Diastereofacial Selectivity of Diels–Alder Reactions of Carbohydrate-Derived Dienes and Their Carbocyclic Analogs†

Robert M. Giuliano*

Department of Chemistry, Villanova University, Villanova, Pennsylvania 19085

Alfonzo D. Jordan, Jr., and A. Diane Gauthier

Department of Medicinal Chemistry, The R. W. Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania 19477

Karst Hoogsteen

Merck Research Laboratories, P.O. Box 2000, Rahway, New Jersey 07065

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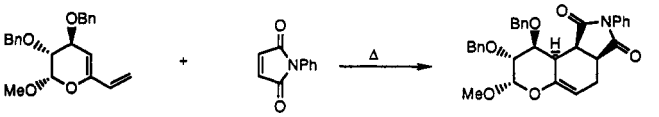
The Diels–Alder reactions of two dienes derived from carbohydrates and their carbocyclic analogs are described. The dienes (2*S*)-3,4-dihydro-2-methoxy-6-vinyl-2*H*-pyran (1) and (4*R*)-3,4-dihydro-4-methoxy-6-vinyl-2*H*-pyran (2) were synthesized from tri-*O*-acetyl-D-glucal. Cycloaddition reactions of these dienes, each of which contains a single methoxy group at either the allylic or anomeric position, were carried out with a series of dienophiles including *N*-phenylmaleimide, dimethyl acetylenedicarboxylate, diethyl azodicarboxylate, and *N*-phenyl-1,2,4-triazoline-3,5-dione. The incorporation of an amine base in the Diels–Alder reactions was found to be essential for the formation of good yields of unrearranged cycloadducts. Structures of the cycloadducts were assigned using NMR methods and X-ray crystallographic analysis. The diastereofacial selectivities observed for dienes 1 and 2 are compared with those of the analogous carbocyclic dienes 3 and 4, the former of which was synthesized for this study from *m*-anisic acid. Cycloadditions to both the carbohydrate-derived dienes and their carbocyclic analogs were found to occur with a preference for addition of the dienophile to the face of the diene opposite the methoxyl group in every case. The degree of stereoselectivity was sensitive to a number of factors including the location of the substituents attached to the ring of the semicyclic diene, the presence of oxygen in the ring, and the type of dienophile. The dominant trend for anti addition in the Diels–Alder reactions is discussed in terms of diene conformation and secondary orbital effects in the transition state for cycloaddition.

Introduction

Carbohydrate derivatives have been utilized as dienes and dienophiles in the Diels–Alder reaction, as substrates in analogous heteroatom processes, and as 1,3-dipoles and dipolarophiles in dipolar cycloadditions.[1] Numerous applications of these methodologies to the synthesis of enantiomerically pure carbocyclic and heterocyclic compounds[2] serve to demonstrate the potential of carbohydrate-based cycloadditions in organic synthesis; however, our understanding of the factors which control facial selectivity in such reactions has remained limited. The principle difficulty in predicting the stereoselectivity of carbohydrate-based cycloadditions results from the presence of multiple stereogenic centers and functionality, as well as conformational properties of carbohydrate systems. The problem is illustrated by the Diels–Alder reaction of dieno-pyranoside **I**,[3] in which the major product **II** resulted from cycloaddition to the face of the diene syn to the allylic substituent, in contrast to the dominant anti-directing effect of allylic ether groups in this position in simpler,



I II

semicyclic dienes.[4,5] From this and other examples with multiply substituted dienes,[6] it is evident that strong stereodirecting effects are exerted by substituents at both the allylic and remote centers; however, it is difficult to assess the influence of any single group. In order to determine the relative effects of pyranose-ring substituents on the diastereofacial selectivity, it was considered important to examine the Diels–Alder reactions of monosubstituted dieno-pyranosides with a variety of dienophiles.

In our previous studies of the Diels–Alder reactions of dieno-pyranosides,[3,7] the cycloadditions of dienes 1 and 2 to maleic anhydride, maleimide, and its *N*-phenyl derivative were attempted. Instead of the expected products, rearranged cycloadducts were obtained from both dienes, presumably by an acid-catalyzed double bond shift in the

† Taken from the Ph.D. thesis of Alfonzo D. Jordan, Jr.

(1) *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; American Chemical Society: Washington, D.C., 1992.

(2) For recent applications, see: (a) Tsang, R.; Fraser-Reid, B. *J. Org. Chem.* **1992**, *57*, 1065. (b) Kim, K. S.; Cho, I. H.; Joo, Y. H.; Yoo, I. Y.; Song, J. H.; Ko, J. H. *Tetrahedron Lett.* **1992**, *33*, 4029. (c) Chmielewski, M.; Grodner, J. *J. Carbohydr. Chem.* **1992**, *11*, 691. (d) Herscovi, J.; Delatre, S.; Antonakis, K. *Tetrahedron Lett.* **1991**, *32*, 1183. (e) Mukhopadhyay, Ali, S.; Husain, M.; Suryawanshi, S. N.; Bhakuni, D. S. *Tetrahedron Lett.* **1989**, *30*, 1853.

(3) Giuliano, R. M.; Buzby, J. H.; Macropulos, N.; Springer, J. P. *J. Org. Chem.* **1990**, *55*, 3555.

(4) Datta, S. C.; Franck, R. W.; Tripathy, R.; Quigley, G. J.; Huang, L.; Chen, S.; Sihaed, A. *J. Am. Chem. Soc.* **1990**, *112*, 8472.

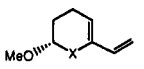
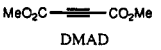
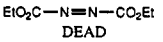
(5) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625.

(6) (a) Lopez, J. C.; Lameignere, E.; Lukacs, *J. Chem. Soc., Chem. Commun.* **1988**, 706. (b) Burnouf, C.; Lopez, J. C.; de los Angeles Laborde, Garcia Calvo-Flores, F. M.; Olesker, A.; Lukacs, G. *J. Chem. Soc., Chem. Commun.* **1990**, 823. (c) Lipshutz, B. H.; Nguyen, S. L.; Elworthy, T. R. *Tetrahedron* **1988**, *44*, 3355.

(7) Giuliano, R. M.; Buzby, J. H. *Carbohydr. Res.* **1986**, *158*, c1.

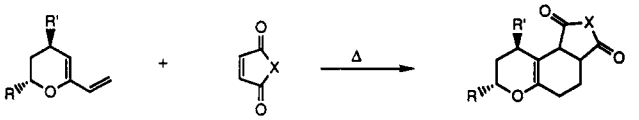
0022-3263/93/1958-4979$04.00/0

Table I. Dienes and Dienophiles[a]

dienes	dienophiles
 1 X = O 3 X = CH_2	 NPM
 2 X = O 4 X = CH_2	 PTAD
	 DMAD
	 DEAD

[a] Dienes 3 and 4 are racemic. (*S*)-1 and (*R*)-2 were prepared from tri-*O*-acetyl-D-glucal.

initial product. As a result of the rearrangement, we were unable to determine the stereodirecting effects of the single (anomeric) substituent in 1, or the single (allylic) substituent in 2 because the critical ring-junction stereocenter is destroyed by the double-bond migration. Furthermore, the effect of the ring oxygen on the diastereofacial selectivity of cycloadditions to 1 or 2 could not be evaluated by comparison with results for the corresponding carbocyclic dienes. The carbocyclic analog of diene 2 has been recently synthesized and a study of its Diels–Alder reactions has been described.[4] The carbocyclic analog of 1, unknown at the outset of our investigation, was developed in our laboratory.

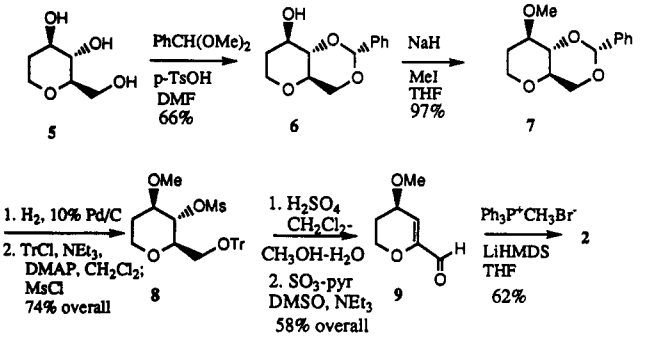


1: R=OMe, R'=H
2: R=H, R'=OMe

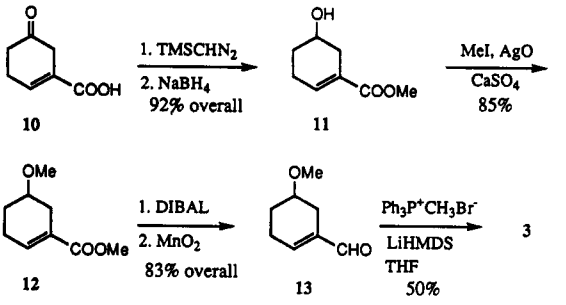
X = O, NH, NPh

In this article, we describe the results of a new study of Diels–Alder reactions of 1 and 2, in which we discovered that rearrangement of the cycloadducts does not occur if the reactions are carried out in the presence of an amine base. The synthesis and Diels–Alder reactions of the carbocyclic analog of 1, diene 3, are also described. Cycloadducts were obtained stereoselectively from dienes 1–3 with a variety of dienophiles (Table I) including *N*-phenylmaleimide (NPM), dimethyl acetylenedicarboxylate (DMAD), diethyl azodicarboxylate (DEAD), and *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD); however, the isomer ratios varied significantly according to diene and dienophile structure. These results allow the stereodirecting effects of single substituents to be evaluated independently of other groups on the diene and for the effect of the ring oxygen to be observed by direct comparisons with carbocyclic dienes. These comparisons have not been described in previous studies of carbohydrate-derived dienes. The stereochemistry of the cycloadducts were assigned by NMR and, in one case, X-ray crystallographic analysis. A rationale for the observed selectivity is presented which takes into account diene substitution and conformation, dienophile geometry, and secondary orbital effects in the cycloaddition transition state. Oxidative transformation of the cycloadducts derived from dienes 1 and 2 was also investigated as a new method for the synthesis of benzannelated pyranosides.

Scheme I. Synthesis of Dieno-Pyranoside 2



Scheme II. Synthesis of Carbocyclic Diene 3



Results

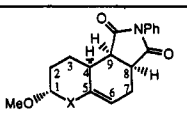
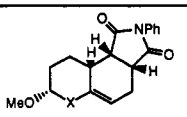
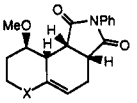
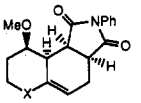
Diene Synthesis. Dieno-pyranoside 1 was synthesized from tri-*O*-acetyl-D-glucal by a general route developed in this laboratory and described in earlier publications.[3,7] With slight modifications, this route was readily adapted to the synthesis of diene 2 (Scheme I) in 17% overall yield. Benzylidenation of triol 5 followed by methylation, hydrogenolysis, and derivatization gave 8, which was converted via the enal 9 to diene 2. Conditions for the Wittig reaction (LiHMDS, THF) were critical; other bases and solvents were found to give lower yields of diene. In all cases, dienes were not stored but rather used immediately in Diels–Alder reactions. The carbocyclic analog of diene 2 is 3-methoxy-1-vinylcyclohexene (4), which was synthesized by Franck and co-workers[4] in their study of face-selective Diels–Alder reactions of semicyclic dienes. Diene 3, the carbocyclic analog of 1, has not been reported in the literature. Using an efficient synthesis of 5-oxocyclohexenecarboxylic acid recently described by Webster and Silverstein,[8] we developed a route to 3 (Scheme II).

Esterification of the keto acid 10 was carried out with (trimethylsilyl)diazomethane,[9] and the resulting keto ester was reduced with sodium borohydride. Methylation of the reduction product 11 gave 12. An alternative sequence to 12 consisting of borohydride reduction of 10 to the hydroxy acid and methylation of both hydroxyl and carboxyl groups in a single step gave inferior results. The double bond in the product of borohydride reduction (10) was prone to migration under the conditions needed to alkylate both acid and hydroxyl functionalities in a single step. Transformation of the ester group to an aldehyde and Wittig alkenation gave the diene 3 in 32% overall yield from 10.

Diels–Alder Reactions. The first Diels–Alder reactions attempted were those of dienes 1 and 2 with *N*-phenylmaleimide in refluxing benzene, conditions which

(8) Webster, F. X.; Silverstein, R. M. *Synthesis* **1987**, 922.
(9) Hashimoto, N.; Hoyama, T.; Shiori, T. *Chem. Pharm. Bull.* **1981**, *29*, 1478.

Table II. Diels–Alder Reactions of Monosubstituted Dienes and Carbocyclic Analogs with *N*-Phenylmaleimide

entry	diene	anti adduct (endo)	syn adduct (endo)	% yield	ratio (anti/syn)[a]
					
1	1	14 X = O	15 X = O	78	6.8:1
2	3	16 X = CH_2	17 X = CH_2	57	2.6:1
					
3	2	18 X = O	19 X = O	76	>30:1
4[b]	4	20 X = CH_2	21 X = CH_2	82	8.1:1

[a] Isomer ratios were determined by ^{1}H-NMR spectral integration. [b] Reference 4.

afforded the best yields of cycloadducts from other carbohydrate-derived dienes in our previous studies. Under these conditions, mixtures of cycloadducts were obtained from 1 and 2 that contained products derived from migration of the double bond to the ring-junction position. Suspecting that rearrangement of the initially formed cycloadducts might be occurring in the presence of traces of acid, we reexamined cycloadditions of 1 and 2 with NPM in the presence of 1 equiv of triethylamine or diisopropylethylamine. In the presence of either base, the expected Diels–Alder adducts were formed in typical yields of 70–80%. Reaction conditions involving solvents other than benzene (acetonitrile, DMF) did not afford higher yields or stereoselectivities in reactions of 1 or 2 with NPM; however, improved yields of cycloadducts were obtained in the reactions of 1 with NPM and DMAD) in benzene at 120 °C in a sealed tube. The lack of a solvent effect is not surprising since the hydroxyl groups on the diene are protected as methyl ethers.[5] Results of the cycloadditions carried out with NPM are shown in Table II for dienes 1 and 2 and their carbocyclic analogs. Diels–Alder adducts 14 (anti) and 15 (syn) were obtained as an inseparable mixture in a ratio of 6.8 to 1 from 1, while diene 2 gave exclusively the anti adduct 18. The structure of 18 was assigned on the basis of analysis of *J*-values in its ^{1}H-NMR spectrum. The value of 8.3 Hz for $J_{3,4}$ in 18 implies a trans relationship for these two protons which would exist in the endo or exo cycloadducts resulting from addition of the dienophile to the face of 2 opposite the allylic methoxyl group, but not in the adducts formed by addition syn to the methoxyl group. The value of 5.35 Hz for $J_{4,9}$ is consistent with a cis relationship for H-4 and H-9, in accord with previous results, and is indicative of the endo orientation. Similar values were observed by Franck and co-workers[4] for the anti adduct 20, obtained from the carbocyclic diene 4 as the major product. The structure of 14, obtained by reaction of diene 1 with NPM, was confirmed by X-ray crystallographic analysis and shows that the pyranoid ring exists in the boat conformation in the solid state with the methoxyl group pseudoequatorial (Figure 1). This stereochemistry of the product indicates that addition of the dienophile to 1 took place from the face opposite the anomeric methoxyl group, in the endo mode. Structural analysis of 14 and its structural analog 16 (obtained from diene 3) by NMR methods proved difficult because of the overlap of the key H-4 resonance with other peaks and the absence of a substituent at C-3. The ^{1}H NMR spectra of 16 and that of the minor adduct 17 showed significant differences in chemical shift and coupling constants. The fortuitous separation of 16 and 17 by column chromatography allowed

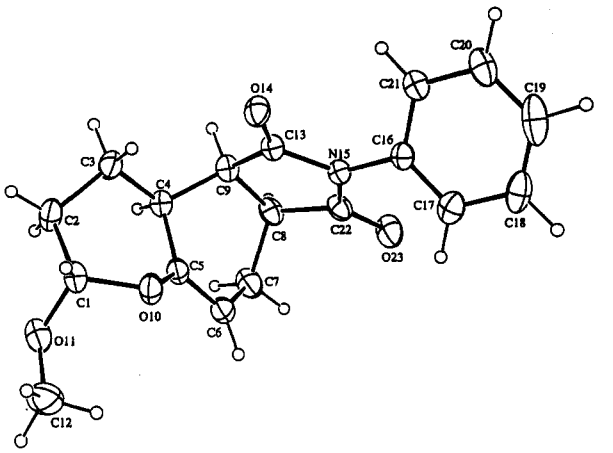
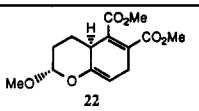
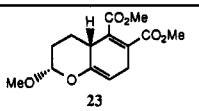
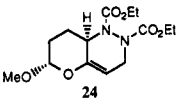
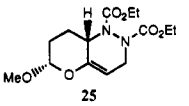
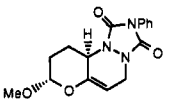
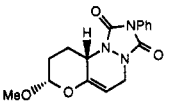


Figure 1. Computer-generated drawing of 14 derived from the X-ray coordinates with the hydrogens omitted for clarity.

us to obtain clean NMR spectra for both isomers. The H-1 resonances for 16 and 17 appear at 2.95 and 3.15 ppm, respectively. In the case of 16, the H-1 peak occurs as a well-resolved eight-line pattern while the H-1 peak for 17 is narrower and less well-defined. Assuming that the ring adopts the chair conformation in the minor (syn) cycloadduct 17, a smaller band width and downfield chemical shift would both be expected for H-1 because it would be equatorial. In the major cycloadduct 16, the chair conformation would require H-1 to adopt an axial position, so an upfield shift and larger band width would be expected. Endo stereochemistry is assumed for 17 as well as the other minor cycloadducts which were obtained from diene 1. This assignment is consistent with the results reported for previous examples of Diels–Alder reactions of dieno-pyranosides with NPM, none of which have been reported to give exo adducts.[7] Furthermore, exo adducts were observed in neither of the two studies of Diels–Alder reactions of substituted vinylcycloalkenes reported by the Franck and Overman groups.[4,5]

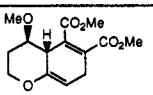
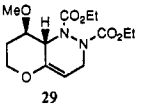
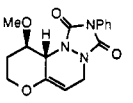
Cycloadditions of 1 and 2 were also attempted with dimethyl acetylenedicarboxylate, diethyl azodicarboxylate (DEAD), *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD), and both benzo- and naphthoquinone. Reactions with the quinonoid dienophiles did not afford significant yields of cycloadducts, giving instead low yields of products which exhibited resonances typical of aromatic compounds in their NMR spectra. Cycloadditions of 1 and 2 occurred smoothly with DMAD and the other two dienophiles (Tables III and IV). The variety of functionality obtained in the resulting adducts and the stereoselectivity of these reactions further demonstrates the versatility of cycload-

Table III. Diels–Alder Reactions of Diene 1 with DMAD, DEAD, and PTAD

entry	dienophile	anti adduct	syn adduct	% yield	ratio (anti/syn)
1	DMAD	 22	 23	83[a]	1.8:1
2	DEAD	 24	 25	73	6.7:1
3	PTAD	 26	 27	60	9:1

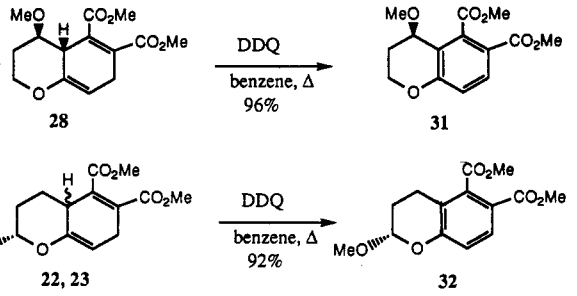
[a] Carried out in a sealed tube at 120 °C for 21 h. A lower yield (30%) and different ratio of anti to syn products (3:1) were observed under the usual conditions (refluxing benzene).

Table IV. Diels–Alder Reactions of Diene 2 with DMAD, DEAD, and PTAD

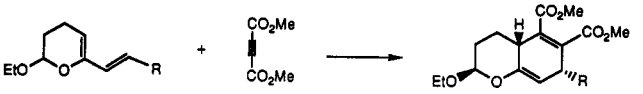
entry	dienophile	anti adduct	% yield
1	DMAD	 28	46[a]
2	DEAD	 29	80
3	PTAD	 30	48

[a] Obtained as a 9:1 mixture of isomers.

Scheme III. Conversion of DMAD Cycloadducts to Benzannelated Pyranosides

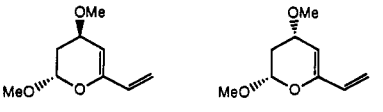


ditions with carbohydrate-derived dienes. The major cycloadducts obtained from diene **2** (Table IV) were those resulting from addition of the dienophile to the face of the diene opposite the allylic methoxyl group in each case. This diastereofacial selectivity was assigned by analysis of the H-3–H-4 coupling constants in each of the products. Values of 10.2 (in **28**), 8.3 (in **29**), and 9 Hz (in **30**) are consistent with trans relationships for H-3 and H-4 which would exist in the cycloadducts resulting from anti addition, but not in those resulting from syn addition. The results obtained for the cycloaddition of diene **1** with the same three dienophiles (Table III) indicate a similar, albeit less pronounced, stereoselectivity favoring the formation of the anti cycloadducts. NOE difference spectroscopy coupled with double irradiation experiments were used to assign the structure of the major cycloadduct **26** obtained from the addition of **1** to PTAD. For example, H-4 in **26** is coupled to H-3*a* with a value of 10.85 Hz and shows a signal enhancement upon irradiation of H-3*e*. The anti stereochemistry of **22** is in agreement with the results observed by Wada for Diels–Alder reactions of 2-ethoxy-6-(1-alkenyl)-3,4-dihydro-2*H*-pyrans with acetylenic dienophiles,[10] in which the major products obtained were the anti isomers resulting from addition of the dienophile to the face of the diene opposite the ethoxy group.



Discussion

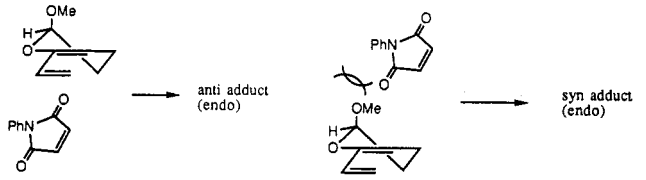
Cycloadditions of both the dieno-pyranosides and their carbocyclic analogs occur with a preference for addition of the dienophile to the face of the diene opposite the methoxyl group in all cases examined in this study. It is also clear from our results that the diastereofacial selectivity of Diels–Alder reactions of **1**–**4** is sensitive to a number of variables including: (1) the location of the substituent on the semicyclic diene, (2) the presence of oxygen in the ring, and (3) the type of dienophile. Each of these factors is considered in the following discussion, and a rationale for the variations in selectivity is presented which includes an analysis of diene conformation and reactivity, and secondary orbital interactions. Diene substitution is considered first. The Diels–Alder reactions of diene **1** exhibit a lower diastereofacial selectivity for anti addition than that for the analogous cycloadditions of **2** in every case examined. Our previous studies of multiply-substituted carbohydrate dienes revealed strong anti-directing effects for groups at both the anomeric and allylic positions, but the anomeric group seemed to have a slightly larger effect in systems that were substituted at *both* sites. For example, cycloaddition of maleimide to dieno-pyranoside **III** occurred preferentially from the face opposite the anomeric group, albeit in lower stereoselectivity than for **IV** which gave a single, anti cycloadduct.[3]


III IV

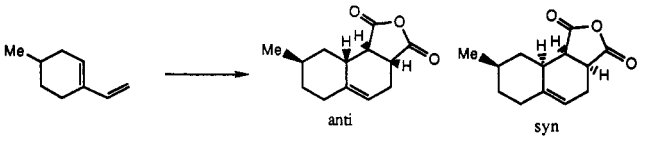
(10) Wada, E.; Kanemasa, S.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1198.

Thus, while the trends in diastereofacial selectivity that are observed with dienes 1 and 2 are consistent with earlier studies involving more highly substituted carbohydrate dienes, the effect of an anomeric group relative to one at the allylic position appears somewhat diminished in these monosubstituted dieno-pyranosides.

The importance of the anomeric effect and other electronic effects due to the ring oxygen emerges from a comparison of the Diels–Alder reactions of 1 and 2 with those of carbocyclic dienes 3 and 4. Carbocyclic diene 4 exhibited slightly less anti selectivity than 2 in its cycloadditions to NPM; however, the selectivity for anti addition was even lower for 3, which gave only a 2.6:1 ratio of anti to syn cycloadducts. This difference may reflect the greater preference for 1 (vis-a-vis 3) to adopt the half-chair conformation in which the anomeric methoxyl group is axial in the transition state for cycloaddition. Endo transition states for both anti and syn addition of NPM to 1 are depicted below. If the diene adopts the half-chair conformer with the methoxyl group pseudoaxial, predicted by the anomeric effect, a high stereoselectivity for anti addition would be expected because of the unfavorable steric effects that would result in the transition state for syn addition. By contrast, if the diene adopted the alternate half-chair conformation in which the methoxyl group is pseudoequatorial, the anomeric substituent would block the face for syn addition less effectively, and a lower preference for anti addition might then be expected. More difficult to understand is the stereoselectivity observed in the Diels–Alder reaction of diene 3, in which the ring oxygen has been replaced by carbon. In the absence of an anomeric effect, one might expect the cyclohexene ring in

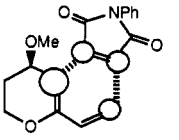


diene 3 to adopt the conformation in which the methoxyl group is pseudoequatorial; however, the preference would be less than that observed in the analogous cyclohexane because of the presence of the ring double bond, which would decrease the 1,3-nonbonded interactions. The preference for anti addition to carbocyclic diene 3 is consistent with results of a previous study of the cycloaddition reactions of a series of 4-alkyl-1-vinylcyclohexenes by Quin and MacDiarmid.[11] The 4-methyl diene shown below gave a 2:1 ratio of anti to syn cycloadducts when

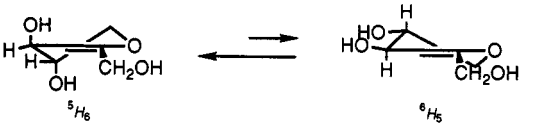


treated with maleic anhydride. The authors caution against an analysis of diastereofacial selectivity which would assume one of the diene conformers to be more reactive; however, they do suggest that the observed kinetic preference for the anti product is more consistent with preferred cycloaddition to the diene conformer in which the methyl group is axial rather than equatorial. In the major (anti) cycloaddition products obtained from the 4-methyl-substituted diene, the methyl group occurs in an axial orientation, while the methyl group is equatorial in the minor syn adducts. The systems studied by Quin are not strictly analogous to 3 because the substituent on the diene is different, and occupies the adjacent site on the ring. The results obtained in both studies suggest an anti directing effect for substituents at these remote locations in semicyclic dienes, but the origin of the effect remains unclear.

A second stereoelectronic effect due to the ring oxygen is manifest in diene 2, which exhibits higher diastereofacial selectivity for anti addition than does its carbocyclic analog 4. The ring oxygen may distort the transition state toward the diene carbon with the largest orbital coefficient, C-3. This distortion would enhance the stereodirecting effect of the allylic substituent which is attached to the adjacent carbon and result in greater selectivity for addition of the dienophile to the face of the diene opposite the allylic group. This same argument was postulated by McDougal in a study of acyclic 2-alkoxy dienes that also contained



allylic substituents.[12] In semicyclic dienes which lack this oxygen substituent, such as 4, this type of distortion in the transition state would not be expected, and the effect of the allylic substituent on facial selectivity would not be as great. An additional stereodirecting effect in 2 may result from the location of the methoxyl group at the allylic position. Electronegative substituents at allylic positions in unsaturated pyranoses have been shown to favor the axial position.[13,14] A recent example of this preference is the glycal below which was shown by ^{1}H-NMR to favor the $^5H_6$ conformation.[15] If diene 2 prefers a conformation in which the methoxyl group is axial, an enhanced degree of anti selectivity would be expected because of the unfavorable steric interactions that would exist in the transition state for syn addition.



The degree of diastereofacial selectivity for dienes 1 and 2 varied with dienophile structure. With PTAD as the dienophile, anti to syn ratios of 9:1 and >30:1 were observed for 1 and 2, respectively. These stereoselectivities are comparable to those observed for the cycloaddition of 1 and 2 to *N*-phenylmaleimide. Both dienes showed lower selectivities when dimethyl acetylenedicarboxylate (DMAD) was the dienophile, however, the decrease was more severe for diene 1, which gave only a 1.8:1 ratio of anti to syn adducts. The lower anti selectivity observed in the reaction of 1 with DMAD reflects the decrease in

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nonbonded interactions in the transition state for syn addition when the dienophile is linear as opposed to cyclic. With cyclic dienophiles such as NPM, the endo transition state for syn addition to 1 suffers from an unfavorable steric interaction of the dienophile carbonyl group with the methoxyl group on the diene. This interaction does not occur in the syn transition state if the dienophile is linear, thus, higher amounts of syn cycloadduct are obtained.

An important factor in determining facial selectivity of cycloadditions to 1 as well as other dieno-pyranosides may be the dominant preference for endo transition states. Estimates of 3–5 kcal/pmol have been postulated for the difference in energies between endo and exo transition states for cycloadditions to cyclopentadiene derivatives.[16] A similar difference in energies for the transition states for endo and exo addition to 1 would result in high diastereofacial selectivity for anti addition, especially in the case of nonlinear dienophiles (NPM, PTAD) which would encounter an unfavorable steric effect in the transition state for syn endo addition because of the proximity of the anomeric methoxyl group. This difference would be also be a factor in cycloadditions involving diene 2, in which the unfavorable interaction involves the vinyl hydrogen of the dienophile, as noted by Franck.[4]

Conclusion

In summary, our study of Diels–Alder reactions of monosubstituted dieno-pyranosides and their carbocyclic analogs enables the various factors that control facial selectivity to be observed and evaluated independently. It is clear that in semicyclic dienes of the type studied herein, a strong preference for anti addition can be expected with most dienophiles, and that the selectivity is the result of a both steric and electronic effects. We have shown that pyranose-derived dienes (1 and 2) exhibit greater diastereofacial selectivity than their carbocyclic analogs (3 and 4) in the Diels–Alder reaction with cyclic as well as linear dienophiles. The enhanced stereoselectivity is ascribed to different stereoelectronic effects of the ring oxygen. Both the anomeric effect and the secondary orbital interactions well known in cycloaddition reactions serve to enhance the diastereofacial selectivity in the Diels–Alder reactions of 1 and 2. The tendency for electronegative groups that occupy an allylic position in pyranoses to adopt an axial orientation may also account for the higher stereoselectivities observed with 2 and other carbohydrate-derived dienes substituted at this position.[3] The trends that emerged from this investigation add to the body of literature on the facial selectivity of Diels–Alder reactions and to the synthetic methodology of carbohydrate cycloadditions.

The cycloadducts obtained from dieno-pyranosides 1 and 2 contain multiple functional groups and are optically active. Our future studies in carbohydrate cycloaddition chemistry will focus on the development of useful chiral synthons for these and related cycloadducts. In preliminary experiments, we have successfully converted the mixture of 22 and 23 to 32, and the single DMAD adduct from diene 2 to 31. This approach to benzannelated pyranosides is complementary to the one developed by Card[17] in which the ring skeleton was constructed by Diels–Alder reactions of carbohydrate-derived dienophiles. The rapid access to optically active carbocyclic compounds that is afforded through cycloaddition reactions of carbohydrate dienes also suggests applications in the important field of C-glycoside chemistry.[6,18]

Experimental Section

General Methods. ^{1}H-NMR spectra were recorded on Bruker AM-400WB (400 MHz) and Bruker ACF-300WB (300 MHz) spectrometers; ^{13}C-NMR spectra were obtained at 100.6 and 75.5 MHz. Tetramethylsilane was used as the internal reference. Melting points were determined with a Thomas-Hoover apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories (Knoxville, TN). EI mass spectra were recorded on a Hewlett-Packard 5970 GC/MS system. CI mass spectra were recorded on a Finnegan 3300–6100 system using ammonia or methane as the reagent gas. FAB mass spectra were recorded on a VG 7070 high resolution mass spectrometer using an argon beam at 7 Kv and 2 mA in a thioglycerol matrix. The progress of reactions was monitored by thin-layer chromatography on Whatman MK6F 250-μm silica gel plates. IR spectra were recorded on a Nicolet 60SX FT instrument. Optical rotations were measured with a Perkin-Elmer 241 polarimeter at 20 °C. Solvents were analytical or reagent grade and were used as purchased.

1,5-Anhydro-2-deoxy-4,6-*O*-(phenylmethylene)-D-*arabino*-hexopyranoside (6). A solution of triol 5[19] (27.08 g, 182.9 mmol), benzaldehyde dimethyl acetal (40 mL, 266 mmol), and *p*-toluenesulfonic acid (8.65 g, 45.5 mmol) in anhydrous dimethylformamide (180 mL) was stirred at room temperature for 27 h. The reaction mixture was quenched with aqueous sodium bicarbonate solution (200 mL) and extracted with chloroform (3 × 200 mL), and the combined chloroform extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated to give solid 6 which was rinsed with hexane and dried in a vacuum oven for 1 d at 50 °C: yield 28.31 g (66%); mp 101.5–102.5 °C; R_f = 0.33 (1:1 ethyl acetate–hexane); $[\alpha]_D$ −32° (*c* 1, $CHCl_3$); IR (cm^{-1}, KBr) 3504 (OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.34 (m, 5 H, Ph-H), 5.55 (s, 1 H, PhCH), 4.30–4.26 (m, 1 H), 4.00–3.96 (m, 1 H), 3.90–3.83 (m, 1 H), 3.70 (t, 1 H), 3.59–3.52 (m, 1 H), 3.43 (t, 1 H), 3.41–3.30 (m, 1 H), 2.64 (m, 1 H, OH), 2.03–1.98 (m, 1 H), 1.85–1.75 (m, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.30, 129.23, 128.35, 126.22, 101.95, 83.93, 71.11, 69.44, 68.86, 66.26, 33.24; CIMS *m/z* (rel inten) 237 (MH^+, 80), 148 (90), 113 (100). Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83. Found: C, 66.15; 6.86.

1,5-Anydro-2-deoxy-3-*O*-methyl-4,6-*O*-(phenylmethylene)-D-*arabino*-hexopyranoside (7). A 1-L three-necked flask was charged with sodium hydride (2.48 g of 80% dispersion in mineral oil, 82.6 mmol NaH) and the mineral oil was removed by washing with pentane (3 × 50 mL) under an atmosphere of nitrogen. Anhydrous THF (100 mL) was added followed by, at 0 °C (ice bath), a solution of 6 (16.04 g, 68 mmol) in THF (200 mL) added dropwise with stirring over a 90-min period. The bath was removed and iodomethane (13 mL, 208 mmol) was added dropwise. The reaction mixture was stirred at room temperature until starting material was consumed and then sodium sulfate decahydrate (20 g) was added. The resulting mixture was partitioned between water (100 mL) and chloroform (300 mL), the layers were separated, and the aqueous phase was extracted with chloroform (100 mL). The combined chloroform extracts were dried (Na_2SO_4) and concentrated to give crude 7 which was purified by flash chromatography on silica gel (250 g) using 35% ethyl acetate in hexane to give 16.54 g (97%) of 7 as a white solid: mp 67–70 °C; R_f = 0.67 (1:1 ethyl acetate–hexane); $[\alpha]_D$ −21.7 (*c* 1, $CHCl_3$); IR (cm^{-1}, KBr) 2935, 2878, 1456, 1385, 1103, 1004; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50–7.30 (m, 5 H, Ph-H), 5.58 (s, 1 H, PhCH), 4.28 (dd, 1 H, *J* = 4.90, 10.57 Hz, H-2), 3.99 (dd, 1

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H, J = 4.97, 11.66), 3.71 (t, 1 H, J = 10.45, 10.15 Hz), 3.59–3.45 (m, 6 H), 3.34 (ddd, 1 H, J = 4.92, 9.59, 9.29), 2.09 (ddd, 1 H, J = 2.10, 4.70, 10.89 Hz, H-2'), 1.69 (dddd, 1 H, J = 5.37, 13.10, 10.84, 13.16); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 137.58 (PhCH), 128.88, 128.19, 126.14, 101.48, 83.62, 77.87, 68.93, 66.37, 58.16 (OCH_3), 31.69 (C-2); CIMS m/z (rel inten) 251 (MH^+, 50), 162 (80), 145 (40), 113 (100). Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.29; H, 7.19.

1,5-Anhydro-2-deoxy-3-*O*-methyl-4-*O*-(methylsulfonyl)-6-*O*-(triphenylmethyl)-D-*arabino*-hexopyranoside (8). A solution of **6** (28.69 g, 115 mmol) in absolute ethanol (125 mL) and glacial acetic acid (10 mL) was hydrogenated under 55 psi of hydrogen using 10% palladium on carbon for 21 d. (Recently, the reaction time was shortened to 2 d by heating to 50 °C.) The catalyst was removed by filtration through a bed of Celite, the bed was washed with ethanol, and the filtrate was concentrated. Azeotropic removal of acetic acid with benzene afforded 18.60 g (99%) of diol (1,5-anhydro-2-deoxy-3-*O*-methyl-D-*arabino*-hexopyranoside) as a yellow syrup: mp 57–59 °C; R_f = 0.22 (4:1 chloroform–methanol); $[\alpha]_D$ −17.9 (c 0.9, $CHCl_3$); IR (cm^{-1}, film) 3397 (OH), 2935, 2865, 1086, 1040; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (dd, 1 H, J = 4.51, 11.74, H-2), 3.87–3.75 (m, 3H), 3.60–3.44 (m, 2 H), 3.43 (s, 3 H, OCH_3), 3.27–3.20 (m, 3H), 2.08 (ddd, 1 H, J = 4.64, 10.67, 2.44 Hz), 1.57–1.50 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 82.22, 80.04, 70.98, 62.64 (C-1), 56.42 (OCH_3), 29.83 (C-2); CIMS m/z (rel inten) 163 (MH^+, 25), 131 ($MH^+ - CH_3OH$, 80), 113 (100). Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.66; H, 8.72. A solution of diol (4.92 g, 30.3 mmol), triphenylmethyl chloride (9.54 g, 34.2 mmol), triethylamine (6.5 mL, 46.6 mol), and (dimethylamino)pyridine (0.158 g, 1.29 mmol) in dichloromethane (100 mL) was stirred at room temperature for 15 h. The reaction mixture was cooled to 0 °C (ice bath) and then a solution of methanesulfonyl chloride (3.2 mL, 41.3 mmol) and triethylamine (4.0 mL, 28.4 mmol) in dichloromethane (20 mL) was added slowly. After stirring at room temperature for 1 h, the reaction mixture was diluted with dichloromethane (200 mL), washed with aqueous ammonium chloride solution and water, dried (Na_2SO_4), and concentrated to a syrup which solidified upon treatment with ethanol to afford 9.93 g (68%) of **8**: mp 151–154 °C, R_f = 0.76 (3:2 ethyl acetate–hexanes); IR (cm^{-1} KBr) 2955, 2861, 1596, 1361; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.20 (m, 15 H, Ph-H), 4.47 (t, 1 H, J = 9.10, 9.21 Hz), 4.10–4.07 (m, 1 H), 3.47–3.33 (m, 7 H), 3.22 (dd, 1 H, J = 10.07, 5.50 Hz), 2.78 (s, 3H, SO_2CH_3), 2.21–2.18 (m, 1H), 1.66 (dddd, 1 H, J = 4.97, 12.68, 11.89, 12.67); ^{13}C NMR (100.6 MHz) δ 143.72, 128.89, 127.74, 126.97, 79.89 (C-5), 79.46, 78.12, 65.29 (C-1), 63.17 (C-6), 56.12 (OCH_3), 38.58 (SO_2CH_3), 30.42 (C-2); FABMS (thioglycerol) m/z (rel inten) 243 (20), 109 (30), 91 (100). Anal. Calcd for $C_{27}H_{30}O_6S$: C, 67.20; H, 6.27; S, 6.64. Found: C, 67.31; H, 6.45; S, 6.64.

(3*R*)-3-Methoxy-1-formyl-3,4-dihydro-2*H*-pyran (9). A mixture of **8** (11.0 g, 22.8 mmol) in dichloromethane–methanol (7:5 v/v, 120 mL) and 10 mL of 0.45 M aqueous sulfuric acid solution was stirred at room temperature for 1 d. Additional dichloromethane (200 mL) was added followed by aqueous sodium bicarbonate solution (200 mL), and the organic phase was separated, dried (Na_2SO_4), and concentrated to give crude hydroxy mesylate which solidified on standing. Flash chromatography (7:3 ethyl acetate–hexane to ethyl acetate) over 400 g of silica gel gave 3.8 g (70%) of crystalline1,5-anhydro-2-deoxy-3-*O*-methyl-4-*O*-methylsulfonyl-D-*arabino*-hexopyranoside: mp 80–82 °C; R_f = 0.17 (3:2 ethyl acetate–hexanes); $[\alpha]_D$ −12.0° (c 1, CH_3OH); IR (cm^{-1}, KBr) 3576 (OH), 2966, 2929, 2882, 1331 (SO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.42 (t, 1 H, J = 9.25, 9.48 Hz), 4.06 (dd, 1 H, J = 4.62, 11.78 Hz), 3.85 (dd, 1 H, J = 2.90, 6.90 Hz), 3.58–3.40 (m,s, 4 H, SO_2CH_3), 3.31 (ddd, 1 H, J = 3.02, 6.03, 6.52 Hz), 3.15 (s, 3 H, OCH_3), 2.47 (t, 1 H, J = 7.05, 7.15 Hz), 2.22 (dd, 1 H, J = 5.02, 13.30 Hz), 1.62 (dddd, 1 H, J = 4.91, 12.68, 11.89, 12.67 Hz); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 79.43, 79.29, 78.65, 65.31 (C-1), 61.11 (C-6), 56.02 (OCH_3), 38.29 (SO_2CH_3), 30.38 (C-2); CIMS m/z (rel inten) 241 (MH^+, 70), 145 (50), 113 (100), 85 (50). Anal. Calcd for $C_8H_{16}O_6S$: C, 39.99; H, 6.71; S, 13.34. Found: C, 39.64; H, 6.50; S, 12.99. A mixture of hydroxy mesylate (3.65 g, 15.2 mmol), triethylamine (20 mL), and methyl sulfoxide (80 mL) was stirred under an argon atmosphere at room temperature for 2 h. Sulfur trioxide–pyridine complex (7.53 g, 47.3 mmol) in DMSO (30 mL) was added over a period of 20 min and the resulting homogenous mixture was stirred for 2 h and then diluted with dichloromethane (200 mL). The mixture was transferred to a separatory funnel and washed with aqueous tartaric acid solution (3 × 150 mL) and aqueous sodium bicarbonate solution (2 × 100 mL). The aqueous phases were extracted with dichloromethane (2 × 50 mL) and the combined dichloromethane and organic phases were dried (Na_2SO_4) and concentrated to a brown liquid which was purified by flash chromatography using 1:3 ethyl acetate–hexanes to afford 1.78 g (83%) of enal as an unstable liquid: R_f = 0.43 (1:1 ethyl acetate–hexanes); IR (cm^{-1}, film) 2946, 1715 (C=O), 1649 (C=C); $[\alpha]_D$ + 167.6° (c 0.98, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1 H, CHO), 5.95 (d, 1 H, J = 4.49 Hz, HC=CHO), 4.30–4.25 (m, 1 H, H-1), 4.08 (ddd, 1 H, J = 3.33, 10.23, 10.68 Hz, H-1), 3.98 (dd, 1 H, J = 4.32, 8.59 Hz, H-3), 3.45 (s, 3 H, OCH_3), 2.10–1.95 (m, 2H, H-2,2'); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 187.46 (CHO), 153.19 (C-5), 118.57 (C-4), 68.33 (C-1), 63.33 (C-3), 55.99 (OCH3), 27.54 (C-2); EIMS m/z (rel inten) 142 (M^+, 77), 127 (M − CH_3, 17), 113 (61), 99 (23), 85 (100), 55 (82), 53 (65); HRMS calcd for $C_7H_{10}O_3$ 142.0629, found 142.0627.

(3*R*)-3-Methoxy-1-vinyl-3,4-dihydro-2*H*-pyran (2). A 50-mL three-neck flask was charged with methyltriphenylphosphonium bromide (1.43 g, 4.01 mmol). LiHMDS (5.0 mL of a 1 M solution in THF) was added followed by a solution of **9** (0.64 g of crude enal, *ca.* 3.56 mmol) in THF (20 mL). The reaction was stirred at room temperature for 15 min and then water (15 mL) was added. The mixture was transferred to a separatory funnel and extracted with petroleum ether (bp 35–60 °C, 2 × 50 mL). The combined organic phases were washed with water (5 × 50 mL), dried (Na_2SO_4), and concentrated to a volume of approximately 5 mL. Without further concentration, this sample was purified by column chromatography on 50 g of Florisil (60–100 mesh) using petroleum ether as the initial eluant followed by 9:1 ether in petroleum ether. Removal of the solvent from the purest fractions (TLC) gave 0.31 g (62%) of diene **2** as a volatile and unstable liquid: R_f = 0.5 (1:4 ethyl acetate–hexanes); IR (cm^{-1}, film) 2974, 1652 (C=C), 1599 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dd, 1 H, J = 10.80, 17.24 Hz, CH=C), 5.02 (dd, 1 H, J = 1.61, 10.74 Hz, CH=C), 4.90 (d, 1 H, J = 4.72 Hz), 4.08–4.01 (m, 1 H, H-1), 3.90 (ddd, 1 H, J = 3.43, 10.69, 10.74 Hz, H-1'), 3.67 (q, 1 H, J = 8.08, 4.12, 4.06 Hz, H-3), 3.24 (s 3 H, OCH_3), 1.86–1.69 (m, 2 H, H-2,2'); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.15 (C-5), 132.39 (C-6), 114.82 (C-7), 101.60 (C-4), 68.95 (C-3), 62.48 (C-1), 55.22 (OCH_3) 28.03 (C-2); EIMS m/z (rel inten) 140 (M^+, 60), 125 (M-CH_3, 10), 109 (100), 97 (15), 85 (55), 55 (90), 43 (35); HRMS calcd for $C_8H_{12}O_2$ 140.0837, found 140.0835.

Methyl 5-Hydroxy-1-cyclohexenecarboxylate (11).[20] (Trimethylsilyl)diazomethane (2.5 mL, 5.0 mmol) was added to a solution of 5-oxo-1-cyclohexenecarboxylic acid (0.42 g, 3.0 mmol) in anhydrous benzene (14 mL) and anhydrous methanol (4 mL) and the reaction mixture was stirred for 3 h. Removal of the solvent and volatiles gave 0.52 g of methyl 5-oxo-1-cyclohexenecarboxylic acid methyl ester as a brown liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20–7.15 (m, 1 H, HC=C), 3.78 (s, 3 H, OCH_3), 3.15 (m, 2 H), 2.69–2.63 (m, 2 H), 2.50 (t, 2 H, J = 6.88, 7.01). The crude keto ester was dissolved in methanol (20 mL) and the solution was cooled at 0 °C (ice bath) and treated with sodium borohydride (0.167 g, 4.42 mmol). After stirring for 10 min, the mixture was allowed to warm to room temperature and aqueous 1 M HCl (5 mL) was added. After an additional 1 h, the reaction mixture was concentrated to a volume of 5 mL and saturated aqueous sodium bicarbonate solution was added. The mixture was then extracted with dichloromethane (3 × 25 mL) and the combined extracts were dried (Na_2SO_4), filtered, and concentrated to give 0.44 g (92%) of **11** as a yellow liquid: R_f = 0.17 (3:7 ethyl acetate–hexanes); IR (cm^{-1}, film) 3427 (OH), 2946, 1714 (C=O), 1646 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–6.96 (m, 1 H, CH=C), 4.08–4.00 (m, 1 H, CHOH), 3.74 (s, 3 H, OCH_3), 2.70–2.63 (m, 1 H), 2.46–2.20 (m, 3 H), 1.88–1.79 (m, 1 H), 1.74 (brs, 1 H, OH), 1.71–1.59 (m, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.44 (C=O), 138.99 (C-2), 127.42 (C-1), 65.94 (C-5), 51.54 (OCH_3), 33.01 (C-6), 29.13 (C-3), 23.42 (C-4); EIMS m/z (rel inten)

(20) For a synthesis of **11** by another route, see: Keay, B. A.; Rajapaksa, D.; Rodrigo, R. *Can. J. Chem.* **1984**, *62*, 1093.

156 (M^+, 2), 138 (M − 18, 46), 137 (86), 124 (66), 113 (79), 97 (23), 81 (92), 79 (74), 67 (53), 53 (100); HRMS calcd for $C_8H_{12}O_3$ (M^+) 156.0786, found 156.0785.

Methyl 5-Methoxy-1-cyclohexenecarboxylate (12). A solution of 11 (0.58 g, 3.72 mmol) in iodomethane (10 mL) was treated with silver(I) oxide (1.08 g, 4.66 mmol) and pulverized calcium sulfate (3.00 g). The resulting suspension was stirred in an aluminum foil covered flask for 6 d at room temperature, after which ether (100 mL) was added and solids were removed by filtration. Concentration of the filtrate and purification of the crude product by column chromatography on 60 g of neutral alumina with 1:4 ethyl acetate–hexanes gave 0.54 g (85%) of 12 as a yellow liquid: R_f = 0.53 (3:7 ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00–6.96 (m, 1 H, HC=C), 3.73 (s, 3 H, $COOCH_3$), 3.58–3.50 (m, 1 H, C*H*OCH_3), 3.39 (s, 3 H, OCH_3), 2.66–2.59 (m, 1 H), 2.41–2.15 (m, 3 H), 1.89–1.80 (m, 1 H), 1.74–1.62 (m, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 167.59 (C=O), 139.24, 127.67, 74.71, 55.76, 51.55, 29.60, 25.89, 23.89; EIMS *m/z* (rel inten) 155 (M^+−15, 1), 138 (42), 123 (3), 79 (26), 58 (100). Anal. Calcd for $C_9H_{14}O_2$ C, 63.51; H, 8.29. Found: C, 63.85; H, 8.23.

1-Formyl-5-methoxycyclohexene (13). To a solution of 12 (0.48 g, 2.82 mmol) in anhydrous ether (15 mL) at −78 °C was added diisobutylaluminum hydride (8.5 mL of a 1 M solution in hexanes) dropwise over a period of 5 min and the resulting reaction mixture was stirred for 2 h. Methanol (0.6 mL) was added and the reaction was allowed to warm to room temperature and diluted with 1 M aqueous sodium potassium tartrate (10 mL). Extraction of the resulting mixture with ethyl acetate (2 × 25 mL), drying (Na_2SO_4), and concentration of the organic phase provided 0.39 g (98%) of product alcohol as a colorless liquid which was used in the next step without further purification: R_f = 0.13 (3:7 ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 1 H, HC=C), 3.99 (s, 2 H, CH_2OH), 3.58–3.51 (m, 1 H, C*H*OCH_3), 3.39 (s, 3 H, OCH_3), 2.41–2.34 (m, 1 H), 2.24–2.01 (m, 3 H), 1.91–1.57 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.00, 122.48, 75.72, 67.01 (CH_2OH), 55.79 (OCH_3), 31.54, 26.87, 22.92; EIMS *m/z* (rel inten) 124 (M^+ − 18, 9), 109 (9), 94 (35), 83 (29), 79 (43), 58 (100). To a solution of the crude allylic alcohol (0.32 g, 2.25 mmol) in dichloromethane (15 mL) cooled to 0 °C (ice bath) was added 3.25 g of manganese dioxide. The mixture was warmed to room temperature and stirred for 18 h, filtered through Celite, and concentrated to give 0.26 g (82%) of 13 as a yellow liquid: R_f = 0.41 (3:7 ethyl acetate in hexanes); IR (cm^{-1}, film) 2930, 2823, 1683 (C=O), 1643 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 (s, 1 H, CHO), 6.84–6.80 (m, 1 H, HC=C), 3.62–3.55 (m, 1 H, C*H*OCH_3), 3.38 (s, 3 H, OCH_3), 2.56–2.21 (m, 4 H), 1.93–1.74 (m, 2 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 193.69 (C=O), 150.33, 138.83, 69.58, 55.79, 26.63, 26.38, 23.77; EIMS *m/z* (rel inten) 140 (M^+, 5), 125 (1), 108 (26), 95 (6), 79 (27), 58 (100); HRMS calcd for $C_8H_{12}O$ (M^+) 140.0837, found 140.0831.

1-Vinyl-5-methoxycyclohexene (3). To a suspension of methyltriphenylphosphonium bromide (0.52 g, 1.45 mmol) in anhydrous THF (5 mL) was added a 1 M LiHMDS solution in THF (2.5 mL). After stirring 10 min, a solution of crude 13 (0.2 g) in THF (10 mL) was added and the reaction mixture was partitioned between petroleum ether (50 mL) and water. The organic phase was dried (Na_2SO_4) and concentrated to a liquid which was purified by chromatography on a Florisil column with petroleum ether as the eluant affording 0.1 g (50%) of diene 3: R_f = 0.73 (3:7 ethyl acetate–hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38 (dd, 1 H, J = 17.45, 10.71 Hz, *H*C=C), 5.73 (m, 1 H, HC=C), 5.12–5.05 (d, 1 H, J = 17.45 Hz, HC=C), 4.94–4.91 (d, 1 H, J = 10.71 Hz, HC=C), 3.57–3.48 (m, 1 H, C*H*OCH_3), 3.41 (s, 3 H, OCH_3), 2.57–2.50 (m, 1 H), 2.34–2.07 (m, 3 H), 1.96–1.88 (m, 1 H), 1.67–1.54 (m, 1 H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 139.30, 133.59, 128.65, 110.13, 75.68, 55.72, 29.82, 27.53, 23.61; EIMS *m/z* (rel inten) 138 (M^+, 12), 123 (1), 106 (69), 91 (95), 79 (100), 78 (52), 58 (26); HRMS calcd for $C_9H_{14}O$ (M^+) 138.1044, found 138.1049.

(2*S*,4a*R*,5*R*,6*S*)-4a,5,6,7-Tetrahydro-2-methoxy-5,6-chromandicarboxamide (14) and (2*S*,4a*S*,5*S*,6*R*)-4a,5,6,7-Tetrahydro-2-methoxy-5,6-chromandicarboxamide (15). A solution of diene 1 (0.65 g, 4.0 mmol), *N*-phenylmaleimide (0.61 g, 3.5 mmol), and diisopropylethylamine (0.16 mL) in anhydrous benzene (25 mL) was heated under reflux for 1 d. The mixture was concentrated and remaining solvent was removed in vacuo to afford 1.13 g of a mixture of 14 and 15. A sample (111 mg) of this product was analyzed by ^{1}H, ^{13}C, and DEPT NMR spectroscopy and found to consist of a 6.8:1 ratio of 14 to 15. Purification by column chromatography on Florisil (60–100 mesh) with 1:3 ethyl acetate in hexanes gave 0.86 g (78%) of the two cycloadducts from which the major one (14) was crystallized by slow evaporation from a mixture of ethyl acetate–hexanes: R_f = 0.23 (3:7 ethyl acetate–hexane); mp 120–123 °C; IR (cm^{-1}, KBr) 3053, 2954, 2917, 2849, 1706 (C=O), 1661 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.32 (m, 2 H, Ph-H), 7.10–7.05 (m, 2 H, Ph-H), 6.98–6.93 (m, 1 H, Ph-H), 5.13 (dt, 1 H, H-6), 4.58 (t, 1 H, $J_{1,2}$ = 5.68 Hz, $J_{1,2'}$ = 5.74 Hz, H-1), 3.18 (s, 3 H, OCH_3), 2.73–2.65 (dddd, 1 H, $J_{7,7'}$ = 16.6 Hz, $J_{7,4}$ = 1.59 Hz, $J_{7,8}$ = 7.8 Hz, H-7), 2.49–2.44 (m, 1 H, H-8), 2.37–2.19 (m, 2 H, H-3, H-9), 1.98–1.85 (m, 2 H, H-2, H-4), 1.81–1.58 (m, 2 H, H-3, H-7), 1.43–1.31 (m, 1 H, H-3); ^{13}C NMR (75.5 MHz, C_6D_6) δ 178.0 (C=O), 176.23 (C=O), 152.64 (C-5), 132.98, 128.89, 128.28, 126.89, 100.71 (C-1), 99.61 (C-6), 55.17 (OCH_3), 44.11 (C-9), 41.19 (C-8), 34.69 (C-4), 29.64 (C-2), 23.79 (C-7), 18.99 (C-3); CIMS *m/z* (rel inten) 314 (MH^+, 20), MH^+ − 32, 98), 254 (20), 71 (100). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.74; H, 6.10; N, 4.32.

(1*R*,2*S*,6*R*,8a*S*)/(1*S*,2*R*,6*S*,8a*R*)-(1,2,3,5,6,7,8,8a-Octahydro-6-methoxy-*N*-phenyl-1,2-naphthalenedicarboxamide (16) and (1*S*,2*R*,6*R*,8a*R*)/(1*R*,2*S*,6*S*,8a*S*)-(1,2,3,5,6,7,8,8a-Octahydro-6-methoxy-*N*-phenyl-1,2-naphthalenedicarboxamide (17). A solution of diene 3 (0.28 g, 2.02 mmol) and NPM (0.34 g, 1.96 mmol) in benzene (10 mL) was stirred under reflux for 2 d. Concentration of the reaction mixture gave a brown syrup which was determined to contain a 2.6:1 ratio of anti to syn cycloadducts (16 to 17) by ^{1}H NMR spectral integration. The crude mixture of cycloadducts was separated by column chromatography on silica gel by gradient elution with 99:1 to 97:3 CH_2Cl_2–acetone to give 230 mg (38%) and 16 and 90 mg of 17 (15%), along with 30 mg of the unresolved mixture. Compound 16: mp 88–90 °C; ^{1}H NMR (300 MHz, C_6D_6) δ 7.44–6.95 (m, 5 H, Ph-H), 5.23 (m, 1 H, H-7), 3.05 (s, 3 H, OCH_3), 2.99–2.89 (m, 1 H), 2.73–2.54 (m, 2 H), 2.44–2.20 (m, 2 H), 2.08–1.80 (m, 5 H), 1.47–1.11 (M, 2 H); ^{13}C NMR (75.4 MHz, C_6D_6) δ 177.95 (C=O), 176.73 (C=O), 137.14, 133.13, 128.95, 127.98, 126.46, 118.84, 78.39, 55.41, 42.18, 39.72, 38.32, 35.68, 31.76, 26.19, 21.93; EIMS *m/z* (rel inten) 311 (M^+, 8), 279 (M − 32, 64), 174 (2), 132 (91), 104 (41), 91 (100). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 72.88; H, 6.97; N, 4.46.

(4*R*,4a*S*,5*S*,6*R*)-4a,5,6,7-Tetrahydro-4-methoxy-5,6-chromandicarboxamide (18). A 25-mL round-bottomed flash was rinsed with triethylamine and then charged with diene 2 (0.5 g, 2.15 mmol), NPM (0.326 g, 1.88 mmol), and benzene (8 mL). The mixture was stirred under reflux for 3 d and concentrated to afford 0.58 g of a yellowish solid. ^{1}H and ^{13}C spectroscopic analysis indicated the presence of a single cycloadduct. Purification of the crude product by column chromatography on Florisil using ethyl acetate in hexanes (1:3 to 1:1) gave 0.45 g (76%), of 18: R_f = 0.24 (3:7 ethyl acetate–hexanes; mp 132–134 °C; $[\alpha]^{20}_D$ +126.4° (*c* 1, $CHCl_3$); IR (cm^{-1}, KBr); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.42 (m, 2 H, Ph-H), 7.39–7.36 (m, 1 H, Ph-H), 7.23–7.21 (m, 2 H, Ph-H), 4.93–4.89 (dt, 1 H, $J_{6,7'}$ = 7.38 Hz, H-6), 4.58–4.50 (m, 1 H, $J_{3,4}$ = 8.3 Hz, H-3), 4.14–4.08 (dt, 1 H, $J_{1,1'}$ = 11.32 Hz, H-1), 3.80–3.72 (ddd, 1 H, H-1′), 3.57–3.52 (dd, 1 H, $J_{4,9}$ = 5.35 Hz, $J_{8,9}$ = 8.75 Hz, H-9), 3.47 (s, 3 H, OCH_3), 3.23–3.16 (ddd, 1 H, $J_{7,8}$ = 1.48 Hz, H-8), 2.69 (dddd, 1 H, J = 1.57, 7.50, 7.75 Hz, H-7), 2.51–2.45 (m, 1 H, $J_{4,3}$ = 8.3 Hz, H-4), 2.32–2.20 (m, 2 H, H-2, H-7′), 1.60 (dddd, 1 H, J = 4.1, 11.9, 11.9, 12.1 Hz, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.83 (C=O), 177.78 (C=O), 152.72 (C-5), 131.86, 128.96, 128.51, 126.44, 95.29 (C-6), 73.42 (C-3), 64.60 (C-1), 56.09 (OCH_3), 41.91 (C-9), 40.84 (C-8), 39.89 (C-4), 28.79 (C-2), 24.09 (C-7); CIMS *m/z* (rel inten) 314 (MH^+, 10), 282 (MH^+ − 32, 100), 254 (15), 163 (17), 135 (60), 71 (30). Anal. Calcd for $C_{18}H_{19}NO_4$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.94, H, 6.24, N, 4.35.

Dimethyl (2*S*,4a*R*)-2-Methoxychroman-5,6-dicarboxylate (22) and Dimethyl (2*S*,4a*S*)-2-Methoxychroman-5,6-dicarboxylate (23). A solution of diene 1 (0.75 g, 5.36 mmol), dimethyl acetylenedicarboxylate (0.37 mL, 3.0 mmol), and diisopropylethylamine (0.15 mL, 0.86 mmol) in dry benzene (5 mL) was

heated in a sealed tube at 120 °C for 21 h. Concentration of the mixture gave 0.58 g of crude product which was purified by column chromatography on Florisil (80 g) with 1:4 ethyl acetate–hexanes to give 0.69 g (83%) of a 1.8:1 ratio of inseparable cycloadducts **22** (anti) and **23** (syn): R_f = 0.43 (3:7 ethyl acetate–hexanes); IR (cm^{-1}, film) 2953, 2839, 1727 (C=O), 1651 (C=C); ^1H NMR (**22**, 300 MHz, C_6D_6) δ 5.08–5.05 (m, 1 H, H-6), 4.25–4.22 (m, 1 H, H-1), 3.51 (s, 3 H, $COOCH_3$), 3.38 (s, 3 H, $COOCH_3$), 3.31 (s, 3 H, OCH_3), 3.30–3.24 (m, 1 H, H-4), 3.12–2.98 (m, 1 H, H-7), 2.84–2.70 (m, 1 H, H-7′), 1.97–1.87 (m, 1 H, H-3), 1.68–1.48 (m, 2 H, H-2,2′), 1.40–1.27 (m, 1 H, H-3′); ^{13}C NMR (**22**, 75.5 MHz, C_6D_6) δ 167.85 (C=O), 166.86 (C=O), 149.52 (C-9), 138.26 (C-8), 129.71 (C-5), 103.84 (C-1), 101.19 (C-6), 55.74 (OCH_3), 51.62 (2-$COOCH_3$), 35.23 (C-4), 30.33 (C-2), 27.51 (C-7), 26.58 (C-3); EIMS *m/z* (rel inten) 282 (M^+, 56), 251 (M-32, 32), 250 (31), 235 (14), 193 (56), 191 (46), 75 (72), 58 (100); HRMS calcd for $C_{14}H_{18}O_6$ 282.1103 (M^+), found 282.1047.

Diethyl (6*S*,8a*R*)-6,7,8,8a-Tetrahydro-6-methoxy-1*H*-pyrano[3,2-*c*]pyridazine-1,2(3*H*)-dicarboxylate (24) and Diethyl (6*S*,8a*S*)-6,7,8,8a-Tetrahydro-6-methoxy-1*H*-pyrano[3,2-*c*]-pyridazine-1,2(3*H*)-dicarboxylate (25). A 25-mL round-bottomed flask was rinsed with diisopropylethylamine and charged with diene **1** (0.52 g, 3.71 mmol), DEAD (0.4 mL, 2.54 mmol), and dry benzene (10 mL). The mixture was stirred under reflux (oil bath, T = 90 °C) for 18 h and then concentrated to an oil which was purified by column chromatography on neutral alumina (Brockmann 1, 100 g) using 1:1 ethyl acetate–hexanes to give 0.58 g (73%) of an inseparable mixture (6.7:1) of **24** and **25**: R_f = 0.69 (6:4 ethyl acetate–hexane); IR (cm^{-1}, film) 1709 (C=O); ^1H NMR (**24**, 400 MHz, DMSO-d_6) δ 5.30–5.10 (m, 1 H, H-6), 4.60-4.40 (m, 2 H, H-1, H-7), 4.40–4.25 (m, 1 H, H-7′), 4.18–3.95 (q, 4 H, OCH_2), 3.65–3.62 (m, 1 H, H-4), 3.38 (s, 3 H, OCH_3), 1.86 (m, 2 H, H-3,3′), 1.79–1.40 (m, 2 H, H-2,2′), 1.30–1.10 (t, 6 H, CH_2CH_3); ^{13}C NMR (**24**, 100.6 MHz, DMSO-d_6) δ 154.00 (C=O), 148.90 (C-5), 103.16 (C-1), 100.89 (C-6), 61.12 (OCH_2), 54.74 (OCH_3), 51.54 (C-4), 41.47 (C-7), 27.96 (C-2), 23.73 (C-3), 13.52 (CH_3); EIMS *m/z* (rel inten) 314 (M^+, 4), 282 (M-32, 6), 243 (13), 199 (10), 171 (100), HRMS calcd for $C_{14}H_{22}N_2O_6$ 314.1478 (M^+), found 314.1462.

(6*S*,8a*R*)-6,7,8,8a-Tetrahydro-6-methoxy-*N*-phenyl-1*H*-pyrano[3,2-*c*]pyridazine-1,2(3*H*)-dicarboximide (26) and (6*S*,8a*S*)-6,7,8,8a-Tetrahydro-6-methoxy-*N*-phenyl-1*H*-pyrano[3,2-*c*]pyridazine-1,2(3*H*)-dicarboximide (27). A solution of diene **1** (0.23 g, 1.6 mmol) in dichloromethane (5 mL) was cooled to −78 °C and treated with a solution of PTAD (0.212 g, 1.21 mmol) in dichloromethane (10 mL). The reaction was stirred for 15 min at −78 °C and then warmed to room temperature and stirred for an additional 30 min. Concentration of the mixture and purification of the crude product on Florisil (50 g) gave 0.23 g (60%) of an inseparable mixture of cycloadducts **26** and **27** in a ratio of 9:1 as determined by ^1H NMR spectral intergration: R_f = 0.86 (ethyl acetate); IR (cm^{-1}, KBr) 2933, 1780, 1712, 1594; ^1H NMR (**26**, 400 MHz, C_6D_6) δ 7.78–7.72 (m, 2 H, PhH), 7.20–7.15 (m, 2 H, PhH), 7.04–6.99 (m, 1 H, PhH), 4.89–4.87 (m, 1 H, H-6), 4.17–4.13 (t, 1 H, $J_{1,2}$ = 5.09 Hz, $J_{1,2'}$ = 4.70 Hz, H-1), 3.99–3.92 (m, 1 H, $J_{3,4}$ = 10.85 Hz, H-4), 3.83–3.75 (m, 1 H, H-7), 3.63–3.56 (m, 1 H, H-7′), 3.23 (s, 3 H, OCH_3), 2.89–2.80 (m, 1 H, $J_{3',4}$ = 5.3 Hz, $J_{3,3'}$ = 10.85 Hz, H-3′), 1.58–1.52 (m, 2 H, H-2,2′), 1.47–1.34 (m, 1 H, H-3); ^{13}C NMR (**26**, 100.6 MHz, C_6D_6) δ 152.56, 151.78, 148.77 (C-5), 132.46, 129.06, 127.66, 125.35, 104.28 (C-1), 99.41 (C-6), 55.91 (OCH_3), 52.93 (C-4), 41.59 (C-7), 28.35 (C-2), 23.03 (C-3); EIMS *m/z* (rel inten) 315 (M^+, 100), 260 (26), 244 (87), 125 (70), 71 (69), 55 (58), 41 (33). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, C, 60.68; H, 5.43; N, 12.97.

(3*R*,4a*R*)-Dimethyl 3-Methoxychroman-5,6-dicarboxylate (28). A solution of diene **2** (0.50 g, 3.57 mmol), dimethylacetylene dicarboxylate (0.25 mL, 2.03 mml), and diisopropylethylamine (0.15 mL, 0.86 mmol) in dry benzene was heated under reflux under an atmosphere of nitrogen for 4 d. Concentration of the reaction mixture and removal of the remaining solvent in vacuo gave 0.61 g of a dark brown oil. Analysis of the crude product by 300-MHz ^1H NMR indicated the presence of unreacted diene and dienophile and a single cycloadduct. (When carried out in a sealed tube at 120 °C, two cycloadducts were obtained in a ratio of 9:1.) Purification of the crude product by column chromatography of Florisil (100 g) using ethyl acetate–hexanes (1:3 followed by 1:1) afforded 120 mg (20%) of **22** as a yellow oil: R_f = 0.30 (3:7 ethyl acetate in hexanes); IR (cm^{-1}, film) 2952, 1726 (C=O), 1642 (C=C), 1436, 1265; ^1H NMR (400 MHz, C_6D_6) δ 5.14–5.11 (m, 1 H, H-6), 3.81–3.74 (m, 1 H, $J_{1,1'}$ = 10.5 Hz), 3.63 (s, 3 H, $COOCH_3$), 3.50–3.34 (m + s, 4 H, H-4, $COOCH_3$), 3.18–3.06 (m, 2 H, H-1′, H-7), 3.02–2.95 (m + s, 4 H, $J_{3,4}$ = 10.25 Hz (irradiation of H-2,2′), H-3, OCH_3), 2.73–2.62 (dddd, 1 H, $J_{4,7}$ = 3.50 Hz, $J_{7,7'}$ = 23 Hz, H-7′), 1.55–1.33 (m, 2 H, H-2,2′); ^{13}C NMR (100.6 MHz, C_6D_6) δ 168.71 (C=O), 166.65 (C=O), 149.39 (C-8), 138.51 (C-9), 128.29 (C-5), 102.94 (C-6), 79.59 (C-3), 66.62 (C-1), 55.69 (OCH_3), 51.47 ($COOCH_3$), 51.45 ($COOCH_3$), 43.89 (C-4), 30.93 (C-2), 27.24 (C-7); FABMS *m/z* (rel inten) 283 (MH^+, 20), 251 (MH^+ − 32, 100), 249 (60), 235 (25), 217 (35), 191 (30), 149 (20), 121 (20). HRMS calcd for $C_{14}H_{18}O_6$ 282.1103 (M^+), found 282.1061.

Diethyl (8*R*,8a*S*)-6,7,8,8a-Tetrahydro-8-methoxy-1*H*-pyrano-[3,2-*c*]-pyridazine-1,2(3*H*)-dicarboxylate (29). A 25-mL round-bottomed flask was rinsed with diisopropylethylamine and charged with diene **2** (0.34 g, 2.43 mmol), DEAD (0.30 mL, 1.90 mmol), and dry benzene (5 mL). This mixture was stirred under reflux for 1 d (oil bath, T = 90 °C) and at room temperature for 2 d. Concentration of the reaction mixture under reduced pressure gave 0.62 g of crude product as a yellow oil. Purification by column chromatography on neutral alumina (Brockman 1, 100 g) using 1:1 ethyl acetate–hexanes gave 0.48 g (80%) of **29** as a light yellow oil: R_f = 0.53 (6:4 ethyl acetate–hexane); IR (cm^{-1}, film) 1712 (C=O); ^1H NMR (400 MHz, DMSO-d_6, 365 K) δ 5.31–5.29 (m, 1 H, H-6), 4.33–4.20 (m, 2 H, H-7,7′), 4.13–4.05 (m, 5 H, OCH_2, H-4), 3.67–3.63 (m, 1 H, H-1), 3.52–3.47 (m, 2 H, $J_{3,4}$ = 8.3 Hz, H-1, H-3), 3.44–3.37 (m, 4 H, OCH_3, H-1′), 2.15–2.11 (m, 1 H, H-2), 1.73–1.67 (m, 1 H, H-2′), 1.22–1.17 (t, 6 H, OCH_3); ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 154.80, 149.46 (C-5), 102.71 (C-6), 76.20 (C-4), 66.75 (C-7), 61.70 (C-1), 61.15 (OCH_2), 58.88 (C-3), 55.99 (OCH_3), 30.68 (C-2), 13.74, 13.67 (CH_3); EIMS *m/z* (rel inten) 314 (M^+, 1), 282 (M^+ − 32, 13), 241 (30), 209 (61), 137 (78), 109 (45), 97 (35), 71 (100), HRMS calcd for $C_{14}H_{22}N_2O_6$ 314.1478 (M^+), found 314.1445.

(8*R*,8a*S*)-6,7,8,8a-Tetrahydro-8-methoxy-*N*-phenyl-1*H*-pyrano[3,2-*c*]pyridazine-1,2(3*H*)-dicarboximide (30). To a solution of diene **2** (0.19 g, 1.36 mmol) in 1:1 THF–CH_2Cl_2 (10 mL) at −78 °C was added PTAD (0.175 g, 1 mmol) as a solution in 1:2 THF–CH_2Cl_2 (15 mL). After addition was complete the reaction was allowed to warm to room temperature and it was stirred for 15 min. Concentration and removal of solvent under vacuum gave 0.33 g of crude product which was purified by column chromatography on Florisil (70 g) using ethyl acetate to give 0.15 g (48%) of **30** as a white solid: R_f = 0.75 (ethyl acetate); mp 149.5–153.5 °C; IR (cm^{-1}, KBr) 2934, 1780, 1719 (C=O), 1595 (C=C); ^1H NMR (300 MHz, C_6D_6) δ 7.82–7.78 (m, 2 H, Ph-H), 7.15–7.10 (m, 2 H, Ph-H), 7.00–6.94 (m, 1 H, Ph-H), 4.86–4.83 (m, 1 H, H-6), 4.41 (dd, 1 H, $J_{3,4}$ = 9.41 Hz, $J_{4,7}$ = 1.04 Hz, H-4), 3.78 (dddd, 1 H, H-7), 3.69–3.63 (m, 1 H, H-1′), 3.37–3.29 (m, 1 H, H-3), 3.28–3.21 (m, 1 H, H-7′), 3.08–3.00 (m + s, 4 H, OCH_3, H-1) 1.50–1.39 (m, 2 H, H-2,2′); ^{13}C NMR (75.5 MHz, C_6D_6) δ 154.59 (C=O), 150.36 (C=O), 149.64 (C-5), 131.24, 128.96, 127.97, 125.33, 102.05 (C-6), 79.08 (C-1), 68.89 (C-3), 57.29 (C-4), 56.21 (OCH_3), 44.17 (C-7), 30.15 (C-2); EIMS *m/z* (rel inten) 315 (M^+, 100), 282 (M^+ − 32, 1), 119 (15), 91 (10), 71 (43). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.70; H, 5.44; N, 13.08.

Dimethyl (4*R*)-4-Methoxy-5,6-chromandicarboxylate (31). A mixture of **22** and **23** (0.12 g, 0.425 mmol) and DDQ (0.193 g, 0.85 mmol) in dry benzene (5 mL) was heated under reflux for 20 h. Solids were removed by filtration through a bed of Celite, and the filtrate was passed through a column of neutral alumina (50 g) using ethyl acetate and then concentrated to give 0.11 g (92 %) of **31** as a viscous syrup: R_f = 0.42 (3:7 ethyl acetate–hexane); IR (cm^{-1}, film) 2950, 2839, 1721 (C=O), 1590 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.73 (d, 1 H, J = 8.64 Hz, Ph-H), 6.84 (d, 1 H, J = 8.66 Hz, Ph-H), 5.10 (t, 1 H, $J_{1,2}$ = 2.67 Hz, $J_{1,2'}$ = 2.70 Hz, H-1), 3.87 (s, 3 H, $COOCH_3$), 3.40 (s, 3 H, OCH_3), 2.86–2.75 (m, 1 H, H-3′), 2.57–2.49 (m, 1 H, H-3), 2.04–1.95 (m, 1 H, H-2′), 1.90–1.79 (m, 1 H, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.03 (C=O), 165.72 (C=O), 155.83 (C-5), 136.56 (C-9), 129.48 (C-8), 120.03 (C-4), 119.94 (C-6), 117.67 (C-7), 98.11 (C-1), 55.68

(OCH_3), 52.38 ($COOCH_3$), 52.05 ($COOCH_3$), 25.36 (C-3), 17.37 (C-2); EIMS *m/z* (rel inten) 280 (M^+, 16), 249 (M-31, 53), 248 (M − 32, 100), 233 (M − 47, 59), 173 (25), 162 (30), HRMS calcd for $C_{14}H_{16}O_6$: 280.0947. Found: 280.0947.

Dimethyl (2*S*)-2-Methoxy-5,6-chromandicarboxylate (32). A mixture of **28** (0.053 g, 0.19 mmol) and DDQ (0.085 g, 0.37 mmol) in dry benzene (2 mL) was treated as described above for the preparation of **31**. Chroman **32** (50 mg, 96%) was obtained as an oil: R_f = 0.26 (3:7 ethyl acetate–hexane); IR (cm^{-1}, film) 2952, 1723 (C=O), 1594 (C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (d, 1 H, *J* = 8.79 Hz, Ph-H), 6.83 (d, 1 H, *J* = 8.79 Hz, Ph-H), 4.44 (t, 1 H, $J_{3,2}$ = 7.13 Hz, $J_{3,2'}$ = 3.58 Hz, H-3), 4.24–4.12 (m, 2 H, H-1,1'), 3.87 (s, 3 H, $COOCH_3$), 3.78 (s, 3 H, $COOCH_3$), 3.32 (s, 3 H, OCH_3), 2.16–2.08 (dq, 1 H, *J* = 3.50, 6.20 Hz, H-2'), 1.97–1.85 (m, 1 H, H-2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 168.87 (C=O), 165.60 (C=O), 158.31 (C-5), 137.59 (C-9), 131.29 (C-8), 120.00 (C-4), 119.94 (C-6), 118.07 (C-7), 68.29 (C-3), 62.08 (C-1), 56.25 (OCH_3), 52.41 ($COOCH_3$), 52.09 ($COOCH_3$), 25.40 (C-2); CIMS (NH_3) *m/z* (rel inten) 281 (MH^+, 12), 266 (MH^+ − 15, 100), 249 (MH^+ − 32, 42), 234 (25), 217 (12), 128 (12); HRMS calcd for $C_{14}H_{16}O_6$ 280.0947, found 280.0951.

X-Ray Crystallography. Suitable crystals of **14** ($C_{18}H_{19}NO_3$) for X-ray diffraction were obtained by recrystallization from ethyl acetate–hexane. The crystals formed in space group $P2_1/c$ with *a* = 11.67(1) Å, *b* = 7.066(9) Å, *c* = 18.911(2) Å, and *B* = 91.428(7)° for *Z* = 4 and a calculated density of 1.267 g/cm^3. An automatic four circle diffractometer equipped with Cu Kα radiation (λ = 1.5418 Å) was used to measure 3498 potential diffraction peaks of which 1898 were observed ($I > 3\sigma I$). Application of a multisolution tangent formula approach to the phase solution gave an initial model for the structure.[21] Anisotropic temperature parameters were refined for the non-hydrogen atoms while isotropic temperature factors were applied to the hydrogens but were not refined. The function $\sum\omega(|F_o|-|F_d|)^2$ with $\omega = 4F_o^2/\sigma^2(F_o^2)$ was minimized with full matrix least squares to give an unweighted residual of 0.062. Figure 1 is a computer generated drawing of **14** showing its stereochemistry.

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Supplementary Material Available: ^1H-NMR spectra of compounds **2**, **3**, **9**, **11**, **13**, **16**, **17**, **22** + **23**, **24** + **25**, **28**, **29**, **31**, and **32** (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(21) The following library of crystallographic programs was used: SHELXS-86, G. M. Sheldrick, University of Gottingen, West Germany (1986); PLUTO, Motherwell, W. D. S.; Clegg, W. University of Cambridge, England (1978); a version of SDPV.3, Enraf-Nonius, Delft, The Netherlands (1985) locally modified for a Sun Microsystems computer. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.