (1H, d, J = 13.1 Hz), 6.87 (2H, d, J = 8.6 Hz), 7.25 (2H, d, J = 8.6 Hz).^{13}C NMR (75 MHz, $CDCl_3$) for (1*Z*,3*E*) isomer: δ (ppm) 14.5, 55.6, 56.7, 73.8, 101.7, 110.4, 114.2, 129.5, 130.0, 140.5, 147.4, 159.8.

1*Z*,3*E*-1-(4-Methoxybenzyloxy)-4-methoxybuta-1,3-diene (2c). This diene has been prepared from acetal **1c** in 91% yield following a procedure similar to that described for **2a** in ref 7c (method A) and was recovered as a colorless oil and as a single (1*Z*,3*E*) isomer. Crude spectral data: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.56 (3H, s), 3.79 (3H, s), 4.74 (2H, s), 4.96 (1H, dd, J = 6.2, 10.9 Hz), 5.79 (1H, dd, J = 10.9, 12.8 Hz), 5.89 (1H, d, J = 6.2 Hz), 6.54 (2H, d, J = 12.8 Hz), 6.88 (2H, d, J = 8.6 Hz), 7.26 (2H, d, J = 8.6 Hz).

1*Z*,3*E*-1-Benzyloxy-4-methoxybuta-1,3-diene (2d). This diene has been prepared from acetal **1d** in 78% yield following a procedure similar to that described for **2a** in ref 7c (method A) and was recovered as a yellowish oil and as a single (1*Z*,3*E*) isomer. Crude spectral data: IR ν_{max} (film) 2934, 2830, 1612, 1454, 734 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.31 (3H,

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s), 4.82 (2H, s), 4.98 (1H, dd, J = 6.2, 11.0 Hz), 5.78 (1H, dd, J = 11.0, 12.8 Hz), 5.89 (1H, d, J = 6.2 Hz), 6.55 (1H, d, J = 12.8 Hz), 7.33 (5H, s).^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 55.9, 72.1, 98.7, 103.7, 127.3, 127.8, 128.4, 138.1, 142.2, 148.7. EIMS (70 eV) m/z 190 (M^+, 100), 159 (80).

6-Methoxy-4-methyl-3-phenoxy-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl esters (4a and 5). A commercial solution of ethyl glyoxylate (50% in toluene, d = 1.03, 2.57 g of glyoxylate, 29.9 mmol) was refluxed for 1 h then kept at 40 °C under argon before adding freshly prepared diene **2a** (800 mg, 4.2 mmol, 1*E*,3*E*/1*Z*,3*E* = 8:92) and 100 mg of hydroquinone. The medium was then warmed to 80 °C and the reaction followed by GC. After 12 h, **2a** was consumed. The solvents were then evaporated and the residual oily mixture directly flash chromatographed on silica gel (eluent: petroleum ether/ethyl acetate 80:20). Two oily adducts were separated (85:15, 822 mg total, 73% yield with respect to the (1*Z*,3*E*) **2a**) which correspond to the endo and exo isomers of the heterocycloadducts **4a**.

Endo isomer: IR ν_{max} (film) 1742, 1594, 1494, 1449, 1374, 1222 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.24 (3H, t, J = 6.9 Hz), 1.90 (3H, s), 3.45 (3H, s), 4.12, 4.23 (2H, $2dq_{AB}$, J = 6.9, 10.7 Hz), 4.53 (1H, d, J = 2.1 Hz), 4.99 (1H, d, J = 2.1 Hz), 5.02 (1H, d, J = 2.7 Hz), 5.69 (1H, J = 2.7 Hz), 6.75−7.20 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.6, 20.1, 55.8, 61.1, 70.5, 71.8, 95.7, 115.8, 121.6, 123.3, 129.5, 134.0, 157.5, 170.0. EIMS (70 eV) m/z 292 ($M^{+\bullet}$, 5), 261 (5), 199 (28), 187 (82), 167 (44), 125 (100).

Exo isomer: IR ν_{max} (film) 1768, 1600, 1499, 1449, 1374, 1232 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.92 (3H, t, J = 6.9 Hz), 1.83 (3H, s), 3.97 (3H, s), 3.76, 4.01 (2H, $2dq_{AB}$, J = 6.9, 10.6 Hz), 4.74, 4.75 (2H, $2d_{AB}$, J = 2.5 Hz), 5.11 (1H, dm, J = 3.3 Hz), 5.71 (1H, dm, J = 3.3 Hz), 6.75−7.20 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.4, 20.1, 55.8, 60.9, 69.9, 72.1, 95.6, 116.3, 121.6, 123.9, 129.1, 134.3, 158.8, 168.0. EIMS (70 eV) m/z 292 ($M^{+\bullet}$, 2), 264 (3), 219 (11), 187 (92), 94 (100).

Anal. Calcd (on the mixture of isomers) for $C_{16}H_{20}O_5$: C, 65.45; H, 7.03. Found: C, 65.75; H, 6.85.

Warming up neat **4a** under argon at 80 °C for 12 h led to a mixture of **4a** and its α-anomer **5** (30:70). Colorless oil. Crude spectral data: ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.03 (3H, t, J = 6.9 Hz), 1.77 (3H, s), 3.43 (3H, s), 4.02, 4.13 (2H, $2dq_{AB}$, J = 6.9, 10.7 Hz), 4.53 (1H, d, J = 8.1 Hz), 5.01 (2H, m), 5.58 (1H, dm, J = 2.9 Hz), 6.75−7.20 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 13.6, 18.3, 55.4, 61.2, 69.8, 71.8, 95.7, 115.4, 121.5, 122.3, 129.7, 137.7, 158.4, 169.6.

6-Methoxy-4-methyl-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (4b). A commercial solution of ethyl glyoxylate (50% in toluene, 7.7 mL, 33.0 mmol) was refluxed for 1 h then cooled to room temperature under argon before adding freshly prepared diene **2b** (1.93 g, 8.3 mmol, 1*E*,3*E*/1*Z*,3*E* = 10:90) and trace amounts of hydroquinone. The resulting mixture was placed under 12 kbar of pressure at 50 °C for 48 h. After release of the pressure and evaporation of the solvents, the resulting oily mixture was flash chromatographed on silica gel (eluent: heptane/ethyl acetate 70:30). Adduct **4b** endo is thus recovered as white solid (1.72 g, 5.1 mmol, 69% yield with respect to (1*Z*,3*E*) **2b**). In a separate fraction, a 50:50 mixture of the endo and exo isomers of cycloadducts deriving from the heterocycloaddition of glyoxylate on the (1*E*,3*E*) isomer of **2b** was also recovered (280 mg, 0.8 mmol, 98% yield, with respect to (1*E*,3*E*) **2b**).

4b endo isomer: IR ν_{max} (film) 2934, 1732, 1612, 1514, 822 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.30 (3H, t, J = 7.2 Hz), 1.81 (3H, s), 3.45 (3H, s), 3.79 (3H, s), 4.16 (3H, m), 4.47 (1H, d, J = 2.6 Hz), 4.47, 4.50 (2H, $2d_{AB}$, J = 10.9 Hz), 4.54 (1H, d, J = 10.9 Hz), 4.96 (1H, s), 5.59 (1H, s), 6.86 (2H, d, J = 8.7 Hz), 7.26 (2H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.4, 20.6, 56.0, 56.2, 61.6, 71.8, 71.9, 73.3, 96.5, 114.2, 123.4, 130.1, 130.3, 135.8, 159.8, 170.8. EIMS (70 eV) m/z 305 ($M^{+\bullet}$, 49), 185 (30), 167 (16.5), 137 (26), 121 (100).

6-Methoxy-3-(4-methoxybenzyloxy)-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (4c). The same procedure as above applied to a mixture of ethyl glyoxylate (50% in toluene, 8.1 mL, 35.0 mmol) and diene **2c** (1.88 g, 8.6 mmol, 100% *ZE* isomer) led to pure **4c** endo (1.11 g, 3.45 mmol, 40%) as a yellowish oil.

IR: ν_{max} (film) 2934, 1732, 1612, 1510, 834 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.24 (3H, t, J = 7.1 Hz), 3.41 (3H, s), 3.73 (3H, s), 4.14 (2H, m), 4.27 (1H, t, J = 3.9 Hz), 4.30 (1H, t, J = 4.9 Hz), 4.47 (2H, s), 4.96 ($1H_1$, s), 5.80 (1H, d, J = 10.6 Hz), 6.01 (1H, dd, J = 3.39, 10.6 Hz), 6.80 (2H, d, J = 8.6 Hz), 7.19 (2H, d, J = 8.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.2, 55.4, 56.0, 61.5, 68.7, 71.1, 74.2, 96.5, 114.0, 128.1, 128.4, 129.7, 130.1, 159.6, 170.0. CIMS (CH_4) m/z 291 (M^+H − MeOH, 3), 185 (6), 154 (7), 121 (100).

6-Methoxy-4-methyl-3-phenoxy-3,6-dihydropyran-2,2-dicarboxylic Acid Diethyl Ester (6). Thermal procedure: Diene **2a** (500 mg, 2.6 mmol, 1*Z*,3*E*/1*E*,3*E* = 92:8) and diethyl ketomalonate (2.29 g, 13.2 mmol, 5.0 equiv) were dissolved in 10 mL of toluene containing 200 mg of hydroquinone and the solution was warmed to 110 °C under argon. The evolution of the medium was followed by TLC, GC, and NMR. After 12 h the 1*E*,3*E* isomer of diene **2a** was consumed while new compounds appeared progressively. The reaction was stopped after 7 days despite some 1*Z*,3*E* diene remaining in the medium. The solvent was evaporated and the oily residue directly flash chromatographed on silica gel (eluent: petroleum ether/ethyl acetate 80:20). A colorless oil was thus recovered, consisting of the two isomers **6** syn and **6** anti (163 mg, yield 18%) in a 58:42 ratio. After 3 days at −20 °C, the anti isomer crystallized spontaneously out of the mixture and was separated, rinsed with ether, and recrystallized in a petroleum ether/ethyl acetate mixture (70:30). A white solid (85 mg) was thus obtained. The supernatant consisted mainly in **6** syn, contaminated with small amounts of **6** anti. The colorless oily **6** syn was then dissolved in a saturated solution of $ZnCl_2$ in $CHCl_3$ (2 mL) and left for 24 h at room temperature. An almost total isomerization into **6** anti occurred (final ratio 95:5).

Hyperbaric procedure: Diene **2a** (500 mg, 2.6 mmol, 1*Z*,3*E*/1*E*,3*E* = 92:8) and diethyl ketomalonate (2.29 g, 13.2 mmol, 5.0 equiv) were dissolved in 5 mL of CH_2Cl_2 containing 200 mg of hydroquinone. The solution was compressed to 13 kbar at room temperature and left for 7 days. A 56:44 mixture of **6** syn and **6** anti was obtained and the overall conversion was about 20% (based on NMR integrations).

6 syn: IR ν_{max} (film) 1740, 1427, 1235, 1221 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.95, 1.25 (6H, 2t, J = 7.0 Hz), 1.83 (3H, s), 3.55 (3H, s), 3.85−4.35 (4H, m), 5.18 (1H, quint, J = 1.2 Hz), 5.29 (1H, s), 5.53 (1H, quint, J = 1.2 Hz), 6.80−7.40 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.5, 20.8, 56.3, 61.6, 72.0, 82.6, 96.2, 116.0, 121.7, 122.0, 129.2, 133.9, 158.5, 167.8. EIMS (70 eV) m/z 364 ($M^{+\bullet}$, 5), 271 (14), 239 (17), 224 (43), 197 (100), 125 (94).

6 anti: IR ν_{max} (film) = 1740, 1427, 1235, 1221 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 0.72, 1.25 (6H, 2t, J = 7.0 Hz), 1.89 (3H, s), 3.49 (3H, s), 3.85−4.35 (4H, m), 5.20 (1H, m, J = 2.9 Hz), 5.25 (1H, s), 5.64 (1H, m, J = 2.9 Hz), 6.80−7.40 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.8, 20.8, 54.6, 61.9, 73.3, 82.6, 95.9, 116.2, 121.7, 123.7, 129.6, 136.0, 158.8, 164.5, 166.3. EIMS (70 eV) m/z. 364 ($M^{+\bullet}$, 4), 271 (14), 239 (16), 197 (100), 125 (96).

Anal. Calcd (on the mixture of syn and anti isomers) for $C_{19}H_{24}O_7$: C, 62.63; H, 6.59. Found: C, 62.33; H, 6.64.

6-Methoxy-4-phenoxymethyl-3,6-dihydropyran-2,2-dicarboxylic Acid Diethyl Ester (8). Diene **7** (70 mg, 0.37 mmol) was prepared from acetal **1a** following a procedure similar to that described for **2a** in ref 7c (method C). It was then dissolved in 2 mL of THF containing diethyl ketomalonate (64 mg, 0.37 mmol, 1 equiv) and 10 mg of hydroquinone and left under argon and at room temperature for 3 days, following the evolution of the medium by TLC. After evaporation of the solvent, the oily mixture was chromatographed on silica gel

(eluent: petroleum ether/ethyl acetate 70:30), providing **8** as a colorless oil (126 mg, 0.35 mmol, 94%).

IR: ν_{max} (film) 1746, 1598, 1496, 1456, 1368, 1242 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.26 (6H, t, J = 6.8 Hz), 2.40 (1H, d, J = 16.8 Hz), 2.87 (1H, d, J = 16.8 Hz), 3.45 (3H, s), 4.00−4.40 (4H, m), 4.52 (2H, s), 5.16 (1H, s), 5.78 (1H, s), 6.80−7.40 (5H, m). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 13.6, 13.8, 28.9, 56.0, 61.6, 61.9, 69.6, 96.2, 114.5, 119.6, 120.9, 129.3, 134.1, 158.1, 168.0. EIMS (70 eV) m/z 364 ($M^{+\bullet}$, 4), 332 (59), 259 (58), 224 (43), 197 (100). Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.63; H, 6.59. Found: C, 62.98; H, 6.48.

(6-Methoxy-4-methyl-3-phenoxy-3,6-dihydro-2*H*-pyran-2-yl)methanol (9). To a solution of ester **4a** (endo *or* exo isomer, 276 mg, 1.0 mmol) in 4 mL of anhydrous ether was added 5 mL of a LAH (76 mg, 2.0 mmol) solution of the same solvent at 0 °C under argon. The mixture was left 1.5 h at room temperature and then quenched by 2 mL of a saturated solution of Na_2SO_4. The medium was filtered on a Celite pad, then washed with ethyl acetate. After drying ($MgSO_4$) and evaporation of all solvents, the crude product was obtained as a colorless oil (248 mg, 1.0 mmol, 99%) that was used as such in the next step.

Endo isomer: IR ν_{max} (film) 3444, 3062, 2922, 1682, 1596, 1234, 754 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.74 (3H, s), 3.48 (3H, s), 3.68 (1H, dd, J = 4.4, 12.0 Hz), 3.75 (1H, m), 3.82 (1H, dd, J = 2.3, 12.0 Hz), 3.96 (1H, m), 4.87 (s, 1H), 5.52 (1H, m), 6.96 (3H, m), 7.32 (2H, m). EIMS (70 eV) m/z 250 (M^+, 8), 218 (65), 187 (61), 157 (54), 124 (100).

Exo isomer: IR ν_{max} (film) 3474, 2930, 1596, 1492, 1226, 1056, 754 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.77 (3H, s), 3.49 (3H, s), 3.72 (1H, dd, J = 5.4, 11.5 Hz), 3.85 (1H, dd, J = 6.5, 11.5 Hz), 4.22 (1H, ddd, J = 2.5, 5.4, 6.5 Hz), 4.42 (1H, d, J = 2.5 Hz), 4.99 (1H, m), 5.70 (1H, m), 7.01 (3H, m), 7.22 (2H, m). EIMS (70 eV) m/z 250 (M^+, 8), 218 (65), 187 (61), 157 (54), 124 (100). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 20.6, 55.4, 61.7, 71.1, 71.9, 95.4, 116.0, 121.5, 124.0, 129.6, 135.3, 159.3. EIMS (70 eV) m/z 250 (M^+, 3), 218 (7), 187 (5), 157 (4), 125 (16), 95 (100).

6-Hydroxymethyl-2-methoxy-4-methyl-5-phenoxytetrahydropyran-3,4-diol (10). The same experimental procedure as above applied to ester **5** led to a colorless oily alcohol that was not isolated. This compound (295 mg, 1.3 mmol) was dissolved in 13 mL of pyridine and added to a solution of osmium tetroxide (387 mg, 1.5 mmol, 1.2 equiv) in 2 mL of pyridine. The mixture stirred for 2 h at room temperature before quenching with 3 mL of saturated solution of $NaHSO_3$, then 5 mL of water. Pyridine was evaporated under reduced pressure before ethyl acetate (20 mL) was added. The organic layers were separated, dried ($MgSO_4$), then evaporated to afford an oily residue that was flash chromatographed on silica gel (eluent: chloroform/methanol 19:1). The triol **10** was obtained as a yellowish oil (264 mg, 0.93 mmol, 80%).

IR: ν_{max} (film) 3382, 2928, 1596, 1494, 1044, 756 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.37 (3H, s), 3.30 (3H, s), 3.49 (1H, d, J = 12.9 Hz), 3.66 (3H,m), 4.50 (1H, d, J = 8.7 Hz), 4.70 (1H, s), 6.68 (1H, t, J = 6.4 Hz), 7.03 (2H, d, J = 8.1 Hz), 7.23 (2H, m), 7.22 (2H, m). CIMS (*t*-BuH, 200 eV) m/z 284 (M^+, 12), 253 (32), 235 (8), 173 (100).

6-Hydroxymethyl-2-methoxy-4-methyl-5-phenoxytetrahydropyran-3,4-diol (11). Dihydropyran **9** exo (6.5 mg, 0.03 mmol) was dissolved in 1 mL of an acetone/water/*tert*-butyl alcohol (2:5:1) mixture and added to a solution of OsO_4 (42 mg, 0.16 mmol, 5 equiv) in 2 mL of an ether/pyridine (1:1) mixture. After the mixture had stirred for 24 h at room temperature, 10 mg of solid $NaHSO_3$ was added and the solution was saturated in NaCl. The mixture was extracted with ethyl acetate (3 × 5 mL). The organic layers were dried ($MgSO_4$) and evaporated under reduced pressure then chromatographed under the same conditions as above. The triol **11** was obtained as a colorless oil (2 mg, 0.01 mmol, 27%).

^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.23 (3H, s), 1.60 (2H, br m), 3.45 (1H, s), 3.50 (3H, s), 3.64 (1H, dd, J = 4.8, 11.0 Hz), 3.78 (1H,dd, J = 7.2, 11.0 Hz), 3.87 (1H, d, J = 3.9 Hz), 4.30 (1H, t, J = 6.0 Hz), 4.35 (1H, s), 4.91 (1H, d, J = 3.9 Hz), 6.92 (3H, m), 7.25 (2H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 21.9, 56.5, 62.3, 68.0, 69.0, 73.9, 79.3, 101.0, 115.7, 121.9, 130.0, 159.2. CIMS (*t*-BuH, 200 eV) m/z 285 (M + 1, 12), 253 (100), 235 (29), 217 (8).

3-Hydroxy-6-methoxy-4-methyl-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (12b). Dihydropyrane **4b** (96 mg, 0.30 mmol, mixture of 3 isomers 86:7:7) was dissolved in 5 mL of a dichloromethane/water/buffer (pH 7.0) mixture (15:1:1). The solid dichlorodicyanoquinone (DDQ, 10 mg, 0.48 mmol, 1.6 equiv) was then introduced and the mixture stirred for 2 h at room temperature. The organic layer was separated and the aqueous one extracted with dichloromethane (4 × 10 mL). The organic layers were gathered, dried ($MgSO_4$), and evaporated under reduced pressure. The oily residue was then flash chromatographed on silica gel (eluent:heptane/AcOEt 40:60) providing **12b** as a yellowish oil (40 mg, 0.19 mmol, 63%). The major isomer was separated from the other two, which are the endo and exo adducts derived from (1*E*,3*E*)-**2b**.

IR: ν_{max} (film) 3436, 2920, 1732, 1446, 1384, 1210, 1142, 1034, 968 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.31 (3H, t, J = 7.3 Hz), 1.88 (3H, s), 2.48 (1H, d, J = 6.6 Hz), 3.47 (3H, s), 4.20−4.27 (2H + 1H, m), 5.01 (1H, s), 5.50 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.3, 19.6, 55.9, 61.7, 66.4, 75.7, 97.5, 122.6, 138.6, 170.7. CIMS (*t*-BuH, 200 eV) m/z 199 ($M^+H - H_2O$, 5) 185 (M^+H − MeOH, 100), 167 (36), 145 (15), 113 (19).

3-Hydroxy-6-methoxy-3,6-dihydro-2*H*-pyran-2-carboxylic Acid Ethyl Ester (12c). The same procedure as above applied to **4c** (603 mg, 2.1 mmol) in 34 mL of the same solvent mixture to which was added DDQ (760 mg, 3.3 mmol, 1.6 equiv) led to **12c** (310 mg, 1.5 mmol, 73%) as a pale yellow oil.

IR: ν_{max} (film) 3436, 2920, 1732, 1446, 1384, 1210, 1142, 1034, 968 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.27 (3H, t, J = 6.2 Hz), 2.62 (1H, br d, J = 4.1 Hz), 3.44 (3H, s), 4.11 (1H, d, J = 7.9 Hz), 4.21 (2H, m), 4.42 (1H, m), 5.05 (1H, dd, J = 1.5, 3.4 Hz), 5.72 (1H, dt, J = 1.9, 10.2 Hz), 5.99 (1H, ddd, J = 1.5, 3.0, 10.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.4, 56.0, 62.0, 63.6, 76.3, 97.7, 128.0, 131.3, 170.6. EIMS (70 eV) m/z 184 ($M - H_2O$, 11), 167 (13), 149 (36), 111 (81), 97 (100).

2-Hydroxymethyl-6-methoxy-4-methyl-3,6-dihydro-2*H*-pyran-3-ol (13b). A solution of ester **12b** (120 mg, 0.55 mmol) in 4 mL of dry ether was added, under argon, to a suspension of $LiAlH_4$ (50 mg, 1.30 mmol, 2.2 equiv) in 5 mL of cool (0 °C) ether in 15 min. After 2 h of stirring at room temperature, the suspension was hydrolyzed successively with 0.1 mL of water, 0.1 mL of a 4.0 M solution of NaOH, and 0.3 mL of water. The resulting solid was filtered on a Celite pad and washed with ethyl acetate. The organic phases are dried (Na_2SO4) then evaporated under reduced pressure. Diol **13b** was obtained as a pale yellow oil (85 mg, 0.49 mmol, 89%) that did not need further purification.

IR: ν_{max} (film) 3386, 2922, 1448, 1364, 1048 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.79 (3H, s), 2.22 (1H, br s), 2.57 (1H, br s), 3.42 (3H, s), 3.70−3.76 (2H + 1H, m), 3.90 (1H, s), 4.94 (1H, m), 5.44 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.5, 55.8, 64.0, 66.9, 78.3, 97.4, 123.0, 139.7. EIMS (70 eV) m/z 173 (M − H, 1), 143 (5), 125 (8), 114 (61), 83 (100).

2-Hydroxymethyl-6-methoxy-3,6-dihydro-2*H*-pyran-3-ol (13c). The same procedure as above applied to **12c** (140 mg, 0.7 mmol) in 4 mL of dry ether added to LAH (60 mg, 1.57 mmol, 2.2 equiv) led to diol **13c** (96 mg, 0.60 mmol, 87%).

IR: ν_{max} (film) 3382, 2934, 1654, 1392, 1064, 812 cm^{-1}.^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.95 (1H, br s), 2.29 (1H, br s), 3.43 (3H, s), 3.67 (1H, dt, J = 1.5, 6.1 Hz), 3.79 (2H, m), 4.14 (1H, br s), 5.01 (1H, d, J = 1.9 Hz), 5.73 (1H, dt, J = 1.5, 10.6 Hz), 5.98 (1H, ddd, J = 1.6, 3.0, 10.6 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 55.7, 63.5, 63.7, 78.6, 97.7, 128.1, 133.0. CIMS (CH_4) m/z 143 ($M^+H - H_2O$, 24), 129 (M^+H − MeOH, 82), 111 (56), 100 (21), 81 (40).

3,4,5-Trihydroxy-6-methoxy-4-methyltetrahydropyran-2-carboxylic Acid Ethyl Ester (14b). The experimental

procedure described above for **10** was applied to dihydropyrane **12b** (27 mg, 0.12 mmol) in 4 mL of pyridine added to an osmium tetroxide (35 mg, 0.14 mmol, 1.2 equiv) solution in 0.5 mL of pyridine. After 2 h at room temperature, the reaction was quenched with $NaHSO_3$ (1 mL of saturated solution) then water (2 mL). After flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 9:1), **14b** was recovered as a colorless oil (18 mg, 0.07 mmol, 60%).

IR: ν_{max} (film) 3451, 2979, 2934, 1739, 1045 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.27 (3H, t, J = 7.1 Hz), 1.37 (3H, s), 2.38 (2H, br s), 3.08 (1H, br s), 3.19 (1H, d, J = 7.5 Hz), 3.51 (3H, s), 3.55 (1H, br d, J = 9.8 Hz), 4.09 (1H, d, J = 9.8 Hz), 4.21 (1H, dq, J = 1.9, 7.1 Hz), 4.26 (1H, dq, J = 1.9, 7.1 Hz), 4.43 (1H, d, J = 7.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.5, 22.7, 57.7, 62.3, 72.8, 73.5, 73.8, 74.4, 102.8, 170.9. EIMS (70 eV) m/z 232 (M − 18, 1), 219 (M − 31, 1), 200 (3), 172 (1), 117 (30), 104 (39), 87 (100). CIMS (CH_4) m/z 251 (MH^+, 17), 219 (M^+H − MeOH, 95), 201 (100), 183 (31), 155 (14), 127 (11).

3,4,5-Trihydroxy-6-methoxytetrahydropyran-2-carboxylic Acid Ethyl Ester (14c). The experimental procedure described above was applied to dihydropyrane **12c** (50 mg, 0.25 mmol) in 4 mL of pyridine added to an osmium tetroxide (70 mg, 0.28 mmol, 1.1 equiv) solution in 0.5 mL of pyridine. After 2 h at room tempeature, the reaction was quenched with $NaHSO_3$ (1 mL of saturated solution) then water (2 mL). After flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 9:1), **14c** was recovered as a colorless oil (60 mg, 0.25 mmol, 100%).

IR: ν_{max} (film) 3418, 2930, 1736, 1084, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.26 (3H, t, J = 7.1 Hz), 2.78 (3H, br s), 3.47 (1H, dd, J = 3.4, 7.1 Hz), 3.49 (3H, s), 3.86 (1H, dd, J = 3.0, 9.0 Hz), 4.16−4.26 (1H + 2H, m), 4.56 (1H, d, J = 6.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.4, 57.8, 62.2, 69.5, 69.7, 71.0, 73.5, 102.4, 170.8. EIMS (70 eV) m/z 218 (M − 18, 1), 205 (M − 31, 2), 186 (4), 158 (3), 117 (47), 104 (84), 89 (93), 71 (100). CIMS m/z 237 (MH^+, 1), 205 (M + H − MeOH, 18), 187 (100), 169 (55), 159 (9).

[3,4,5-Tris(*tert*-butyldimethylsilanyloxy)-6-methoxytetrahydropyran-2-yl]methanol (15). To a solution of triol **14c** (60 mg, 0.25 mmol) and imidazole (170 mg, 2.5 mmol, 10 equiv) in pyridine (2 mL) was added, at room temperature and under argon, *tert*-butyldimethylsilyl chloride (634 mg, 4.3 mmol, 17 equiv). After 48 h at room temperature, the reaction was quenched with water (0.5 mL). The yellow oily residue thus obtained was directly reduced by LAH (20 mg, 0.5 mmol, 2 equiv) in ether as described above for **13b**. After chromatography (eluent: heptane/AcOEt 95:5), **15** was obtained as a colorless oil (22 mg, 0.05 mmol, 20% for the 2 steps).

IR: ν_{max} (film) 3447, 2928, 2855, 1471, 1250, 1090, 836 cm^{-1}. ^1H NMR (300 MHz, C_6D_6) δ (ppm) 0.27 (15H, s), 0.35 (3H, s), 1.11 (18H, s), 1.13 (9H, s), 2.20 (1H, br s), 3.34 (3H, s), 3.51 (1H, d, J = 6.0 Hz), 3.63 (1H, d, J = 8.7 Hz), 3.90 (3H, m), 4.11 (1H, s), 4.71 (1H, d, J = 7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 19.8, 26.6, 39.8, 57.6, 63.6, 69.5, 73.8, 74.6, 75.3, 102.0.

4,5-Dihydroxy-6-methoxy-3-(4-methoxybenzyloxy)tetrahydropyran-2-carboxylic Acid Ethyl Ester (16). The experimental procedure described above for **10** was applied to dihydropyrane **4c** (87 mg, 0.27 mmol) in 4 mL of pyridine added to an osmium tetroxide (76 mg, 0.30 mmol, 1.1 equiv) solution in 0.4 mL of pyridine. After 2 h at room temperature, the reaction was quenched with $NaHSO_3$ (1 mL of saturated solution) then water (1.5 mL). After flash chromatography on silica gel (eluent: CH_2Cl_2/MeOH 9:1), **16** was recovered as a colorless oil (86 mg, 0.24 mmol, 89%).

IR: ν_{max} (film) 3446, 2922, 1742, 1514, 1248, 822 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.23 (3H, t, J = 7.2 Hz), 2.39 (2H, br s), 3.43 (3H, s), 3.46 (1H, m), 3.73 (3H, s), 3.85 (1H, dd, J = 3.0, 7.1 Hz), 4.15 (3H, m), 4.27 (1H, d, J = 7.5 Hz), 4.44, 4.50 (2H, $2d_{AB}$, J = 11.0 Hz), 4.58 (1H, d, J = 6.0 Hz), 6.79 (2H, d, J = 8.7 Hz), 7.16 (2H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.5, 55.7, 57.8, 61.9, 66.8, 71.2, 72.5, 72.8, 76.8, 102.9, 114.4, 130.0, 159.8, 169.8.

4-Methoxy-7-(4-methoxybenzyloxy)-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyran-6-carboxylic Acid Ethyl Ester (17). Diol **16** (85 mg, 0.24 mmol) prepared above was dissolved in a mixture of dry acetone (6 mL) and 2,2-dimethoxypropane (2 mL) to which was added a catalytic amount of dry camphorsulfonic acid. The mixture was stirred overnight at room temperature under argon. The solvents were then evaporated under reduced pressure and the oily residue directly flash chromatographed on silica gel (eluent: heptane/ethyl acetate 60:40) to provide **17** (65 mg, 0.18 mmol, 75%) as a pale yellow oil.

IR: ν_{max} (film) 3066, 2936, 1744, 1514, 1250, 1094, 822 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.26 (3H, t, J = 7.5 Hz), 1.28 (3H, s), 1.46 (3H, s), 3.36 (3H, s), 3.73 (3H, s), 4.00 (1H, dd, J = 2.9, 6.0 Hz), 4.17 (3H, m), 4.29 (1H, d, J = 9.0 Hz), 4.34 (1H, dd, J = 3.0, 5.9 Hz), 4.45 (1H, d, J = 3.0 Hz), 4.53 (2H, s), 6.79 (2H, d, J = 8.7 Hz), 7.20 (2H, d, J = 8.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.5, 25.4, 27.2, 55.7, 56.9, 61.8, 71.4, 72.1, 72.51, 72.53, 76.1, 101.3, 111.0, 114.1, 130.1, 130.3, 159.8, 171.0. EIMS (70 eV) m/z 364 (M + H − 15, 2), 186 (5), 121 (100).

7-Hydroxy-4-methoxy-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyran-6-carboxylic Acid Ethyl Ester (18). The procedure described above for **12b** and applied to ester **17** (65 mg, 0.16 mmol) and DDQ (55 mg, 0.24 mmol, 1.5 equiv) provided alcohol **18** after the same purification procedure described for **12b** (36 mg, 0.13 mmol, yield 81%) as a colorless oil.

IR: ν_{max} (film) 3468, 2986, 2934, 1744, 1094 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 1.26 (3H, t, J = 7.2 Hz), 1.31 (3H, s), 1.47 (3H, s), 1.60 (1H, br s), 2.79 (1H, d, J = 6.0 Hz), 3.41 (3H, s), 4.14 (1H, dd, J = 2.6, 7.2 Hz), 4.19−4.27 (3H, m), 4.50 (1H, d, J = 3.3, 7.2 Hz), 4.55 (1H, d, J = 2.7 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 14.5, 25.3, 26.9, 56.8, 62.1, 66.0, 72.2, 73.2, 75.9, 100.5, 111.1, 171.9. EIMS (70 eV) m/z, 261 (M + H− 15, 28), 229 (16), 85 (100).

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Supporting Information Available: Copies of the ^1H NMR and/or ^{13}C spectra for compounds **1c**−**d**, **2b**−**d**, **4b**,**c**, **5**, **9**, **10**, **11**, **12b**,**c**, **13b**,**c**, **14b**,**c**, and **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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