Synergic Effect of Vicinal Stereocenters in [3 + 2] Cycloadditions of Carbohydrate Azadipolarophiles and Mesoionic Dipoles: Origin of Diastereofacial Selectivity

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The intermolecular [3 + 2] cycloaddition of carbohydrate-derived 1,2-diaza-1,3-butadienes and 1,3-thiazolium-4-olates provides a conceptual basis for the problem of diastereofacial preference in the acyclic series of unsaturated sugars. Experimental results employing a side chain of D-arabino configuration have shown the stereodifferentiation exerted by the first stereogenic center that renders the *Re,Re* face of the acyclic sugar-chain azadiene eligible for cycloaddition (*J. Org. Chem.* **2000**, *65*, 5089). The results of the present work, now utilizing an alternative framework of D-lyxo configuration, evidence the discriminating power of the second stereogenic carbon, which induces the preferential approach to the *Re,Si* face of the heterocyclic dipole. This scheme of face selectivity is also grounded in theoretical calculations at a semiempirical level. In addition to dihydrothiophenes, which are the expected products of the [3 + 2] cycloaddition, bicyclic systems based on dihydrothieno[2,3-*c*]piperidine skeleton can also be obtained.

Introduction and Background

Diastereoselection and diastereoselective relationships constitute a large and multifaceted topic that can conveniently be exploited to provide access to optically active compounds and, in general, to structures with a well-defined stereochemical pattern.[1] Most chemists are aware of the basic question here: when an additional ligand is going to be bound to the reactive atom, what will the preferred new configuration be? Addition and cycloaddition reactions to trigonal centers from the two faces need not be equally facile, and their stereodifferentiation is a common problem in synthetic strategies.[2] As noted by Gung and Le Noble in their introductory remarks in a recent special issue devoted to diastereoselection,[1a] sterically controlled selectivities still enjoy a lively development and are essentially noncontroversial. Sometimes, however, it is not intuitively obvious how steric crowding could have led to the resulting products, and a series of often controversial stereoelectronic effects have been invoked as the key factors that govern stereoselection in sterically unbiased systems.[3] A challenging scenario to study diastereotopic face selection and diastereotopic ligand selection is to examine the stereochemical impact of preexisting stereogenic centers in probe molecules. Within this strategy, it is not surprising that carbohydrates were examined as reaction partners, not only because these substances can lead to stereochemically complex carbocycles and heterocycles, but also because they offer a varied range of functionality where non-carbohydrate ligands can be temporarily attached.[4] In general, acyclic sugars exhibit relatively low facial diastereoselectivities that may be ascribed to the conformational flexibility of the chain. With the exception of a few configurational arrangements, in which a planar zigzag conformation of the chain is largely favored,[5] acyclic sugars present nonextended conformations separated by low energy barriers. Accordingly, the stereodirecting effects found in acyclic sugar templates should be examined in the light of precise geometries of the transition structures determined by computation. Salient examples of improved selectivity and synthetic efficiency have been found by Franck and others in acyclic dienes with allylic stereogenic centers.[6] During the past decade, our research group has studied asymmetric [3 + 2] cycloadditions where acyclic carbohydrates are employed as stereodifferentiators and mesoionic heterocycles serve as the masked dipoles.[7] A clear-cut statement obtained from these studies is the fact that higher stereoselectivies were observed in acyclic chains where the acyloxy substituents located at the first two stereocenters exhibit a relative threo relationship. Thus, in a recent study, we have shown that cycloadditions of 1,3-thiazolium-4-olates with homochiral 1,2-diaza-1,3-butadienes bearing an acyclic

(1) (a) For an excellent and comprehensive survey on diastereoselection, see: Gung, B. W., Le Noble, B., Eds. *Chem. Rev.* **1999**, *99*, 1067−1480. (b) Franck, R. W. *Conformational Behavior of Six-Membered Rings*; Juaristi, E., Ed.; VCH: New York and Weinheim, 1995; pp 159−200.

(2) For a revision of addition and cycloaddition reactions to carbon and heteroatom bonds: *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5.

(3) (a) Kaselj, M.; Chung, W.-S.; Le Noble, W. J. *Chem. Rev.* **1999**, *99*, 1387−1413. (b) Adcock, W.; Trout, N. A. *Chem. Rev.* **1999**, *99*, 1415−1435. (c) Mehta, G.; Chandrasekhar, J. *Chem. Rev.* **1999**, *99*, 1437−1467. (d) Wipf, P.; Jung, J.-K. *Chem. Rev.* **1999**, *99*, 1469−1480.

(4) *Cycloaddition Reactions in Carbohydrate Chemistry*; Giuliano, R. M., Ed.; ACS Symposium Series 494; American Chemical Society: Washington, DC, 1992.

(5) Blanc-Muesser, M.; Defaye, J.; Horton, D. *Carbohydr. Res.* **1980**, *87*, 71−86.

(6) (a) Franck, R. W.; Argade, S.; Subramanian, C. S.; Frechet, D. M. *Tetrahedron Lett.* **1985**, *26*, 3187−3190. (b) Reitz, A. B.; Jordan, A. D., Jr.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4800−4802. (c) McDougal, P. G.; Jump, J. M.; Rojas, C.; Rico, J. G. *Tetrahedron Lett.* **1989**, *30*, 3897−3900. (d) Franck, R. W. in ref 4; pp 24−32. (e) López, J. C.; Lukacs, G. In ref 4; pp 33−49 and references therein.

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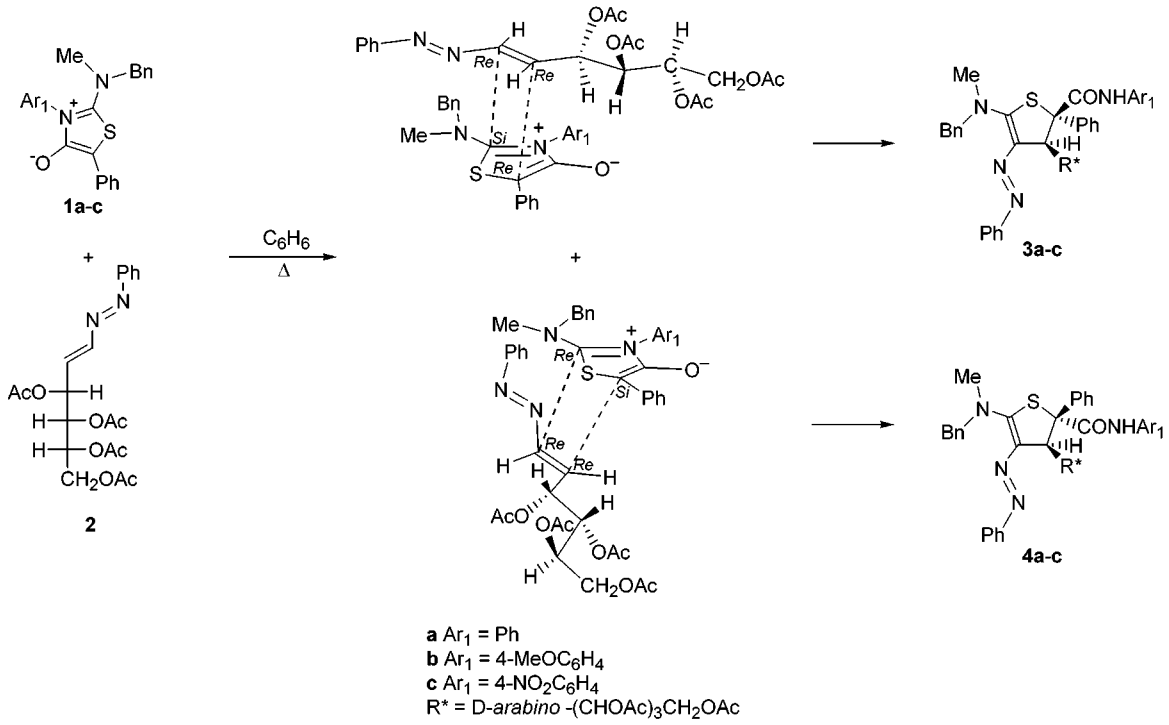
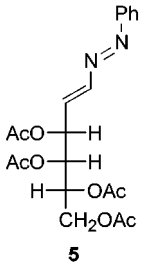
Scheme 1



chain of D-arabino configuration was completely regioselective and also proceeded with complete facial selectivity with respect to the azoalkene.[8] The resulting dihydrothiophenes exclusively arise from the attack of the mesoionic dipole to the *Re*,*Re* face[9] of the unsaturated sugar (Scheme 1).

Within this context, it is pertinent to mention a series of cycloadditions of nitrones to allylic ethers described by Saito and his group where a vicinal diol controller with a relative threo configuration provides a high diastereofacial differentiation.[10] Likewise, another work reports on high levels of acyclic stereodifferentiation in intramolecular nitrone-alkene cycloadditions of 3-*O*-allylmonosaccharides with a threo configuration at the adjacent chiral tether.[11]

To gain further insight into the problem of diastereofacial preference of acyclic carbohydrates in the abovementioned cycloadditions, we have now evaluated the cycloadditions of mesoionic dipoles **1a**−**c** with compound **5**, which contains a sugar framework with an L-erythro configuration in the two stereocenters attached to the carbon−carbon double bond.



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The results have been used to assess the prediction attained in a previous study, confirmed by theoretical calculations as well, that the first stereocenter of the sugar alkene determines the most reactive face, while the degree of selectivity is provided by the relative arrangement of the two vicinal stereocenters.[12] As we shall see, and in a counter-intuitive way, it appears that the second stereocenter exerts a strong stereoface directing effect with respect to the heterocyclic dipole. Again, a computational study at a semiempirical level is sufficient to provide a satisfactory rationale of the stereochemical outcome, thereby validating models previously suggested for the interpretation of [3 + 2] cycloadditions.[13]

Results and Discussion

Asymmetric Reactions. As described previously in the case of a D-arabino-configured chain,[8] the present cycloadditions of the 1,2-diaza-1,3-butadiene attached to

(7) (a) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Diánez, M. J.; Estrada, M. D.; Jiménez, J. L.; López-Castro, A.; Palacios, J. C.; Garrido, S. P. *J. Chem. Soc., Chem. Commun.* **1995**, 2213−2214. (b) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738−3748. (c) Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Commun.* **1998**, 459−460. (d) Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1999**, *64*, 1494−1502. (e) Avalos, M.; Babiano, R.; Bravo, J. L.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Eur. J.* **2000**, *6*, 267−277. (f) Arévalo, M. J.; Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Tetrahedron* **2000**, *56*, 1247−1255.

(8) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C.; Raithby, P. R. *J. Org. Chem.* **2000**, *65*, 5089−5097.

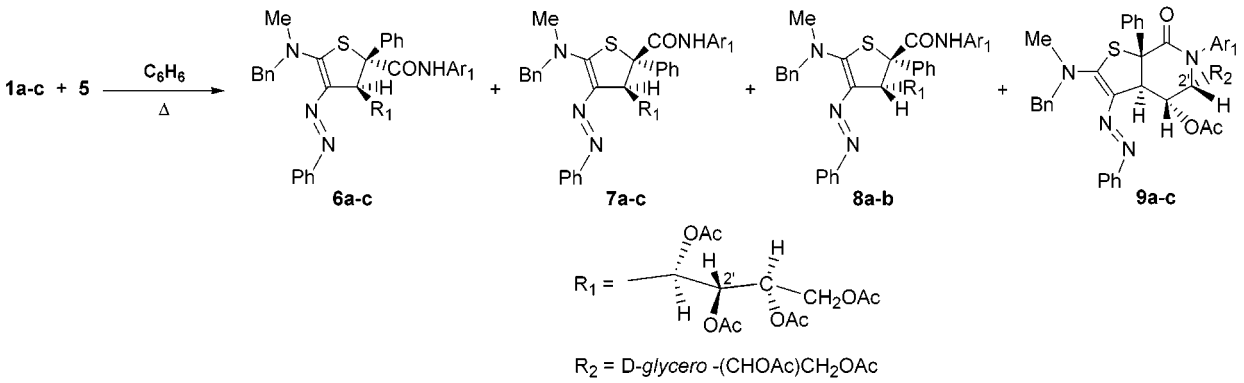
(9) The descriptors *Re* and *Si* indicate the two-dimensional chirality of heterotopic faces. The symbols *re* and *si* should be restricted to cases giving rise to pseudoasymmetric centers. See: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; Chapter 8.

(10) (a) Saito, S.; Ishikawa, T. *Synlett* **1994**, 279−281. (b) Saito, S.; Narahara, O.; Ishikawa, T.; Asahara, M.; Moriwake, T.; Gawronski, J.; Kazmierczak, F. *J. Org. Chem.* **1993**, *58*, 6292−6302. (c) Saito, S.; Ishikawa, T.; Moriwake, T. *J. Org. Chem.* **1994**, *59*, 4375−4377. (d) Ishikawa, T.; Tajima, Y.; Fukui, M.; Saito, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1863−1864.

(11) Shing, T. K. M.; Zhong, Y.-L.; Mak, T. C. W.; Wang, R.-J.; Xue, F. *J. Org. Chem.* **1998**, *63*, 414−415.

(12) Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Jiménez, J. L.; Palacios, J. C.; Sánchez, J. B. *J. Org. Chem.* **1999**, *64*, 6297−6305.

Scheme 2



an extended acyclic template of D-lyxo configuration (**5**) with **1a**−**c** were performed in refluxing benzene. TLC analysis (diethyl ether/hexane, 7:1) revealed the formation of three (in the case of the starting dipole **1a**) or four new products (in the cases of **1b** and **1c**), which could be separated by flash chromatography and further purified by preparative chromatography (Scheme 2). The latter protocol had to be used in view of the high face selection of the cycloadditive process favoring the formation of **6a**−**c**, whereas the rest of stereoisomers were formed in very small amounts. Facial selectivities between **6a** and **7a** and **6b** and **7b** lie in the range 34:1 and 20:1, respectively. The prevalent formation of **6a**−**c** was also detected in the crude mixtures by 400-MHz ^{1}H NMR. It should also be noted that an interesting side product, **9c**, could be isolated in the cycloaddition of **1c** plus **5** in 9% yield, while similar reactions involving **1a** and **1b** afforded **9a** and **9b**, respectively, in minute amounts (ca. 1% yield).

Dihydrothiophenes **6a**−**c** and **7a**−**c** arise from attack on the *Re*,*Re* face of the 1,2-diaza-1,3-butadiene derivative, a fact in full agreement with previous studies involving acyclic sugar chains with the same configuration at the first stereogenic center.[8,12]

The main argument, illustrated in Scheme 3, for the observed face selectivity is based on the assumption that the acyloxy group attached to the first stereocenter moves away from the heterocyclic dipole. It is worth noting that in acyclic sugar heterodienes in which the first stereocenter has the opposite configuration, the face exposed for attack has been observed to be the *Si*,*Si* face.[7b] The most noticeable observation concerning face selectivity is, however, that the chain having the D-lyxo stereochemistry favored attack at the *Re*,*Si* face of the dipole instead of the *Si*,*Re* face observed for a D-arabino configuration,[8] which seems to indicate that the effect on the facial diastereoselection is also ruled by the second stereocenter.

A precise identification of the diastereomeric structures **6**−**8** could be accomplished by spectroscopic comparison with model compounds, which were unequivocally solved by X-ray crystallographic analysis.[8]

In particular, ^{13}C NMR chemical shifts for C-2 and C-3 in compounds **6**−**8** lie in the typical values observed for those of **3** and **4** (Table 1). These results are consistent with a cis disposition between the phenyl group and the sugar moiety in the cases of dihydrothiophenes **6a**−**c** and

Scheme 3. Face Selectivity for the [3 + 2] Cycloadditions of 1a−c and 5

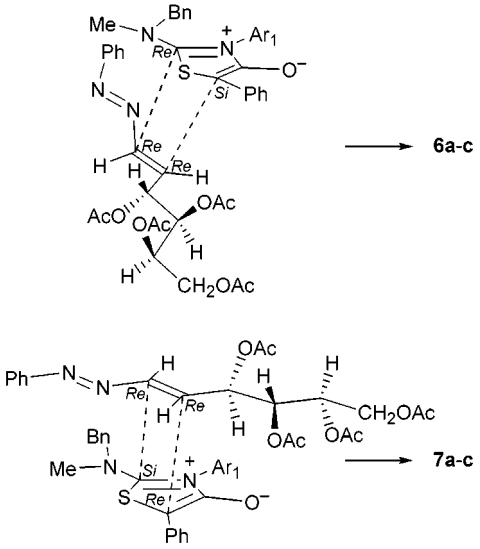


Table 1. Comparison of ^{13}C NMR Resonances for Structural Assignments of Dihydrothiophenes 6−8

compd	C-2	C-3
3a	74.51	44.88
3b	74.31	44.92
3c	74.09	44.74
4a	70.75	47.13
4b	70.72	47.16
6a	70.82	48.86
6b	70.75	48.77
6c	70.71	49.44
7a	74.78	44.67
7b	74.67	44.70
7c	74.28	44.45
8a	70.93	49.66
8b	71.07	49.91

8a,**b** and an alternative trans arrangement of the same groups for **7a**−**c**.

The structure of dihydrothieno[2,3-*c*]piperidines attributed to trans-fused bicyclic systems **9a**−**c** is based on their ^{1}H and ^{13}C NMR spectra and high-resolution mass spectra, which evidence the loss of acetic acid with respect to the parent dihydrothiophenes. Both H-2′ and C-2′ resonances for **9a**−**c** appear more deshielded ($\Delta\delta_H$ ~2.6−1.5 ppm and $\Delta\delta_C$ ~4.2−2.3 ppm, respectively) than those of **6**−**8**. These changes are consistent with the presence of a nitrogen atom at C-2′ instead of the expected oxygenated function. Such observations suggest that compounds **9a**−**c** stem from the same cycloadduct

(13) (a) Jursic, B. S.; Zdravkovski, Z. *Tetrahedron* **1994**, *50*, 10379−10390. (b) Jursic, B. S.; Zdravkovski, Z. *THEOCHEM* **1995**, *332*, 39−45.

Scheme 4. Cycloadduct Transformation Leading to Dihydrothiophenes or Dihydrothieno[2,3-*c*]piperidines

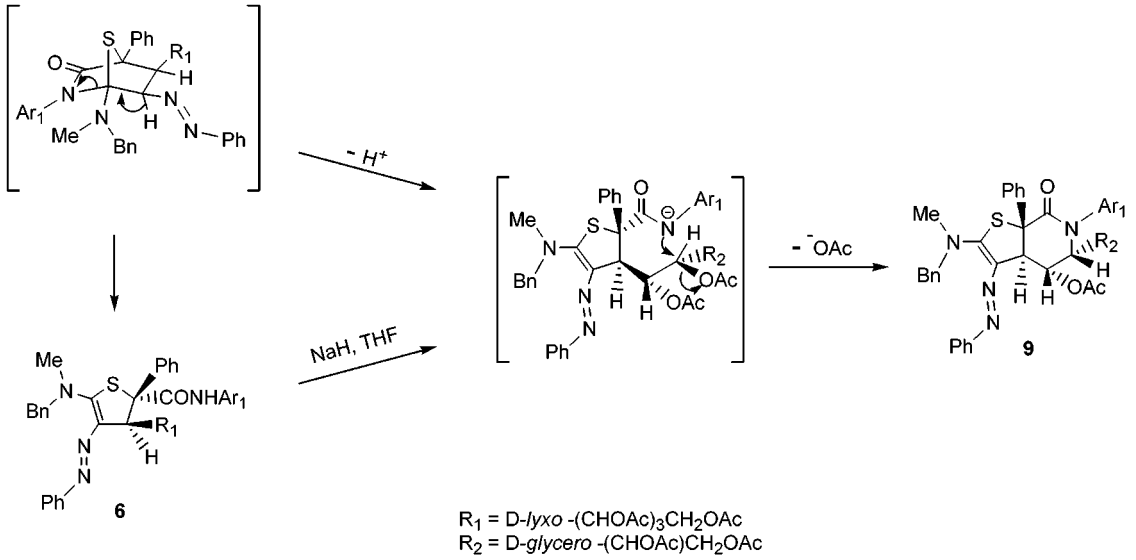


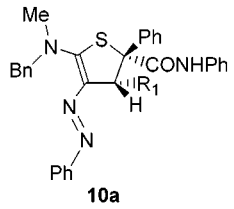
Table 2. Energetics (kcal/mol) and Bond Lengths (Å) for Transition Structures TS6-TS8 and TS10

	ΔE	$\Delta E^{\ddagger}$	C2−C3	C4−C5
TS6	−122.0	35.8	3.31	1.93
TS7	−121.0	36.9	3.15	1.96
TS8	−120.1	37.7	3.36	1.96
TS10	−119.7	38.2	3.23	1.99

leading to **6**−**8** (Scheme 4). The intermediate anion should be greatly stabilized by an electron-withdrawing group such as the 4-nitrophenyl substituent present in **1c**. This scheme could be validated by the direct formation of **9a** from **6a** after treatment with NaH in dry THF. It should finally be pointed out that this route discloses a novel access to a *trans*-fused-dihydrothieno[2,3-*c*]piperidines, which have been scarcely described in the literature.[14]

Theoretical Analysis. The reactants and the four possible transition structures were fully optimized at the PM3 level[15] using the GAUSSIAN 94 package.[16] In each case, the transition structures were characterized by only one imaginary harmonic vibrational frequency, which corresponds to the formation of carbon−carbon bonds. The predicted heats of formation for transition structures **TS6**−**TS8** and **TS10** as well as the corresponding activation enthalpies are listed in Table 2. Such transition structures would afford dihydrothiophenes **6a**, **7a**, **8a**, and **10a**, respectively (Scheme 5).

The most stable transition structures (**TS6** and **TS7**) involve the participation of the *Re*,*Re* face of the carbohydrate dipolarophile, the former being lower in energy and stemming from selective attack on the *Re*,*Si* face of the mesoionic dipole. In stark contrast, the most unstable transition structure (**TS10**) would give the remaining dihydrothiophene **10a**, although this substance could neither be detected nor isolated in the present study.



Anyway, the energy differences observed are lower than those found in the cycloadditions of **1a**−**c** with **2**,[8] which accounts for a greater product distribution. An examination of carbon−carbon bond-forming distances in the transition structures reveals a considerable degree of asynchronicity, although **TS7** was the less asynchronous structure. A further consideration of dihedral angles in the transition structures also evidences that a greater deformation of both dipole and dipolarophile, with respect to the starting materials, occurs in the most stable **TS6**.

Comparison between **TS6** and **TS7** also indicate that the phenylazo group is placed in *endo* and *exo* orientations, respectively. Nevertheless, this substituent induces a minimal repulsion as the aromatic ring becomes almost coplanar with the heterocyclic dipole and where the steric hindrance is lowest owing to the larger distance between C2 and C3 (>3.1 Å in all cases). Assuming that the phenyl group at C5 in the dipole and the acyclic dipolarophile are much closer than the rest of substituents, the preference for formation of **TS6** with favored *Re*,*Si* attack should likely be based on that interaction.

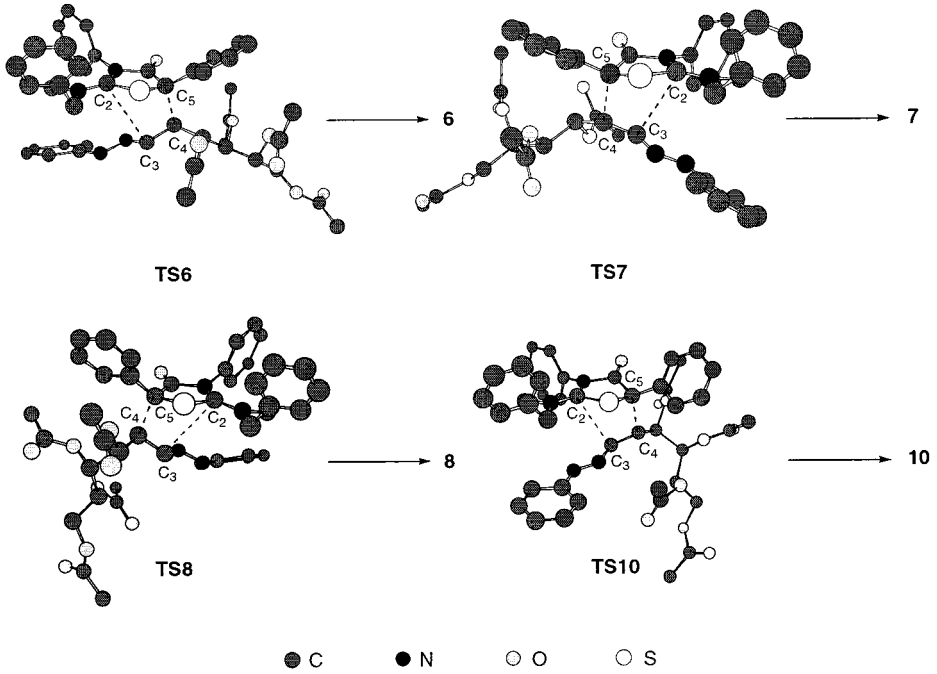
The opposite configuration at C2′ in a D-lyxo framework (with respect to a D-arabino-configured chain) causes a major steric hindrance between the acetate group at C2′ with the dipole phenyl group at C5. As a result, the sugar chain deviates from the expected zigzag arrangement and the dihedral angle C2−C3−C1′−C2′ in **TS6** and **TS7** becomes 113° and 119°, respectively. These shifts contrast with the values observed in a sugar chain of

(14) (a) Gramain, J.-C.; Troin, Y.; Vallée, D. *J. Chem. Soc., Chem. Commun*. **1981**, 832−833. (b) Gramain, J.-C.; Troin, Y.; Vallée-Goyet, D. *Tetrahedron* **1991**, *47*, 7301−7308.

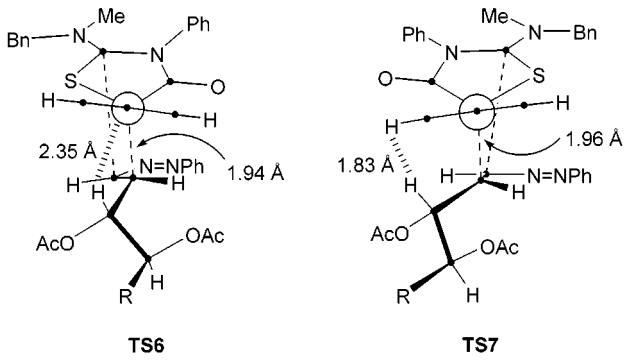
(15) Stewart, J. J. P. *J. Comput. Chem*. **1989**, *10*, 209−220.

(16) (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.

Scheme 5. Computed Transition Structures (PM3 level) Leading to the Formation of Dihydrothiophenes 6a−8a and 10a



Scheme 6. Face-to-Face Approach of the Chiral Azadipolarophile (5) to the Heterocyclic Dipole (1a−c) Showing the Steric Interactions with the Ortho Hydrogens of the Phenyl Substituent Located at C5



D-arabino configuration because the dihedral angles in the corresponding transition structures leading to **3a** and **4a** are 147° and 135°, respectively.[8] In **TS6**, no appreciable interactions take place between the sugar chain, especially the first stereocenters, and the ortho hydrogens in the phenyl group positioned at C5 as indicated by nonbonding distances higher than 2.3 Å. In fact, in this case the shortest nonbonding distance (2.35 Å), as depicted in Scheme 6, occurs between the substituted carbon at the phenyl group and the hydrogen atom (H1′) at the first stereogenic center in the carbohydrate moiety. The disfavored attack emerging from **TS7** can in turn be rationalized if one now admits that some steric interaction should occur between the ortho hydrogen atoms of the phenyl group and the H1′ at the first stereogenic center at ~1.8 Å, yet moving away the alkoxy group at C2′ (Scheme 6). Overall, the steric effect of the second stereocenter reinforces the *Re,Si*-face attack with respect to the dipole, while decreasing the face selectivity of the dipolarophile as some *Si,Si*-face attack occurs as well. Thus, it appears evident that a combination of steric and conformational factors are implicated and that the configuration of the first stereocenters can be used in a synergic way to determine the diastereofacial selectivity of acyclic sugar azadienes in these reactions.

Conclusions

We have shown that consideration of configurational arrangements of acyclic azoalkenes derived from carbohydrates enables a control of the most reactive faces in dipolar cycloadditions with mesoionic compounds, exemplified here in the cases of 1,3-thiazolium-4-olates **1a−c**. The relative configuration of 1,2-bisacyloxy groups adjacent to the dipolarophilic carbon atoms in the substrates play a pivotal role in stereocontrol by biasing the diastereotopic face of the acyclic sugar with a concomitant selection of the heterocyclic face. While the first stereocenter appears to dictate the most reactive face of the dipolarophile to a large extent, the second one imposes a further steric control that discriminates the faces of the mesoionic ring. These and previous experimental results are supported by the computation of transition structures. Our results evidence the importance of chirogenic elements as controllers of reactive centers in acyclic compounds which, due to conformational mobility, can be regarded as sterically unbiased models well suited for the analysis of the factors that govern stereoselection.

Experimental Section

General Methods. Melting points were determined on a capillary apparatus and are uncorrected. Optical rotations were measured at the sodium line at 18 ± 2 °C. Analytical and preparative TLC were performed on silica gel with monitoring by means of UV light at 254 and 360 nm and iodine vapors. Flash chromatography[17] was performed with silica gel (400−230 mesh). IR spectra were recorded on KBr pellets. ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz,

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

respectively, in $CDCl_3$ (Me_4Si as internal standard) unless otherwise specified. High-resolution mass spectra (HRMS/FAB$^+$ or HRMS/CI$^+$) were obtained by the Servicio de Espectrometría de Masas at the Universidad de Córdoba, Spain. Compounds **1a**−**c**[2b] and **5**[18] were prepared according to literature procedures.

Cycloadditions of Mesoionics with Azadienes: General Procedure for the Synthesis of (2*R*,3*R*)-, (2*S*,3*R*)-, and (2*S*,3*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5-(*N*-methylbenzylamino)-2-phenyl-4-[(1*E*)-phenylazo]-2-phenylcarbamoyl-2,3-dihydrothiophenes (6a−8a) and (3a*R*,4*R*,5*S*,7a*R*)-4-*O*-acetyl-5-(1′,2′-di-*O*-acetyl-D-*glycero*-ditol-1-yl)-2-(*N*-methylbenzylamino)-7-oxo-6,7a-diphenyl-3-[(1*E*)-phenylazo]-3a*H*,7a*H*-thieno[2,3-*c*]piperidine (9a). To a suspension of **1a** (0.50 g, 1.3 mmol) in benzene (25 mL) was added **5** (0.38 g, 0.9 mmol). The reaction mixture was refluxed until the complete disappearance of **5** (1−2 h, TLC analysis: diethyl ether−*n*-hexane 7:1) and the appearance of four new products **6a** (R_f 0.5), **7a** (R_f 0.6), **8a** (R_f 0.1), and **9a** (R_f 0.3). The solvent was evaporated, and the resulting residue was flash chromatographed using a gradient from diethyl ether−*n*-hexane 1:1 at the beginning to diethyl ether at the end. Further purification by preparative TLC (using diethyl ether−*n*-hexane 4:1 as eluent) gave **6a** (0.268 g, 37.0%), **7a** (0.008 g, 1.1%), **8a** (0.005 g, 0.7%), and **9a** (0.004 g, 0.6%) as orange solids.

Synthesis of 9a from 6a. 0.200 g (0.2 mmol) of **6a** were dissolved in 3 mL of a saturated solution of NaH in THF. After 40 min the appearance of **9a** and other unidentified side products were observed. The solid residue was filtered and the mother liquors were concentrated. Compound **9a** was obtained by preparative TLC (diethyl ether−*n*-hexane 5:1) (0.020 g, 10.7%).

Compound 6a: mp 92 °C; $[\alpha]_D$ +352.9° (*c* 0.5, $CHCl_3$); IR (KBr) 3340, 1745, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.65−7.09 (m, 20 H), 6.12 (dd, J = 8.6, 1.6 Hz, 1H), 5.65 (dd, J = 8.4, 1.8 Hz, 1H), 5.28 (m, 1H), 4.98 (d, J = 1.8 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.73 (d, J = 15.6 Hz, 1H), 4.21 (dd, J = 11.6, 5.1 Hz, 1H), 3.89 (dd, J = 11.6, 7.4 Hz, 1H), 3.34 (s, 3H), 2.09 (s, 3H), 1.96 (s, 3H), 1.95 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.2, 170.1, 170.0, 166.9, 158.4, 154.2, 143.1, 137.3, 135.9, 129.0, 128.8, 128.7, 128.6, 128.0, 127.9, 127.2, 126.6, 126.3, 124.9, 121.3, 120.3, 72.5, 70.8, 68.2, 67.8, 62.8, 61.0, 48.8, 42.9, 20.9, 20.8, 20.6, 20.1. Anal. Calcd for $C_{43}H_{44}N_4O_9S$: C, 65.14; H, 5.59; N, 7.06; S, 4.04. Found: C, 64.62; H, 5.65; N, 6.85; S, 4.02.

Compound 7a: mp 89 °C; $[\alpha]_D$ −59.2° (*c* 0.4, $CHCl_3$); IR (KBr) 3380, 1730, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−6.95 (m, 21 H), 6.67 (m, 1H), 5.93 (dd, J = 9.8, 3.4 Hz, 1H), 5.50 (d, J = 9.8 Hz, 1H), 4.89 (m, 3H), 4.17 (dd, J = 11.3, 8.4 Hz, 1H), 3.79 (dd, J = 11.5, 4.4 Hz, 1H), 3.29 (s, 3H), 2.04 (s, 3H), 1.96 (s, 3H), 1.86 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.3, 169.6, 167.5, 158.4, 154.1, 141.9, 138.18, 135.6, 129.6, 128.9, 128.7, 128.2, 127.6, 127.3, 127.0, 126.2, 126.1, 124.0, 123.0, 120.8, 118.7, 74.8, 71.5, 71.0, 69.3, 63.2, 61.1, 44.7, 43.3, 21.4, 20.8, 20.4; HRMS (CI$^+$) found 793.290726 ($C_{43}H_{44}N_4O_9S$ + H$^+$ requires 793.290726), Δ = −0.3 ppm.

Compound 8a: mp 128 °C; $[\alpha]_D$ +31.3° (*c* 0.6, $CHCl_3$); IR (KBr) 3350, 1745, 1680 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.69−7.04 (m, 20 H), 5.77 (dd, J = 9.2, 1.7 Hz, 1H), 5.38 (d, J = 1.8 Hz, 1H), 5.03 (m, 3H), 4.86 (d, J = 15.9 Hz, 1H), 4.19 (dd, J = 11.8, 4.7 Hz, 1H), 3.85 (dd, J = 11.7, 7.6, 1H), 3.49 (s, 3H), 2.30 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 170.1, 169.7, 169.5, 169.3, 155.3, 154.0, 137.4, 136.3, 134.0, 128.9, 128.8, 128.6, 128.5, 127.8, 127.0, 126.8, 124.5, 121.6, 119.7, 71.8, 70.9, 68.4, 66.6, 62.9, 61.2, 49.6, 43.4, 21.0, 20.9, 20.6, 20.5. Anal. Calcd for $C_{43}H_{44}N_4O_9S$: C, 65.14; H, 5.59; N, 7.06; S, 4.04. Found: C, 65.14; H, 5.56; N, 7.02; S, 4.29.

Compound 9a: mp 107 °C; $[\alpha]_D$ −163.3° (*c* 0.3, $CHCl_3$); IR (KBr) 1745, 1675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−6.96 (m, 20 H), 5.78 (dd, J = 9.7 Hz, J <1.0 Hz, 1H), 5.08 (d, J < 1.0 Hz, 1H), 4.9 (m, 3H), 4.30 (dd, J = 11.3, 5.0 Hz, 1H), 4.15(dd, J = 11.4, 7.5 Hz, 1H), 3.45 (bs, 1H), 2.09 (s, 3H), 1.84 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 169.6, 167.2, 166.6, 153.0, 141.8, 136.6, 135.2, 129.3, 129.1, 128.9, 128.8, 128.7, 128.1, 126.3, 125.8, 125.1, 120.8, 120.0, 73.1, 70.8, 68.7, 68.4, 63.4, 46.6, 44.0, 29.7, 21.2, 20.6, 20.4; HRMS (CI$^+$) found 733.266342 ($C_{41}H_{40}N_4O_7S$ + H$^+$ requires 733.269597), Δ = 4.4 ppm and 751.281906 ($C_{41}H_{40}N_4O_7S$ + H_3O^+ requires 751.280162) Δ = −2.3 ppm; HRMS (FAB$^+$) found 751.282206 ($C_{41}H_{40}N_4O_7S$ + H_3O^+ requires 751.280162) Δ = −2.7 ppm.

Synthesis of (2*R*,3*R*)-, (2*S*,3*R*)-, and (2*S*,3*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-2-(4-methoxyphenyl)carbamoyl-5-(*N*-methylbenzylamino)-2-phenyl-4-[(1*E*)-phenylazo]-2,3-dihydrothiophenes (6b−8b) and (3a*R*,4*R*,5*S*,7a*R*)-4-*O*-Acetyl-5-(1′,2′-di-*O*-acetyl-D-*glycero*-ditol-1-yl)-6-(4-methoxyphenyl)-2-(*N*-methylbenzylamino)-7-oxo-7a-phenyl-3-[(1*E*)-phenylazo]-3a*H*,7a*H*-thieno[2,3-*c*]-piperidine (9b). These substances were obtained from **1b** and **5** according to the general procedure described above: **6b** (R_f 0.5), **7b** (R_f 0.6), **8b** (R_f 0.3), and **9b** (R_f 0.4). They were purified by flash chromatography using a gradient from diethyl ether−*n*-hexane 1:1 at the beginning to diethyl ether at the end. Further purification by preparative TLC (using diethyl ether−*n*-hexane 7:1 as eluent) gave **6b** (0.284 g, 35.5%), **7b** (0.015 g, 1.8%), **8b** (0.013 g, 1.6%), and **9b** (0.008 g, 1.0%) as orange solids.

Compound 6b: mp 96 °C; $[\alpha]_D$ +340.1° (*c* 0.7, $CHCl_3$); IR (KBr) 3420, 1730, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.59−6.85 (m, 19 H), 6.10 (dd, J = 8.3, 1.7 Hz, 1H), 5.65 (dd, J = 8.3, 1.8 Hz, 1H), 5.28 (m, 1H), 4.95 (d, J = 1.9 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 4.76 (d, J = 15.6 Hz, 1H), 4.19 (dd, J = 11.6, 4.9 Hz, 1H), 3.89 (dd, J = 11.6, 7.5 Hz, 1H), 3.78 (s, 3H), 3.33 (s, 3H), 2.08 (s, 3H), 1.95 (s, 3H), 1.93 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.1, 169.9, 166.6, 158.5, 156.8, 154.1, 143.1, 135.8, 130.3, 128.8, 128.7, 128.6, 127.9, 127.8, 127.1, 126.9, 126.5, 126.2, 122.1, 121.2, 114.0, 72.5, 70.7, 68.2, 67.9, 62.8, 60.9, 55.4, 48.8, 42.8, 20.9, 20.8, 20.5, 20.2. Anal. Calcd for $C_{44}H_{46}N_4O_{10}S$: C, 64.22; H, 5.63; N, 6.80; S, 3.89. Found: C, 63.51; H, 5.68; N, 7.02; S, 3.89.

Compound 7b: mp 207 °C; $[\alpha]_D$ −268.3° (*c* 0.2, $CHCl_3$); IR (KBr) 3345, 1740, 1675 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−6.78 (m, 20 H), 6.65 (m, 1H), 5.92 (dd, J = 9.5 Hz, J = 3.3 Hz, 1H), 5.46 (d, J = 9.7 Hz, 1H), 4.90 (m, 3H), 4.17 (dd, J = 11.3 Hz, J = 8.4 Hz, 1H), 3.79 (dd, J = 11.4 Hz, J = 4.2 Hz, 1H), 3.76 (s, 3H), 3.29 (s, 3H), 2.05 (s, 3H), 1.98 (s, 3H), 1.87 (s, 3H), 1.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.5, 170.3, 169.6, 167.1, 1619, 156.0, 154.2, 142.1, 135.7, 131.6, 129.7, 128.8, 128.7, 128.1, 127.6, 127.0, 126.2, 126.0, 120.9, 120.1, 113.9, 74.7, 71.5, 71.1, 69.2, 63.2, 61.1, 55.4, 44.7, 43.3, 21.4, 20.9, 20.8, 20.4; HRMS (CI$^+$) found 823.300618 ($C_{44}H_{46}N_4O_{10}S$ + H$^+$ requires 823.301291), Δ = 0.8 ppm.

Compound 8b: mp 104 °C; $[\alpha]_D$ +26.7° (*c* 0.5, $CHCl_3$); IR (KBr) 3350, 1715, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.69−6.76 (m, 19 H), 5.76 (dd, J = 9.2, 1.9 Hz, 1H), 5.37 (d, J = 1.9 Hz, 1H), 5.02 (m, 3H), 4.87 (d, J = 15.9 Hz, 1H), 4.19 (dd, J = 11.8, 4.7 Hz, 1H), 3.85 (dd, J = 11.7, 7.6, 1H), 3.75 (s, 3H), 3.49 (s, 3H), 2.29 (s, 3H), 1.95 (s, 3H), 1.88 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.4, 170.0, 169.7, 169.6, 156.8, 155.6, 154.2, 136.6, 134.4, 130.8, 129.2, 128.9, 128.8, 128.7, 128.1, 127.2, 127.1, 121.8, 114.2, 72.0, 71.1, 68.6, 66.8, 63.1, 61.4, 55.7, 49.9, 43.7, 21.3, 21.2, 20.9, 20.7. Anal. Calcd for $C_{44}H_{46}N_4O_{10}S$: C, 64.22; H, 5.63; N, 6.80; S, 3.89. Found: C, 64.13; H, 5.75; N, 7.21; S, 3.41.

Compound 9b: mp 109 °C; $[\alpha]_D$ −98.9° (*c* 0.4, $CHCl_3$); IR (KBr) 1740, 1660 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−6.80 (m, 19 H), 5.80 (dd, J = 9.6 Hz, J < 1.0 Hz, 1H), 5.06 (d, J < 1.0 Hz, 1H), 4.93 (m, 3H), 4.30 (dd, J = 11.4, 5.2 Hz, 1H), 4.15(dd, J = 11.5, 7.6 Hz, 1H), 3.75 (s, 3H), 3.45 (bs, 3H), 2.09 (s, 3H), 1.85 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.7, 169.6, 167.3, 166.5, 157.0, 153.1, 142.0, 135.2, 129.6, 129.3, 129.1, 128.9, 128.6, 128.1, 126.9, 126.3, 125.7,

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122.7, 120.0, 114.0, 73.0, 70.9, 68.7, 68.3, 63.5, 55.4, 46.7, 43.9, 21.3, 20.6; HRMS (CI^+) found 763.279112 ($C_{42}H_{42}N_4O_8S + H^+$ requires 763.280162), Δ = 1.4 ppm; HRMS (FAB^+) found 781.290133 ($C_{42}H_{42}N_4O_8S + H_3O^+$ requires 781.290726) Δ = 0.8 ppm.

Synthesis of (2*R*,3*R*)- and (2*S*,3*R*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*lyxo*-tetritol-1-yl)-5-(*N*-methylbenzylamino)-2-(4-nitrophenyl)carbamoyl-2-phenyl-4-[(1*E*)-phenylazo]-2,3-dihydrothiophenes (6c, 7c) and (3a*R*,4*R*,5*S*,7a*R*)-4-*O*-Acetyl-5-(1′,2′-di-*O*-acetyl-D-*glycero*-ditol-1-yl)-2-(*N*-methylbenzylamino)-6-(4-nitrophenyl)-7-oxo-7a-phenyl-3-[(1*E*)-phenylazo]-3a*H*,7a*H*-thieno[2,3-*c*]piperidine (9c). These substances were obtained from **1c** and **5** according to the general procedure described above: **6c** (R_f 0.5), **7c** (R_f 0.6), and **9c** (R_f 0.4). They were purified by flash chromatography using a gradient from diethyl ether-*n*-hexane 1:1 at the beginning to diethyl ether at the end. Further purification by preparative TLC (using diethyl ether−*n*-hexane 4:1 as eluent) gave **6c** (0.098 g, 14.7%), **7c** (0.008 g, 1.2%), and **9c** (0.060 g, 9.0%) as orange solids.

Compound 6c: mp 99 °C; $[\alpha]_D$ +345.0° (*c* 0.8, $CHCl_3$); IR (KBr) 3420, 1715, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1H), 8.26−7.09 (m, 19 H), 6.10 (dd, *J* = 7.7, 1.6 Hz, 1H), 5.52 (dd, *J* = 7.8, 1.9 Hz, 1H), 5.3 (m, 1H), 4.02 (d, *J* = 1.9 Hz, 1H), 4.82 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 4.15 (dd, *J* = 11.7, 4.8 Hz, 1H), 3.87 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.37 (s, 3H), 2.07 (s, 3H), 1.99 (s, 3H), 1.98 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.6, 170.5, 170.0, 167.9, 158.1, 154.1, 144.2, 143.1, 135.9, 129.4, 129.1, 129.0, 128.5, 128.1, 127.3, 127.1, 126.7, 126.6, 125.9, 125.1, 121.4, 120.1, 72.7, 70.7, 68.6, 68.4, 63.0, 61.3, 49.4, 43.2, 21.2, 21.0, 20.8, 20.4. Anal. Calcd for $C_{43}H_{43}N_5O_{11}S$: C, 61.34; H, 5.17; N, 8.36; S, 3.83. Found: C, 61.03; H, 5.12; N, 8.14; S, 4.03.

Compound 7c: mp 82.4 °C; $[\alpha]_D$ −173.2° (*c* 0.3, $CHCl_3$); IR (KBr) 3420, 1740, 1720 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17−6.94 (m, 20 H), 6.66 (m, 1H), 5.92 (dd, *J* = 10.0, 3.3 Hz, 1H), 5.56 (d, *J* = 10.0 Hz, 1H), 4.91 (d, *J* = 15.5, 1H), 4.84 (bd, *J* = 3.5, 2H), 4.20 (dd, *J* = 11.4, 8.5 Hz, 1H), 3.78 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.30 (s, 3H), 2.03 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 170.3, 168.4, 161.4, 153.9, 143.7, 141.2, 135.4, 129.1, 128.7, 128.5, 127.7, 126.9, 126.3, 126.0, 125.0, 120.8, 118.4, 74.3, 71.6, 70.8, 69.6, 63.2, 61.4, 44.4, 43.4, 21.5, 20.7, 20.4; HRMS (CI^+) found 838.274109 ($C_{43}H_{43}N_5O_{11}S + H^+$ requires 838.275805), Δ = 2.0 ppm.

Compound 9c: mp 114 °C; $[\alpha]_D$ −217.19° (*c* 0.6, $CHCl_3$); IR (KBr) 1770, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18−7.14 (m, 19 H), 5.74 (dd, *J* = 9.7 Hz, *J* < 1.0 Hz, 1H), 5.14 (d, *J* < 1.0 Hz, 1H), 4.93 (m, 3H), 4.29 (dd, *J* = 11.5, 4.8 Hz, 1H), 4.12 (dd, *J* = 11.5, 7.8 Hz, 1H), 3.47 (bs, 3H), 2.07 (s, 3H), 1.85 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.4, 169.7, 167.3, 166.6, 152.9, 144.0, 142.8, 141.1, 135.0, 129.5, 129.2, 128.9, 128.1, 127.0, 126.0, 125.7, 124.7, 120.3, 120.1, 72.9, 70.4, 88.4, 63.4, 61.2, 46.2, 44.0, 21.1, 20.6, 20.4; HRMS (CI^+) found 778.257042 ($C_{41}H_{39}N_5O_9S + H^+$ requires 778.254675), Δ = −3.0 ppm; HRMS (FAB^+) found 796.263481 ($C_{41}H_{39}N_5O_9S + H_3O^+$ requires 796.265240) Δ = 2.2 ppm.

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Supporting Information Available: Cartesian coordinates of transition structures **TS6**−**TS8** and **TS10** with their computed total energies. This material is available free of charge via the Internet at http://pubs.acs.org

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