Hetero-Diels−Alder Reactions of Homochiral 1,2-Diaza-1,3-butadienes with Diethyl Azodicarboxylate under Microwave Irradiation. Theoretical Rationale of the Stereochemical Outcome†

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The stereoselective normal electron demand Diels−Alder reactions of chiral 1,2-diaza-1,3-butadienes, derived from acyclic carbohydrates having different configurations (**1**−**6**), with diethyl azodicarboxylate (DEAD) are disclosed. Reactions proceed slowly in benzene solution at room temperature, but are greatly accelerated by *microwave irradiation* to form the corresponding functionalized 1,2,3,6-tetrahydro-1,2,3,4-tetrazines (**7**−**18**) in good yields. The observed stereoselectivity is markedly dependent on the *relative* stereochemistry at C-1′,2′. Thus, 1,2-diazoalkenes derived from per-*O*-acylated sugars having *threo* configuration at C-1′,2′ give tetrazines with a high facial selectivity, whereas those having *erythro* configuration at C-1′,2′ afford products in lower diastereomeric ratios. The facial diastereoselection has been rationalized by a PM3 computational study. These results prove that in the transition structures (TSs) the reacting azoalkene exhibits formal negative charges at C-3 and N-2, the former being of greater magnitude, while the heterodienophile displays a partial positive charge at the substituent attached to the nitrogen atom. Accordingly, a stabilizing electrostatic interaction will only occur in TSs involving an *endo* orientation of the azodicarboxylate in its approach to the azadiene, a fact consistent with the experimental observations.

Introduction and Background

The Diels−Alder reaction still remains an active research field and a crucial key step in a wide variety of natural product syntheses.[1] For practitioners of this protocol and for synthetic chemists in general, it is probably the most powerful construction process in organic synthesis. Few reactions can compete with the Diels−Alder reaction. The importance and usefulness of the Diels−Alder reaction stem from its unique characteristics: high regio- and stereoselectivity, formation of two new carbon−carbon bonds, and potentially, four new stereogenic centers. A useful variation involves the use of heterodienes or -dienophiles, the so-called hetero-Diels−Alder reaction, which represents an elegant and versatile procedure in the preparation of noncarbogenic systems.[2] In particular, the process enables the synthesis of biologically important nitrogen- and oxygen-containing heterocycles hitherto inaccessible or difficult to achieve by using standard methodology.[3]

The stereodifferentiating characteristics of the Diels−Alder reaction can be profitably enhanced if cycloadditions are performed on chiral precursors or with chiral catalysts. In this context, carbohydrate-based cycloadditions represent an attractive and emerging approach in organic synthesis.[4] This strategy combines the powerful stereoselection provided by a cycloadditive process along with the stereodirecting effect of an appropriate sugar template.

In recent years, our research group has reported on all-carbon and heteroatom cycloadditions from carbohydrates, either Diels−Alder or 1,3-dipolar reactions.[5]

† Dedicated respectfully to the memory of Michael J. S. Dewar (1918−1997), who taught us the usefulness of computational chemistry through his "semiempirical" life.

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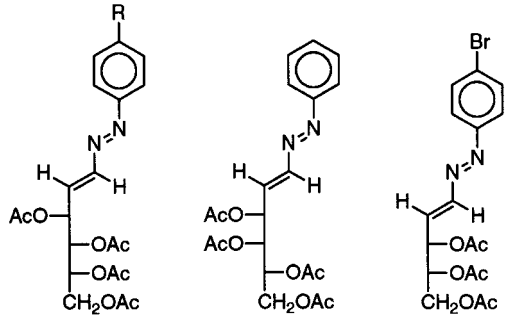
These cycloadditions with sugar-derived substrates have potential value for access to enantiomerically pure polysubstituted heterocycles. As part of our broad program concerned with asymmetric cycloadditions employing acyclic unsaturated sugars as dienes, we describe here the results of a new study of asymmetric hetero-Diels−Alder reactions of 1-aryl-1,2-diaza-1,3-butadienes (**1**−**6**) with diethyl azodicarboxylate (DEAD) in order to expand and generalize the synthetic approach to nitrogen heterocycles. These crystalline precursors, having different carbon side chains of defined and controllable absolute stereochemistry, are readily accessible from the corresponding sugar hydrazones.[6] Preliminary results were reported a few years ago,[5a] but herein we describe novel and optimized procedures which enhance the versatility still further. In addition, theoretical data full corroborate the experimental findings of diastereofacial selectivity.



1 R = H
2 R = Cl
3 R = Me
4 R = OMe

5 **6**

Results and Discussion

Hetero-Diels−Alder Reactions. Our initial experiments to explore the cycloadditive chemistry of sugar 1,2-diazadienes were unfruitful and discouraged further attempts. The apparent inertness of these heterodienes, compared with simpler diazadienes,[2] was evidenced by reaction failures with reactive dienophiles such as dimethyl acetylenedicarboxylate (DMAD), *N*-sulfonylimine, isocyanates, and isothiocyanates. Gratifyingly, success came with both benzo- and naphthoquinone as described in our preliminary study.[5a] Reactions with quinonoid dienophiles did not afford significant yields of cycloadducts (15−30%), due to omnipresent tarry side products, presumably quinone polymers. However, these unprecedented reactions proceeded with high facial diastereoselectivity, and structures of major adducts were determined by NMR spectroscopy.

Concerning the reactivity toward DEAD, the synthetic results and an analysis of the stereochemical outcome far exceeded our expectations. Cycloadducts were obtained stereoselectively, and the isomer ratios varied significantly depending on the structure of the heterodiene. The results allow evaluation of the stereodirecting effects of sugar chains. With a few exceptions,[7] these comparisons have not been reported in previous studies of carbohydrate-based cycloadditions.

Reactions with DEAD were conducted initially in benzene solutions at room temperature. Significantly long reaction times (∼30 days) were usually required for completion. Alternatively, these processes could be run at reflux to effect the aza-Diels−Alder addition in shorter reaction times, but the mixtures were accompanied by unidentified side products. Realizing that Diels−Alder reactions are sensitive to thermal and pressure effects, we then turned our attention to nonconventional activation methods such as microwaves[8] or ultrasound.[9] Ultrasonic irradiation in a bath operating at ∼20 kHz gave much cleaner reactions, although a few days are still required for completion. When reactions were carried out without solvent ("dry-media reactions") using a 1:2.5 azoalkene−DEAD molar ratio and irradiated with focused microwaves,[10] the reaction partners gave the corresponding adducts (**7**−**18**) within 6 h, and remarkably, without byproducts. It is noteworthy that both yields and selectivities were identical to those obtained in benzene solution. In all cases, tetrahydro-1,2,3,4-tetrazines were isolated with excellent overall yields, ranging from 80 to 96%, as a mixture of (6*R*)- and (6*S*)-diastereomers as evidenced by 400-MHz NMR analyses of the crude mixtures (Scheme 1). Such stereoisomers could further be separated by chromatography and/or crystallization. Attempts to purify the minor isomers **13** and **14** have not yet been successful. The products thus obtained in a single synthetic operation are chiral, densely functionalized polynitrogen rings. These partially reduced 1,2,3,4-tetrazines, which have been previously known,[11] are also potential heterodienophiles. The structurally related 1,2,4,5-tetrazines may participate in [4 + 2] cycloadditions with electron-rich dienophiles as recognized by Boger and his group.[12]

Chiral 1,2-diazoalkenes bearing an acyclic chain of D-*arabino* configuration (**1**−**4**) reacted with high stereodifferentiation, while heterodienes either with D-*lyxo* (**5**) or D-*erythro* (**6**) configurations gave a lower discrimination between both diastereomers (Table 1).

Structural Determination. The structures of cycloadducts **7**−**12** and **15**−**18** were supported by their spectroscopic data and elemental analyses. Some oily samples gave no satisfactory combustion analyses or high-resolution mass spectra, although they were chromatographically homogeneous (TLC) and characterized by high-resolution ^{1}H and ^{13}C NMR in an unambiguous

(6) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Sánchez, J. B. *Tetrahedron: Asymmetry* **1995**, *6*, 945−956. This optimized protocol involves a two-step sequence from commercially available unprotected sugars.

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(9) For a comprehensive survey on ultrasound-assisted cycloadditions: Fillion, H.; Luche, J.-L. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum Press: New York, 1998; pp 91−106 and references therein.

(10) Reactions were run in a monomode reactor with focused electromagnetic radiation (see Experimental Section). This enables a homogeneous distribution of the electric field and consequently an almost complete reproducibility of experiments. Similar results can also be obtained with a domestic oven operating at the same frequency, but the reproducibility is often poorer.

(11) Sommer, S.; Schubert, U. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 696−697.

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Scheme 1

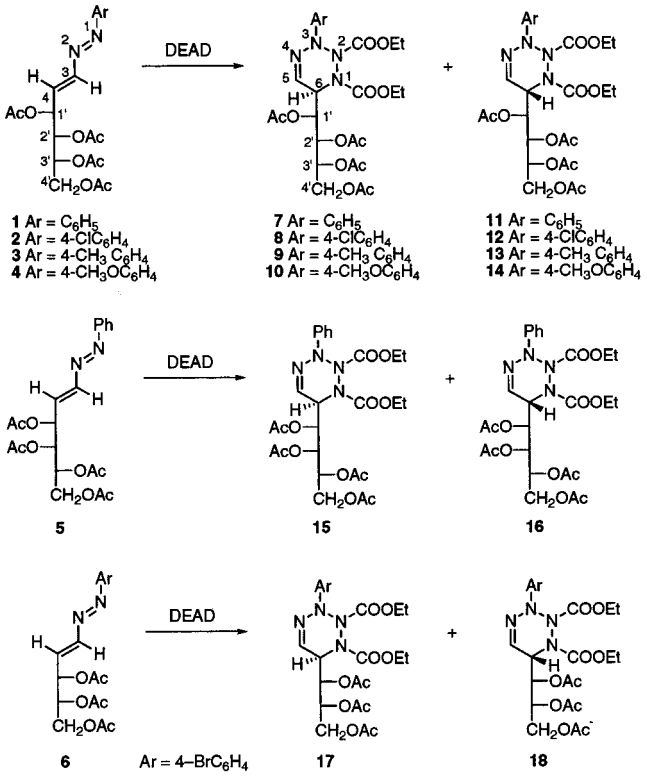


Table 1. Normal Electron Demand Aza-Diels−Alder Reactions of Carbohydrate-Based 1-Aryl-1,2-diaza-1,3-butadienes (1−6) with DEAD

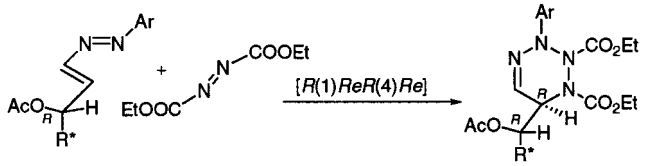
heterodiene	cycloadducts	diastereoemeric ratio[a]	yield (%)[b]
1	**7** + **11**	85:15	93
2	**8** + **12**	84:16	96
3	**9** + **13**	88:12	87
4	**10** + **14**	85:15	92
5	**15** + **16**	66:33	91
6	**17** + **18**	35:65	80

[a] Determined by ^{1}H NMR peak integration in $CDCl_3$ solution. [b] Combined yields of (6*R*)- and (6*S*)-diastereomers.

fashion (see Experimetal Section). In addition, the solid-state structure of **8** could be unequivocally determined by single-crystal X-ray diffractometry.[13] The X-ray investigation was carried out to elucidate the configuration of the new stereogenic center at C-6.[14] The results of the crystal structure determination indicate that the new chiral center is *R*, a fact that can be harnessed to rationalize the steric course (vide infra). It should also be noted that the tetrahydrotetrazine ring exhibits a conformation near to a half-boat, with a dihedral angle between the heterocycle mean plane and the aromatic ring of 153.2°, and that between the tetrahydrotetrazine mean plane and the sugar chain plane of 71.3°.[13]

Double irradiation experiments were used to assign the remaining protons in the ^{1}H NMR spectra of adducts. The two diethyl groups resonate at different chemical shifts, thereby evidencing the different environment surrounding both carboxylates in the heterocyclic ring. The most

Scheme 2



deshielded signal appears at ∼7 ppm as a doublet, which can be attributed to H-5, the azomethine proton. Also ^{13}C NMR spectra were used to confirm such structures: the chemical shifts of C-1′ to C-4′ carbon signals are consistent with typical values found for acyclic carbohydrate skeleta,[15] and the resonance at ∼135 ppm is characteristic of the azomethine carbon[16] at C-5.

Furthermore, these tetrazines were analyzed by mass spectrometry and three different fragmentation patterns were observed: (a) the loss of a CO_2Et moiety followed by sequential elimination of acetic acid and acetate units, (b) the elimination of ketene (CH_2CO) and acetate units, and (c) the initial elimination of an ArN_2 fragment followed by the loss of acetate and acetic acid as key fragments. These results provided clear information on the overall sugar and heterocycle compositions. For compound **8**, the presence of the above series of fragment ions at *m*/*z* 570 and 568 $[M - AcOH]^{\bullet+}$, 557 and 555 $[M - CO_2Et]^{\bullet+}$, and 489 $[M - ArN_2]^{\bullet+}$ accompanied by abundant ions at *m*/*z* 141 and 139 $[ArN_2]^{\bullet+}$, 73, 60, and 43 gave positive evidence for the formation of cycloadducts.

Configurational Assignment and Steric Course. Having demonstrated by X-ray diffractometry that the major diastereomers display (6*R*)-configurations if the chiral descriptor of the heterodiene at C-1′ (the first stereogenic center of the sugar chain) is *R* (e.g., **1**−**5**), we see that the relative induction arises from the preferential reaction of DEAD with the *Re* face of the azoalkene (Scheme 2). This results in a like (*lk*) combination,[17] and the stereochemical course can be designated in a self-consistent fashion as [*R*(1)*Re*R(4)*Re*].[18]

These assumptions fully agree with the experimental results. Thus compound **12**, epimer of **8** at C-6, should have the opposite configuration at that stereogenic carbon. Furthermore, the circular dichroism (CD) spectra of **8** and **12** are approximately mirror images (Figure 1). This does mean that the sign of the CD and its ellipticity will largely be dependent on the absolute configuration at C-6, with little or no influence provided by the remaining stereocenters of the polyacetylated chain. Since the CD spectrum of **17** is analogous to that of **8**, such substances should have the same configuration (*R*) at C-6. In stark contrast, the CD spectra of **12** and **18** exhibit opposite signs over the entire wavelength range, consistent with their (6*S*)-configuration (Figure 2).

The above data are also corroborated by the values of optical rotation. This fact has allowed us to establish a useful empirical correlation between the sign of the

(13) Diánez, M. J.; Estrada, M. D.; López-Castro, A.; Pérez-Garrido, S. *Acta Crystallogr.* **1994**, *C50*, 1972−1974.

(14) For compound **8** we had assigned[5a] the absolute configuration *S* by comparison of its circular dichroism spectrum with that of a model compound: Ogura, H.; Sakaguchi, M.; Nakata, K.; Hida, N.; Takeuchi, H. *Chem. Pharm. Bull.* **1981**, *29*, 629−634.

(15) Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27−66.

(16) Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Tablas para la Elucidación Estructural de Compuestos Orgánicos por Métodos Espectroscópicos*; Alhambra: Madrid, 1980; p 89.

(17) Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654−660.

(18) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. *Tetrahedron: Asymmetry* **1996**, *7*, 2333−2342.

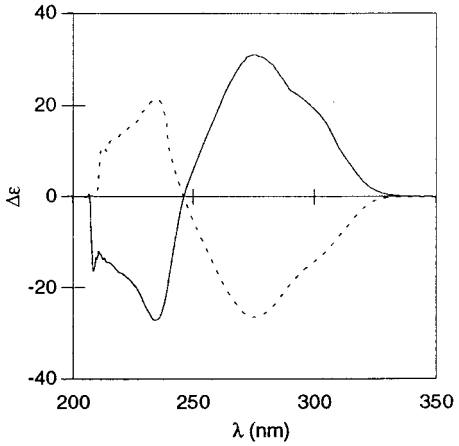


Figure 1. Circular dichroism spectra of **8** and **12** (dotted line) recorded in EtOH.

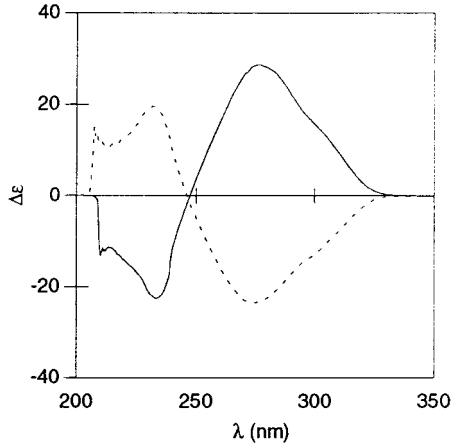


Figure 2. Circular dichroism spectra of diastereomers **17** and **18** (dotted line) in EtOH solution.

Table 2. Configuration (C-6) and Optical Rotation of Adducts 7−12 and 15−18

cycloadduct	configuration (C-6)[a]	$[\alpha]_D$ (deg)[b]
7	*R*	+333.5
8	*R*	+381.5
9	*R*	+422.3
10	*R*	+417
11	*S*	−165.6
12	*S*	−174
15	*R*	+414
16	*S*	−403.2
17	*R*	+408
18	*S*	−361

[a] By X-ray analysis and empirical correlation (see text). [b] See Experimental Section for details.

optical rotation and the configuration of adducts. Table 2 depicts the magnitude and sign of the optical rotation along with the configuration at C-6 as previously established.

From these data, it can be seen that adducts **7** and **11** exhibit large optical rotations but with opposite configurations. Applying van't Hoff's principle of optical superposition[19,20] and using an analysis similar to that of Hudson's rules,[21] it is possible to calculate the contribution of C-6 to the rotatory power. Thus, the optical rotation of **8** would be the sum of C-6 (*R*) and acyclic chain (*C*) contributions to the rotatory power:

$$[\alpha]_D = +382° = R + C \quad (1)$$

and analogously, it is possible to establish a relationship for its epimer **12** (since $R = -S$):

$$[\alpha]_D = -174° = S + C = -R + C \quad (2)$$

The subtraction of both equations gives the contribution of C-6(*R*):

$$+556° = 2R \Rightarrow R = +278°$$

Likewise, the addition of (1) and (2) gives the chain contribution:

$$+208° = 2C \Rightarrow C = +104°$$

Since the magnitude of C-6(*R*) is greater than that of *C*, the absolute configuration at C-6 will be determined by the sign of the optical rotation, a surmise in agreement with experimental data from Table 2. An analogous reasoning can be applied to other epimeric pairs such as **15**/**16** ($R = +205°$, $C = +6°$) and **17**/**18** ($R = +193°$, $C = +24°$). Consequently, in the case of adducts arising from a cycloaddition of 1,2-diazoalkenes with DEAD, *a positive value of the optical rotation indicates R-configuration at C-6, whereas a negative value agrees with S-configurations*.

Conventional wisdom has held that the nearest stereocenter to a reacting moiety greatly influences the asymmetric induction. This is de facto an indirect confirmation of the principle of optical superposition, which has also been observed, for instance, by Franck and coworkers in the facial diastereoselectivity of Diels−Alder reactions with chiral 1,3-butadienes.[22] Table 1 provides an outstanding confirmation of this principle: starting from **6**, whose absolute configuration at C-1′ is *S*, the major stereoisomer (**18**) has now (6*S*)-configuration. An additional striking point, already mentioned, is the fact that the diastereomeric ratio is also dependent on the configuration of the second stereocenter. *A threo vicinal relationship causes a higher level of diastereoselection than the corresponding erythro arrangement*. Even though the latter rule should be applied with caution, we have found that this structural feature has a predictive value on acyclic stereoselection.[23]

Reaction of 1,2-Diazoalkenes with DEAD. A Theoretical Study. A systematic molecular orbital (MO) calculation appeared to be essential in order to rationalize the results obtained in the above-mentioned experimental studies of 1,2-diaza-1,3-butadienes. The importance of this study is 2-fold. Unlike monoaza-1,3-butadienes which

(19) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 1081−1082 and references therein.

(20) The principle of optical superposition states that individual chiral centers in a chiral compound make independent contributions to the molar rotation. Although it ignores solvent and concentration effects, its application has proven to be successful in many instances. Sometimes the existence of vicinal stereocenters renders the principle invalid (see ref 19).

(21) (a) Hudson, C. S. *J. Am. Chem. Soc.* **1909**, *31*, 66−86. (b) Hudson, C. S. *J. Am. Chem. Soc.* **1916**, *38*, 1566−1575. (c) Ferrier, R. J. In *The Carbohydrates. Chemistry and Biochemistry*; Pigman, W., Horton, D., Wander, J. D., Eds.; Academic Press: New York, 1980; Vol. IB, pp 1356−1362.

(22) Tripathy, R.; Franck, R. W.; Onan, K. D. *J. Am. Chem. Soc.* **1988**, *110*, 3257−3262.

(23) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C. Unpublished results.

Table 3. Enthalpies (ΔH_f, kcal/mol), Bond Lengths (Å), and Dihedral Angles (deg) for Cycloadducts and TSs 20−23

	cycloadducts (PM3)				transition structures (PM3)			
	20	**21**	**22**	**23**	**TS_{20}**	**TS_{21}**	**TS_{22}**	**TS_{23}**
ΔH_f	−145.72	−145.58	−142.54	−147.29	−105.61	−97.71	−98.40	−98.10
N1−C6	1.511	1.517	1.506	1.514	2.054	2.026	2.056	2.019
N2−N3	1.525	1.488	1.529	1.492	1.845	1.887	1.847	1.889
CO−N1−N2−CO	130.20	127.36	131.83	128.19	152.54	152.10	152.79	152.99

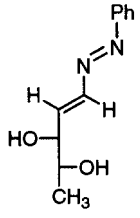
have been the subject of numerous theoretical studies at semiempirical and ab initio levels,[24] 1,2-diazadienes remain a rather unexplored domain.[25] On the other hand, it is necessary to check the precise effect of the chiral framework on the facial selectivity.

Previous studies on the TSs of 2-aza-1,3-butadienes involved in Diels−Alder reactions[24d,e] reveal that the presence of a nitrogen atom in the diene enhances the electrophilicity and lowers the energy of the MOs, thereby making the heterodiene less reactive than 1,3-butadiene toward electron-withdrawing dienophiles. Inverse Diels−Alder reactions with electron-rich dienophiles are favored by substituting the azadiene with electron-withdrawing groups, which makes the latter still more electron-deficient. In contrast, normal electron demand reactions occur when the azadiene is substituted with electron-donating groups. It is also interesting to note that the HOMO of 2-azadiene is slightly polarized, although the effect of the nitrogen substitution on the LUMO is more pronounced with the C-1 coefficient larger than that of C-4. Anyhow, the regioselectivity displayed by substituted 2-aza-1,3-butadienes is similar to that of a substituted 1,3-butadiene.[24e]

When dealing with computational methods, the most important question is to ascertain whether a reduced model can reproduce accurately the behavior of the experimental systems, which do not react generally in the gas phase. Accordingly, we have undertaken different studies to evaluate the influence of a chiral substituent at C-4 with a relative *threo* configuration, the presence of an aromatic ring at N-1 of the 1,2-diazadiene, the configuration and substituents of the heterodienophile, and its possible *endo*/*exo* approaches.

Owing to the increasing molecular size of these models, which include numerous heteroatoms, ab initio MO calculations could not be performed at a reasonable computational cost. Alternatively, semiempirical calculations at PM3 level,[26] one of the most robust methods, were carried out involving full optimizations using the Gaussian 94 series of programs.[27] Preliminary examination of these data reveal that calculations closely match the experimental results.

We first examined the reacting system consisting of 1,2-diaza-1,3-butadiene **19** plus DEAD. This is very close to the real situation. Compound **19** possesses a D-*threo* side chain, the same relative configuration found in the two stereogenic carbons (C-1′ and C-2′) of the protected heterodienes **1**−**4**.



19

The frontier orbital calculations (FMO)[28] of diazadiene **19** and DEAD determined by PM3 calculations predict the tendency to react in a normal $HOMO_{diene}$-controlled Diels−Alder reaction because the energy gap $HOMO_{diene} - LUMO_{dienophile}$ ($\Delta E = 8.78$ eV) is lower than the energy of the interaction $HOMO_{dienophile} - LUMO_{diene}$ ($\Delta E = 9.46$ eV). For the fact that neither the H_{ij} differential overlap integrals or steric effects are included in the FMO analysis, the TSs for the reactions of **19** were calculated.

Assuming that DEAD maintains its (*E*)-configuration during the Diels−Alder reaction, there are four possible TSs (**20**−**23**) concerning the approaches to both *Re* and *Si* faces of the heterodiene **19**. Nevertheless, the rapid configurational inversion of the chiral nitrogen atoms in the heterocyclic ring results in cycloadducts that only differ by (*R*)- or (*S*)-configuration at C-6 (Scheme 3).

Table 3 depicts the most significant parameters calculated from PM3-optimized geometries of the TSs and the corresponding cycloadducts (Figures 3 and 4).

It is noteworthy the greater stability of the TS **20** which accounts for the preferential formation of adduct **20** having (6*R*)-configuration. This result agrees with the experimental observation favoring (6*R*)-configurated cycloadducts such as **7**−**10**. The diastereoselective formation of these products can be rationalized to result from steric interactions, since the *Re* face of the heterodiene is readily accessible while the approach to the *Si* face is impeded by the chiral substituent at C-4 of the heterodiene. However, the distances of the forming bonds (N1−C6 and N2−N3) as well as the torsional angle of DEAD display similar features. Globally, in these studies the N1−C6 distance differs by <0.01 Å in cycloadducts and

(24) (a) Nomura, Y.; Takeuchi, Y.; Tomoda, S.; Ito, M. M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2779−2785. (b) Boger, D. L.; Corbett, W. L.; Curran, T. T.; Kasper, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 1713−1729. (c) Bachrach, S. M.; Liu, M. *J. Am. Chem. Soc.* **1991**, *113*, 7929−7937. (d) Bachrach, S. M.; Liu, M. *J. Org. Chem.* **1992**, *57*, 6736−6744. (e) González, J.; Houk, K. N. *J. Org. Chem.* **1992**, *57*, 3031−3037. (f) Sisti, N. J.; Motorina, I. A.; Tran Huu Dau, M.-E.; Riche, C.; Fowler, F. W.; Grierson, D. S. *J. Org. Chem.* **1996**, *61*, 3715−3728. (g) Pinho e Melo, T. M. V. D.; Fausto, R.; Rocha Gonsalves, A. M. A.; Gilchrist, T. L. *J. Org. Chem.* **1998**, *63*, 5350−5355. (h) Augusti, R.; Gozzo, F. C.; Moraes, L. A. B.; Sparrapan, R.; Eberlin, M. N. *J. Org. Chem.* **1998**, *63*, 4889−4897.

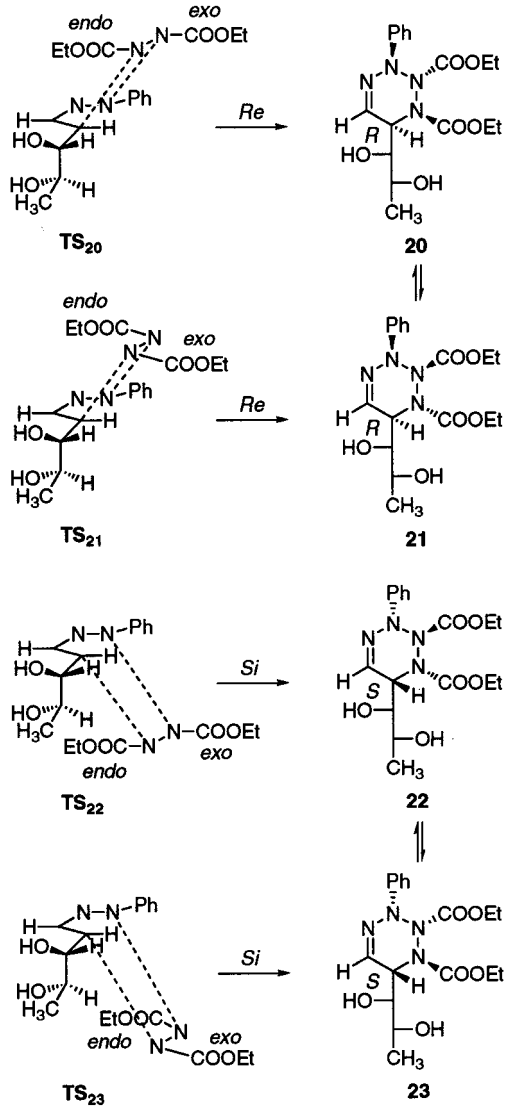
(25) For instance: Orsini, F.; Sala, G. *Tetrahedron* **1989**, *45*, 6531−6536.

(26) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

(27) (a) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. M.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision D.1; Gaussian, Inc.: Pittsburgh, PA, 1995. (b) Frisch, M. J.; Frisch, Æ.; Foresman, J. B. *Gaussian 94 User's Reference*; Gaussian, Inc.: Pittsburgh, PA, 1994−1996.

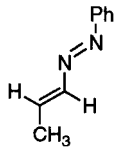
(28) (a) Dewar, M. J. S. *Molecular Orbital Theory for Organic Chemists*; McGraw-Hill: New York, 1969. (b) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; Chapter 2, pp 5−32.

Scheme 3



by no more than 0.04 Å in TSs. The other distance N2−N3 differs by less than 0.05 Å. The cycloadditions are all asynchronous by virtue of the distinctive nature of bonds involved, but they also exhibit a high degree of concertedness.

To evaluate the influence of the acyclic side chain, we did study a reduced model (**24**) in which the *threo*-configured substituent was replaced by a methyl group, but preserving the characteristic (*E*,*E*)-configuration of 1,2-diazabutadienes.



24

The absence of stereogenic centers in **24** now renders both approaches enantiotopic, a fact that also reduces the diastereomeric possibilites by half, both of them interconvertible by configurational inversion of nitrogen atoms N-1 and N-2 (Scheme 4, Table 4).

Again, the energy for the TS **25** is lowered to a much greater extent than the energy for the TS **26** (ΔE = 8.02 kcal/mol). Such a difference is similar to the energy gap between the TS **20** and TS **21** (vide supra) and accounts for the preferential formation of **25** involving an *endo* approach of DEAD to C-4 and an *exo* attack to N-1 of the heterodiene. Unfortunately, a clear-cut explanation for the selective orientation of DEAD (e.g., its facial selection) during its approach to the heterodiene does not issue from the above data. Perhaps, the existence of either an aromatic substituent at N-1 of the heterodiene or an aliphatic one at C-4 also dictates the stereochemical outcome. For this reason, we performed a calculation for the prototype Diels−Alder reaction of 1,2-diazabutadiene **27** plus DEAD leading to **28** and **29** (Scheme 5). The energy gap between both TSs (ΔE = 6.67 kcal/mol) was similar to those found between **25** and **26**, and **20** and **21**. A similar result (ΔE = 6.24 kcal/mol) was also encountered for the reaction of **27** and HN=NH.

Table 4. Heats of Formation (ΔH_f, kcal/mol), Characteristic Bond Lengths (Å), and Torsion Angles (deg) for the TSs and Cycloadducts of 24 + DEAD

	cycloadducts (PM3)		transition structures (PM3)	
	25	**26**	**TS_{25}**	**TS_{26}**
ΔH_f	−57.21	−56.04	−16.60	−8.58
N1−C6	1.510	1.516	2.064	2.030
N2−N3	1.525	1.490	1.844	1.887
CO−N1−N2−CO	129.99	128.94	152.92	151.64

Table 5. Charge Distribution on Atoms for the TSs of Diels−Alder Reactions

	heterodiene		heterodienophile
	q(N2)	*q*(C3)	*q*(C=O)
TS_{20}	−0.02	−0.27	+0.44
TS_{21}	−0.04	−0.23	+0.42
TS_{25}	−0.02	−0.31	+0.44
TS_{26}	−0.03	−0.27	+0.42
TS_{28}	−0.06	−0.26	+0.44
TS_{29}	−0.06	−0.26	+0.41

These results rule out the influence of substituents, at least critically, on the steric course. On the other hand, the energy differences >6 kcal/mol cannot be rationalized to result from weak secondary orbital interactions. To have a partial appreciation of the electronic component which contributes, or likely controls, the regiochemistry of the Diels−Alder reaction, the charge distributions were examined. Mulliken population analysis shows that in all cases the charge distribution on the individual atoms N-2 and C-3 of the heterodiene have a negative value (q < 0). In stark contrast the carbon atom of the carboxylate group lying on the *endo* orientation with respect to the heterodiene has a positive value (Table 5). For each TS, the atoms superposed in the approach of both reaction partners are underlined. The electrostatic interaction is significant for the TSs **20**, **25**, and **28**, which are model structures for the formation of the (6*R*)-configurated adducts **7**−**10**.

Conclusions

The normal aza-Diels−Alder reactions of optically active 1,2-diaza-1,3-butadienes derived from carbohydrates (**1**−**6**) react with DEAD to afford a diastereomeric mixture of (6*R*)- and (6*S*)-configured 1,2,3,6-tetrahydro-1,2,3,4-tetrazines (**7**−**18**) in good yields. Diastereomeric ratios of ∼85:15 are obtained from heterodienes having

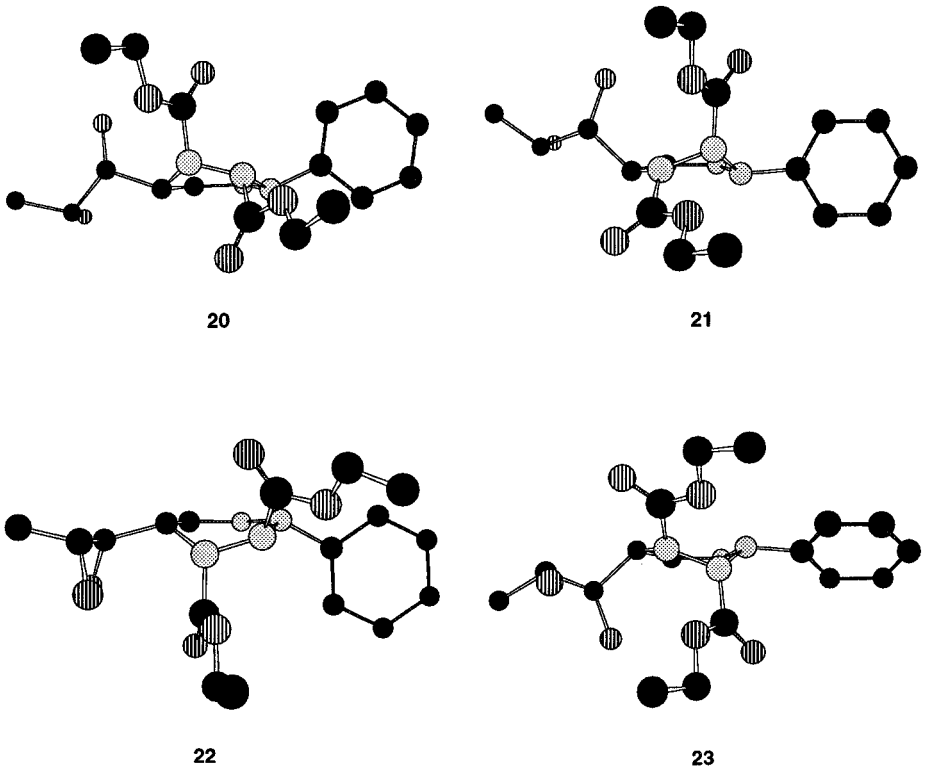
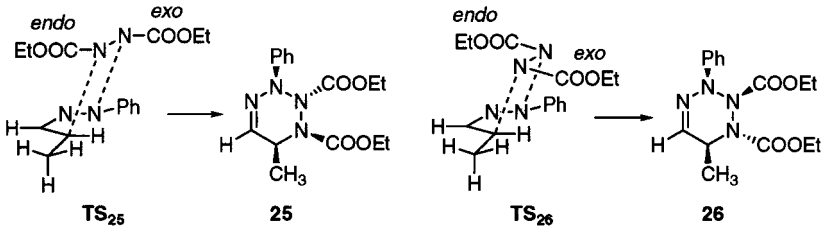


Figure 3. PM3-optimized geometries of the cycloadducts **20**−**23** generated by face-selective reactions of **19** and DEAD. For clarity, hydrogen atoms have been omitted.

Scheme 4



threo configuration at C-1′,2′ of the side chain, whereas a lower stereoselection is obtained from a relative *erythro* configuration. The reactions are impractical at room temperature, but are completed within a few hours under microwave heating with the same sense and level of stereoselection. A careful inspection of the optical rotations of cycloadducts enables anticipation of a useful correlation between the rotatory power and the absolute configuration of tetrazines at C-6. The approach of DEAD to the *Re* face of the heterodiene occurs if the first chiral center of the sugar chain is *R* and results in (6*R*)-configured cycloadducts. To rationalize the experimental results, theoretical calculations on the reactants, products, and transition structures were performed at a semiempirical level, which we have been forced to employ because of the complexity of the system under study. This exploration reveals that the steric course is not critically affected by the nature of substituents, and a better stabilization is due to the electrostatic interaction during the approach of both reactants.

Experimental Section

General Methods. Melting points were determined on a capillary apparatus and are uncorrected. Reactions were monitored by TLC on silica gel 60 F254; the positions of the spots were detected with 254-nm UV light and with iodine vapors. Flash chromatography[29] was performed on columns of silica gel (400−230 mesh) using ether−hexane (1:1, v/v) as eluent. Optical rotations were measured on a polarimeter at 25 °C in the stated solvent. ^{1}H and ^{13}C NMR spectra were recorded at 20 °C in $CDCl_3$ on spectrometers operating at 400 or 200 MHz and at 100 or 50.3 MHz, respectively. Chemical shifts are expressed in ppm positive values downfield from internal TMS and apparent coupling constants are given in hertz. Circular dichroism spectra were recorded on a automatic spectropolarimeter; the concentrations of the CD samples were ascertained from the UV spectra. High-resolution mass spectra (HRMS/EI) were obtained at 70 eV with an ionizing current of 100 μA and accelerating voltage of 4 kV. Elemental analyses were performed by the Servei de Microanàlisi del CSIC, Barcelona.

Microwave-Assisted Syntheses. Reactions were run in a reactor of focused microwaves with a magnetron operating at a frequency at 2.45 GHz and a maximum power output of 300 W. The quartz flask, protected with a polyurethane coating and by a quartz glove finger, is heated in a closed cavity located inside the instrument with continuous stirring. The temperature is measured by an IR pyrometer in the range from 0 to

(29) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

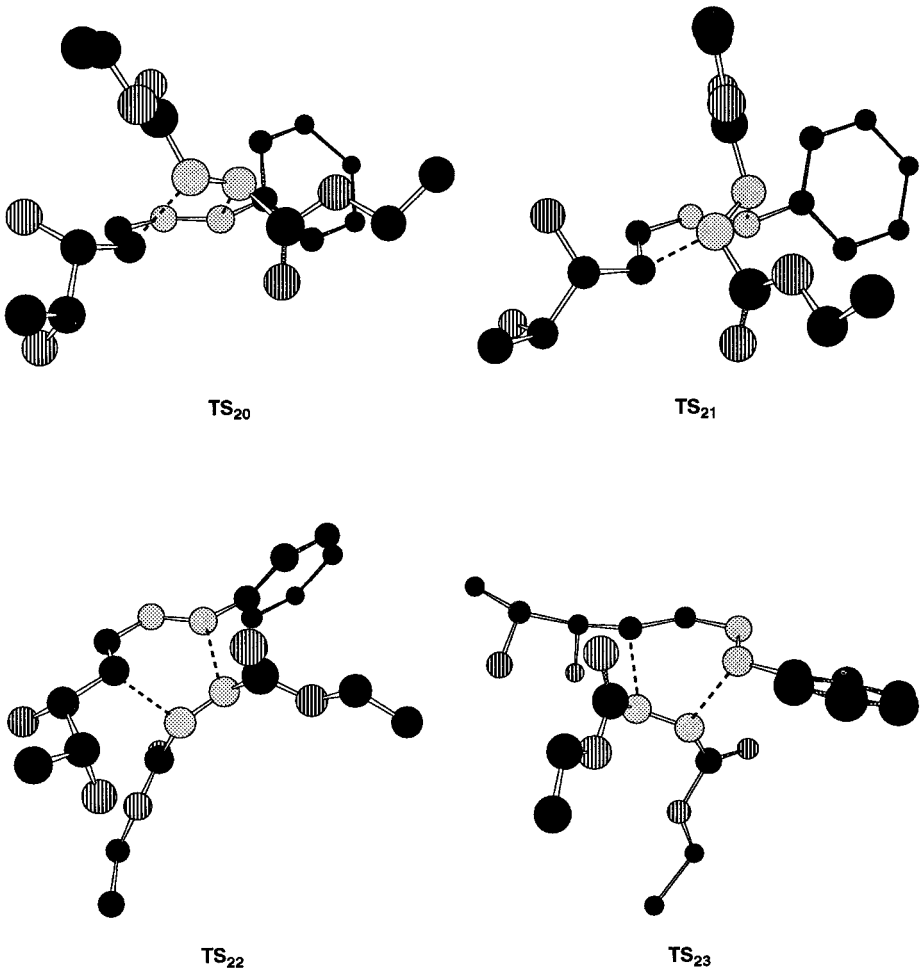
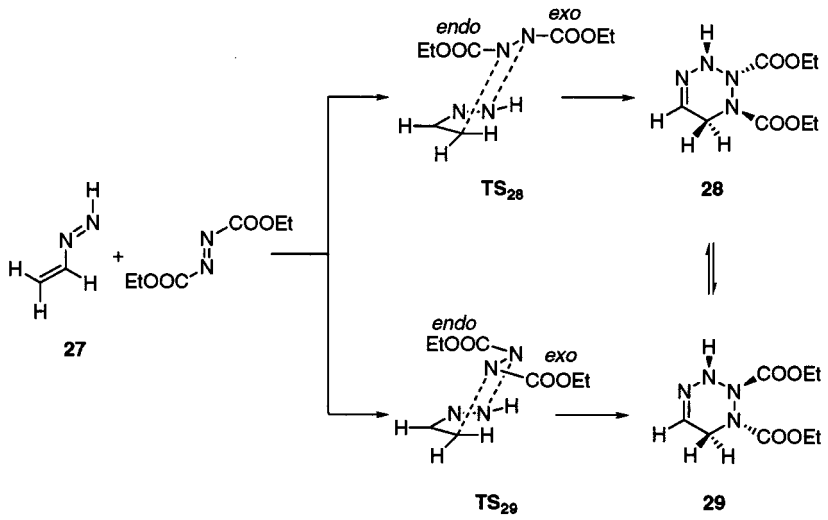


Figure 4. PM3-optimized geometries of TSs **20**−**23**. For the sake of clarity, hydrogen atoms have been omitted.

Scheme 5



450 °C. The microwave module is driven by computer which controls temperature curves and power setpoints (between 0 and 100%).

General Procedures for the Preparation of 6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-aryl-1,2-bis-(ethoxycarbonyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazines (7−12). Method A: To a solution of the corresponding (1*E*,3*E*)-4-(1′,2′,3′,4′-tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-1-aryl-1,2-diaza-1,3-butadiene (**1**−**4**) (4.60 mmol) in dry benzene (35 mL) was added diethyl azodicarboxylate (DEAD) (3.6 mL, 21.72 mmol), and the reaction mixture was kept at room temperature. TLC monitoring (ether−hexane, 2:1) revealed, after 24 h, the formation of two yellow spots with approximate R_f values of 0.5 (compounds **7**−**10**, **15**, **17**) and 0.4 (compounds **11**−**14**, **16**, **18**). After 30 days, the solvent was removed under vacuum, and the residue was flash column chromatographed.

Method B: A suspension of the corresponding 1,2-diaza-1,3-butadiene (**1**−**4**) (1.0 mmol) in neat DEAD (0.4 mL, 2.5 mmol) was subjected to microwave irradiation (300 W, 5%). TLC monitoring (ether−hexane, 2:1) revealed, after 15 min,

the appearance of two yellow spots with R_f values of ~0.5 and ~0.4. After 6 h the solvent was evaporated, and cycloadducts were isolated as described above.

(6*R*)- and (6*S*)-6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-1,2-bis(ethoxycarbonyl)-3-phenyl-1,2,3,6-tetrahydro-1,2,3,4-tetrazines (7 and 11). These substances were obtained as yellowish oils in 93% overall yield. The diastereomeric ratio (85:15) was determined by ^{1}H NMR integration of the residue. Compound **7** had $[\alpha]_D$ +333.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 5H), 6.92 (d, J = 3.5 Hz, 1H), 5.64 (dd, J = 8.1 Hz, 1.7 Hz, 1H), 5.52 (dd, J = 10.2 Hz, 1.7 Hz, 1H), 5.23 (m, 1H), 4.83 (dd, J = 10.2 Hz, 3.5 Hz, 1H), 4.38−4.02 (m, 6H), 2.16 (s, 6H), 2.05 (s, 6H), 1.26 (t, J = 7.1 Hz, 3H), 1.09 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.7, 169.7, 169.6, 154.8, 144.4, 135.1, 128.5, 122.4, 115.0, 69.0, 68.3, 67.5, 64.4, 63.6, 62.4, 51.1, 20.7, 20.6, 20.5, 20.4, 14.0, 13.8; HRMS found 594.2147 ($C_{26}H_{34}N_4O_{12}$ requires 594.2173), Δ = 4.3 ppm. Compound **11**: $[\alpha]_D$ −165.6° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5H), 7.01 (d, J = 3.0 Hz, 1H), 5.75 (dd, J = 6.5 Hz, 5.1 Hz, 1H), 5.48 (dd, J = 6.5 Hz, 4.6 Hz, 1H), 5.36 (m, 1H), 4.99 (dd, J = 4.6 Hz, 3.0 Hz, 1H), 4.44 (dd, J = 11.5 Hz, 3.7 Hz, 1 H), 4.35−4.10 (m, 5H), 2.10 (s, 6H), 2.07 (s, 6H), 1.26 (t, J = 7.0 Hz, 3H), 1.16 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.6, 169.4, 155.5, 153.5, 145.0, 134.1, 128.6, 122.5, 115.0, 70.0, 69.2, 63.9, 63.7, 61.3, 53.1, 20.6, 20.5, 14.2, 14.0.

(6*R*)- and (6*S*)-6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-3-(4-chlorophenyl)-1,2-bis(ethoxycarbonyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazines (8 and 12). These diastereomers were obtained in 96% overall yield (dr = 84:16). Compound **8** was crystallized from ether and had mp 112 °C, $[\alpha]_D$ +381.5° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 4H), 6.90 (d, J = 3.5 Hz, 1H), 5.63 (dd, J = 8.2 Hz, 1.9 Hz, 1H), 5.50 (dd, J = 10.1 Hz, 1.9 Hz, 1H), 5.23 (ddd, J = 8.2 Hz, 6.6 Hz, 2.9 Hz, 1H), 4.82 (dd, J = 10.1 Hz, 3.5 Hz, 1H), 4.43−4.23 (m, 3H), 4.15−4.01 (m, 3H), 2.16 (s, 3H), 2.15 (s, 3H), 2.05 (s, 6H), 1.33 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.8, 169.7, 169.7, 154.8, 154.7, 143.1, 135.5, 128.6, 127.5, 116.1, 69.0, 68.3, 67.6, 64.7, 63.9, 62.5, 51.2, 20.8, 20.7, 20.7, 20.6, 14.1, 14.0; HRMS found 628.1781 ($C_{26}H_{33}ClN_4O_{12}$ requires 628.1783), Δ = 0.4 ppm. Anal. Calcd for $C_{26}H_{33}ClN_4O_{12}$: C, 49.65; H, 5.24; N, 8.90. Found: C, 49.58; H, 5.22; N, 8.83.

Compound **12**: yellow oil, $[\alpha]_D$ −174° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 4H), 7.00 (d, J = 3.2 Hz, 1H), 5.74 (dd, J = 6.4 Hz, 4.9 Hz, 1H), 5.48 (dd, J = 6.4 Hz, 4.5 Hz, 1H), 5.36 (m, 1H), 4.99 (m, 1H), 4.48−4.07 (m, 6H), 2.11 (s, 3H), 2.09 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 1.38−1.13 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.5, 169.6, 169.4, 169.4, 155.4, 153.3, 143.1, 134.4, 128.6, 127.5, 116.1, 70.1, 70.0, 69.3, 64.1, 63.9, 61.3, 53.1, 20.7, 20.6, 20.5, 14.2, 14.0.

(6*R*)-6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-1,2-bis(ethoxycarbonyl)-3-(4-methylphenyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazine (9). This compound was isolated as an oil in 87% yield: $[\alpha]_D$ +422.3° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.16 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.6 Hz, 2H), 6.91 (d, J = 3.6 Hz, 1H), 5.63 (dd, J = 8.2 Hz, 1.7 Hz, 1H), 5.50 (dd, J = 10.2 Hz, 1.7 Hz, 1H), 5.23 (ddd, J = 8.2 Hz, 6.7 Hz, 2.9 Hz, 1H), 4.85 (dd, J = 10.2 Hz, 3.6 Hz, 1H), 4.40−4.00 (m, 6H), 2.29 (s, 3H), 2.15 (s, 3H), 2.14 (s, 3H), 2.04 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.4, 169.7, 169.7, 169.6, 154.8, 142.4, 135.0, 132.0, 129.0, 115.4, 68.9, 68.3, 67.5, 64.4, 63.5, 62.4, 51.0, 20.8, 20.7, 20.6, 20.5, 20.4, 14.1, 13.8; HRMS found 608.2330 ($C_{27}H_{36}N_4O_{12}$ requires 608.2329), Δ = 0.2 ppm.

(6*R*)-6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-1,2-bis(ethoxycarbonyl)-3-(4-methoxyphenyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazine (10). This diastereomer was isolated as an oil in 92% yield: $[\alpha]_D$ +417° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.19 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 3.5 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 5.67 (dd, J = 8.3 Hz, 1.6 Hz, 1H), 5.50 (dd, J = 10.3 Hz, 1.6 Hz, 1H), 5.23 (ddd, J = 8.3 Hz, 6.6 Hz, 2.9 Hz, 1H), 4.85 (dd, J = 10.3 Hz, 3.5 Hz, 1H), 4.36−4.22 (m, 3H), 4.13−3.95 (m, 3H), 3.73 (s, 3H), 2.13 (s, 6H), 2.01 (s, 6H), 1.36 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8, 169.2, 169.2, 155.5, 154.4, 138.4, 136.0, 127.7, 117.4, 113.2, 68.3, 67.7, 67.0, 63.8, 62.9, 61.9, 54.7, 50.4, 20.1, 20.0, 19.8, 19.8, 13.6, 13.3; HRMS found 624.2273 ($C_{27}H_{36}N_4O_{13}$ requires 624.2279), Δ = 0.9 ppm.

(6*R*)- and (6*S*)-6-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1′-yl)-1,2-bis(ethoxycarbonyl)-3-phenyl-1,2,3,6-tetrahydro-1,2,3,4-tetrazines (15 and 16). These diastereomers were isolated in 91% overall yield (dr = 66:33). Compound **15**: crystals from benzene, mp 140 °C, $[\alpha]_D$ +414° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.29 (m, 4H), 7.17 (d, J = 3.5 Hz, 1H), 7.00 (m, 1H), 5.58 (t, J = 4.6 Hz, 1H), 5.47 (m, 1H), 5.36 (dd, J = 4.1 Hz, 3.1 Hz, 1H), 4.98 (t, J = 3.1 Hz, 1H), 4.31 (dd, J = 12.0 Hz, 4.7 Hz, 1H), 4.24−4.10 (m, 5H), 2.16 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 169.9, 169.4, 169.2, 154.3, 154.0, 144.6, 136.4, 128.6, 122.5, 114.9, 72.9, 69.8, 68.6, 64.1, 63.4, 61.6, 52.5, 20.7, 20.6, 20.5, 14.0, 14.0. Anal. Calcd for $C_{26}H_{34}N_4O_{12}$: C, 52.51; H, 5.76; N, 9.42. Found: C, 52.51; H, 5.90; N, 9.49.

Compound **16**: $[\alpha]_D$ −403.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31−7.21 (m, 4H), 7.02−6.94 (m, 1H), 6.91 (d, J = 3.7 Hz, 1H), 5.74 (bs, 1H), 5.52 (dd, J = 10.2 Hz, 2.8 Hz, 1H), 5.35 (ddd, J = 8.1 Hz, 4.0 Hz, 1.5 Hz, 1H), 4.95 (t, J = 3.4 Hz, 1H), 4.40 (dd, J = 11.8 Hz, 4.0 Hz, 1H), 4.37 (bs, 2H), 4.13−3.95 (m, 2H), 3.81 (bs, 1H), 2.16 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.46 (bs, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.3, 170.2, 169.7, 169.4, 155.6, 153.5, 144.6, 134.3, 128.6, 122.4, 115.0, 68.1, 68.0, 67.6, 63.8, 63.7, 62.9, 52.6, 20.8, 20.6, 20.5, 14.2, 13.8.

(6*R*)- and (6*S*)-6-(1′,2′,3′-Tri-*O*-acetyl-D-*erythro*-tritol-1′-yl)-3-(4-bromophenyl)-1,2-bis(ethoxycarbonyl)-1,2,3,6-tetrahydro-1,2,3,4-tetrazines (17 and 18). Diastereomers were isolated in 80% overall yield (dr = 35:65). Compound **17**: Crystals from ether−hexane, mp 132 °C, $[\alpha]_D$ +408° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 9.0 Hz, 2H), 6.94 (d, J = 3.6 Hz, 1H), 5.59 (dd, J = 10.1 Hz, 2.6 Hz, 1H), 5.51 (m, 1H), 4.99 (dd, J = 3.6 Hz, 2.6 Hz, 1H), 4.50−4.20 (m, 4H), 4.18−4.01 (m, 2H), 2.12 (s, 3H), 2.05 (s, 3H), 2.01 (s, 3H), 1.37 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.2, 169.4, 168.9, 155.0, 153.1, 143.4, 135.0, 131.3, 116.2, 114.6, 68.2, 67.5, 63.7, 63.6, 61.0, 52.7, 20.7, 20.3, 14.0, 13.8; HRMS found 600.1063 ($C_{23}H_{29}BrN_4O_{10}$ requires 600.1067), Δ = 0.8 ppm. Anal. Calcd for $C_{23}H_{29}BrN_4O_{10}$: C, 45.93; H, 4.91; N, 9.32. Found: C, 45.93; H, 4.92; N, 9.24.

Compound **18**: $[\alpha]_D$ −361° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.39 (d, J = 9.0 Hz, 2H), 7.18 (d, J = 9.0 Hz, 2H), 7.15 (d, J = 3.4 Hz, 1H), 5.49 (dt, J = 6.1 Hz, 3.9 Hz, 1H), 5.38 (t, J = 3.9 Hz, 1H), 4.94 (dd, J = 3.9 Hz, 3.4 Hz, 1H), 4.45 (dd, J = 12.2 Hz, 3.9 Hz, 1H), 4.33 (dd, J = 12.2 Hz, 6.1 Hz, 1H), 4.28−4.13 (m, 4H), 2.13 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.35−1.19 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.0, 169.2, 169.0, 154.0, 153.7, 143.5, 136.5, 131.3, 116.1, 114.6, 72.8, 69.9, 64.2, 63.3, 61.4, 52.1, 20.5, 20.3, 13.9, 13.8.

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