Mechanism of the Diastereoselective, Boron Trifluoride-Catalyzed Cyclization of Olefinic Tosylhydrazones to Stereolabeled, Bridgehead-Substituted Azoalkanes

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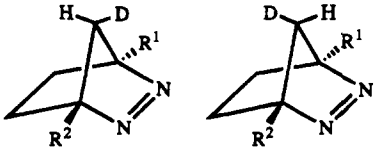
Abstract: For the first time 1,4-dialkylated 2,3-diazabicyclo[2.2.1]hept-2-enes (**5a−c**) with stereolabels at the C-7 position have been prepared via the intramolecular cyclization of stereolabeled γ,δ-unsaturated tosylhydrazones under acidic conditions. The stereochemically labeled olefinic carbonyl compounds **3**, required for the preparation of the tosylhydrazones **4**, were made by *syn* carbometalation of the appropriate terminal alkynes **1a,b**(D) with dialkylcuprates in THF at 0 °C. Hydrolysis of the ketal functionality in the resulting linear alkenes **2** afforded the desired ketones **3**. Although the boron trifluoride-catalyzed cyclization of the tosylhydrazones **4** led in all cases to mixtures of stereochemically labeled azoalkanes, the process is highly diastereoselective in that the initial *syn/anti* diastereomeric ratio of the tosylhydrazones **4** dictates the stereochemistry of the final azoalkanes **5**. Thus, in the deuterium-labeled substrates, the *syn* tosylhydrazone of (*E*)-**4a**(D) affords the azoalkane *syn*-**5a**(D) through the orthogonal *syn*-**A** arrangement of the tosylhydrazone and olefin functionalities, while the *anti* tosylhydrazone of (*E*)-**4a**(D) leads to the azoalkane *anti*-**5a**(D) through the parallel *anti*-**B** arrangement, irrespective of the stereolabeled olefin geometry. A delicate balance of steric effects in the orthogonal and parallel conformers for the *syn* and *anti* diastereomers of the tosylhydrazones seems to control the observed diastereoselectivity.

Introduction

For our mechanistic studies on the thermal,[1] photochemical,[2] and electron transfer induced[3] deazetation of the 2,3-diazabicyclo-[2.2.1]hept-2-ene type (DBH), we required a convenient stereoselective synthesis of 1,4-dialkylated DBH derivatives with stereolabels at the C-7 position as the *syn* and *anti* diastereomers.



syn *anti*

The classical route for the preparation of azoalkanes,[4] namely, the cycloaddition of triazolinediones to substituted cyclopentadienes, catalytic hydrogenation of the resulting urazole, hydrolysis, and final oxidation, poses serious preparative problems to comply with this required substitution pattern. These include the difficulty of preparing the appropriate cyclopentadiene precursors, and their propensity to isomerize by a 1,5 hydrogen shift, formation of diastereomers which are tedious if not impossible to separate, and limitations in the choice of the stereochemical label.

The alternative useful synthesis of DBH derivatives, namely, the Diels−Alder cycloaddition of substituted isopyrazoles with alkene dienophiles,[5] suffers from the drawback that disubstitution at the C-5,6 position in the cycloadduct is dictated by the choice of olefin partner. Besides, diastereomeric mixtures of cycloadducts are still obtained, which are usually difficult to separate. Moreover, thermal and photochemical deazetation leads preferentially to housanes with retention of configuration due to steric repulsion between the substituents at the C-5,6 positions and the stereolabel at C-7.[5d] Thereby the stereochemical information sought, e.g., to assess the mechanistic details of the double inversion process,[6] is erased.

These problems can be circumvented in principle by intramolecular cyclization of γ,δ-olefinic tosylhydrazones under acidic conditions,[7] which is predestined for the synthesis of 1,4-dialkylated DBH derivatives. Despite the moderate yields (usually 42−55%), this BF_3-catalyzed process should be useful for the introduction of stereolabels at the C-7 site of the DBH-type azoalkanes. We were interested, therefore, in testing the stereoselectivity in the BF_3-catalyzed cyclization of appropriately labeled γ,δ-olefinic tosylhydrazones. The method of choice in the stereoselective synthesis of the γ,δ-enones for the required tosylhydrazones constitutes carbometalation of alkynes by organometallic reagents.[8] The synthetic sequence that was

[†] Undergraduate Research Participant, Spring 1992.

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(2) (a) Adam, W.; Denninger, U.; Finzel, R.; Kita, F.; Platsch, H.; Walter, H.; Zang, G. *J. Am. Chem. Soc.* **1992**, *114*, 5027−5035. (b) Adam, W.; Finzel, R.; Kita, F. *Tetrahedron Lett.* **1991**, *32*, 2211−2214. (c) Adam, W.; Schulte Oestrich, R.; Wilson, R. M. *Spectrum* **1991**, *4*, 8−17. (d) Adam, W.; Grabowski, S.; Wilson, R. M. *Acc. Chem. Res.* **1990**, *23*, 165−172. (e) Adam, W.; Oppenländer, T. *Angew. Chem.* **1986**, *98*, 659−670.

(3) (a) Adam, W.; Dörr, M. *J. Am. Chem. Soc.* **1987**, *109*, 1570−1572. (b) Adam, W.; Chen, G.-F.; Walter, H.; Williams, F. *J. Am. Chem. Soc.* **1992**, *114*, 3007−3014. (c) Adam, W.; Sendelbach, J. *J. Org. Chem.* **1993**, *58*, 5310−5315, 5316−5322. (d) Adam, W.; Sahin, C.; Sendelbach, J.; Walter, H.; Chen, G.-F.; Williams, F. *J. Am. Chem. Soc.* **1994**, *116*, 2576−2584.

(4) (a) Review: Adam, W.; DeLucchi, O. *Angew. Chem.* **1980**, *92*, 815−832. (b) Criegee, R.; Rimmelin, A. *Chem. Ber.* **1957**, *90*, 414−417.

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(6) Allred, E. L.; Smith, R. L. *J. Am. Chem. Soc.* **1969**, *91*, 6766−6775.

(7) (a) Wilson, R. M.; Rekers, J. W. *J. Am. Chem. Soc.* **1979**, *101*, 4005−4007. (b) Wilson, R. M.; Rekers, J. W.; Packard, A. B.; Elder, R. C. *J. Am. Chem. Soc.* **1980**, *102*, 1633−1641. (c) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756−3766.

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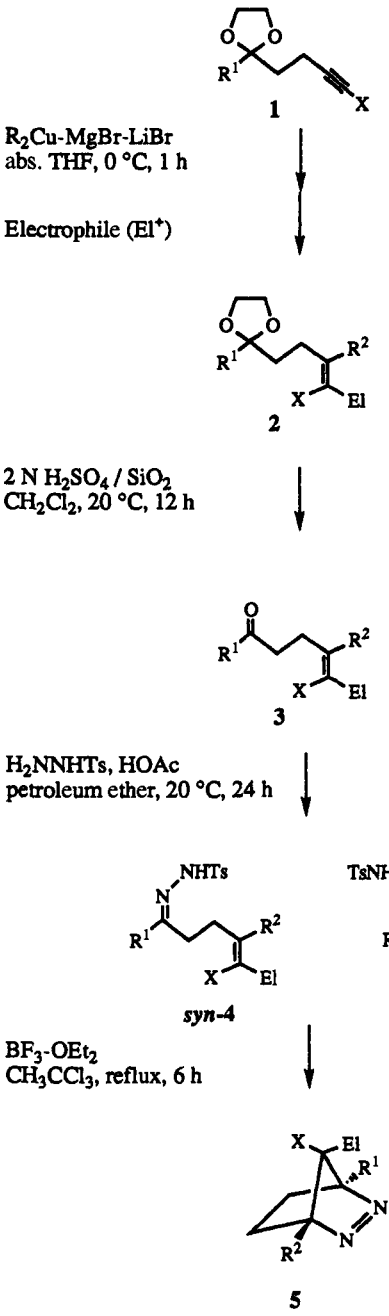
Scheme 1



1	R^1	X
a	Me	H
a(D)	Me	D
b	Et	H
b(D)	Et	D

2-4	R^1	R^2	X	El
a	Me	Et	H	H
E-**a**(D)	Me	Et	H	D
Z-**a**(D)	Me	Et	D	H
Z-**b**(D)	Me	*t*Bu	H	D
E-**b**(D)	Me	*t*Bu	D	H
E-**c**(D)	Et	Et	H	D
Z-**c**(D)	Et	Et	D	H

5	R^1	R^2	X	El
a	Me	Et	H	H
syn-**a**(D)	Me	Et	H	D
anti-**a**(D)	Me	Et	D	H
syn-**b**(D)	Me	*t*Bu	H	D
anti-**b**(D)	Me	*t*Bu	D	H
syn-**c**(D)	Et	Et	H	D
anti-**c**(D)	Et	Et	D	H

followed is displayed in Scheme 1. Indeed, the cyclization affords the required C-7 stereolabeled azoalkanes but depends on the *syn/anti* stereochemistry of the tosylhydrazone functionality. Valuable mechanistic insight into the cyclization process has been acquired, and we present herein the results.

Results

Stereoselective Cuprate Addition to Terminal Alkynes 1 for Synthesis of Alkenes 2. The preparation of the protected alkynones **1a,b**(D) started from the symmetrically substituted 1,3-alkanediones,[9] which were converted by propargylation and ketone cleavage to the desired alkynones.[10] Ketalization[11] afforded substrates **1a,b** in excellent yield, which, upon deprotonation[12] with ethylmagnesium bromide in refluxing THF and subsequent reaction with D_2O, gave the deuterium-labeled 1-alkynes **1a,b**(D) in 68–83% yield and with quantitative deuteration.

When the 1-alkynes **1a,b**(D) were treated with diethyl- or di-*tert*-butylcuprates[13a] in THF at 0 °C (see Table 1), in most cases only the terminal alkenes were isolated after workup. Thereby the intermediary vinylcuprates were either stereoselectively protonated (Table 1; entries 1, 3, 5, 7) or stereoselectively deuterated (Table 1; entries 2, 4, 6).

(8) (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841–870. (b) Normant, J. F. *Synthesis* **1972**, 63–80. (c) Posner, G. H. *Org. React. (N.Y.)* **1975**, *22*, 253–400. (d) Posner, G. H. *Org. React. (N.Y.)* **1972**, *19*, 1–113.

(9) 2,4-Pentanedione is commercially available, whereas 3,5-heptanedione was prepared according to the following: Paine, J. B., III; Dolphin, D. *J. Org. Chem.* **1985**, *50*, 5598–5604.

(10) Flahaut, J.; Miginiac, P. *Helv. Chim. Acta* **1978**, *61*, 2275–2285.

(11) Abidi, J. L. *J. Org. Chem.* **1986**, *51*, 2687–2694.

(12) Eaton, B.; King, J. A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 1359–1360.

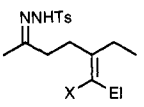
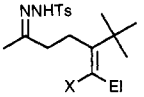
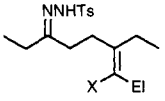
(13) (a) Westmijze, H.; Meijer, J.; Bos, H. J. T.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 304–307, (b) 299–303. (c) Such oxidative dimerizations are known to proceed with retention of configuration; cf.: Normant, J. F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* **1974**, *77*, 269–279.

Table 1. Product Studies of Carbometalation of Alkynes **1**

entry	substrate **1**			$R^2_2Cu-M-LiBr$[a]		electrophile	conv of **1**[b]	product distribn[c]		yield[d]
		R^1	X	R^2	M	El^+	(%)	(*E*)-**2**	(*Z*)-**2**	(%)
1	**1a**	Me	H	Et	MgBr	NH_4Cl	>95	90[e]		83
2	**1a**	Me	H	Et	MgBr	D_2O	>95	89[e]		77
3	**1a**(D)	Me	D	Et	MgBr	NH_4Cl	>95		90[e]	81
4	**1a**	Me	H	*t*-Bu	MgCl	D_2O	89	4	78[f]	80
5	**1a**(D)	Me	D	*t*-Bu	MgCl	NH_4Cl	66	77	5[f]	85
6	**1b**	Et	H	Et	MgBr	D_2O	>95	90[e]		76
7	**1b**(D)	Et	D	Et	MgBr	NH_4Cl	>95		89[e]	62

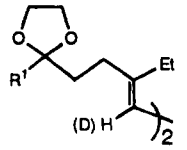
[a] 1.1 equiv of $R_2Cu-M-LiBr$ relative to **1** was used (ref 13a). [b] Error limits ±3% of stated values. [c] The regioselectivity (branched/linear) is higher than 99:1, except in the *tert*-butyl case, where it is 82:18; mass balance >95% determined by ^1H NMR spectroscopy of the crude reaction mixture. [d] Yield of isolated olefins **2** after distillation. [e] The remainder was the dimers $(\mathbf{2})_2$. [f] The remainder was the linear alkene **2b'**.

Table 2. Product Studies of Boron Trifluoride-Catalyzed Cyclization of Tosylhydrazones **4** to Azoalkanes **5**

entry	structure	tosylhydrazone **4**			*anti*:*syn*[a]	solvent[b]	yield[c] (%)	azoalkane **5**[d] *anti*:*syn*
			X	El				
1		(*E*)-**4a**(D)	H	D	82:18[e]	benzene	26	82:18
2		(*E*)-**4a**(D)	D	H	82:18[e]	benzene	23	18:82
3		(*Z*)-**4b**(D)[f]	H	D	84:16[e]	1,1,1-trichloroethane	37	84:16
4		(*Z*)-**4c**(D)	D	H	57:43[g]	1,1,1-trichloroethane	26	43:57

[a] Hydrazone diastereomers, determined by ^1H NMR spectroscopy; error ±3% of stated values. [b] Cyclization conditions: 1.3 equiv of $BF_3{\cdot}OEt_2$, heated for 6 h reflux. [c] Isolated material after flash chromatography and Kugelrohr distillation. [d] Azoalkane diastereomers, determined by ^1H NMR spectroscopy; error ±3% of stated values. [e] Petroleum ether (bp 30–50 °C), ca. 20 °C, 24 h, HOAc. [f] Note that according to the Cahn–Ingold–Prelog rule the *tert*-butyl group has a higher priority. [g] Petroleum ether (bp 30–50 °C), reflux 4 h, HOAc.

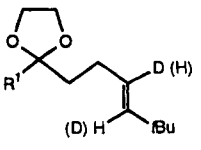
For all ethylcuprate cases (Table 1; entries 1–3, 6, 7), alkenes **2** were contaminated with variable amounts (10–17%) of dimers $(\mathbf{2})_2$. The latter derive presumably from oxidative dimerization



$(\mathbf{2})_2$

R^1 = Me (δ 5.92)

R^1 = Et (δ 5.97)



2b'

of the intermediary vinylcuprates.[13a,b] The resonances of the olefinic protons in the dimers $(\mathbf{2a,c})_2$ were absent when deuterated alkynes **1a,b**(D) instead of unsubstituted alkynes **1a,b** were employed.[13c]

For the *tert*-butyl derivative (Table 1; entries 4, 5), besides the desired branched regioisomers **2b**, linear alkenes **2b'** were also formed in 18% yield. The partial loss of the regioselectivity is due to steric hindrance exercised by the bulky *tert*-butyl group.[13a]

While strict *syn* addition applies for the ethylcuprate (Table 1), for the more basic and reactive *tert*-butylcuprate some (ca. 5%) *anti* adduct was also observed.[13a] The slight loss of the diastereoselectivity is not due to proton abstraction from the 1-alkyne, since the corresponding alkylation products of the 1-alkenylcopper(I) intermediate were not observed.[13a] Moreover, in the presence of LiBr, known to suppress proton abstraction,[13a,b] still ca. 5% *anti* addition occurred for the di-*tert*-butylcuprate. Presumably steric effects are operating again.

All attempts to transfer a methyl group from $Me_2Cu-MgCl-LiBr$,[13a] Me_2CuLi,[14a] $MeCu-MgBrCl-Me_2S$,[14b] or $Me_3Cu_2-MgCl-(LiBr)_2$[14c] to the triple bond of alkyne **1a** failed; only the starting material was reisolated after workup. Instead of cuprate addition, deprotonation of the terminal H or D atom was observed, as confirmed by substantial deuterium loss (ca. 80%) when substrate **1a**(D) was subjected to these reaction conditions.

Stereoselective BF_3-Catalyzed Cyclization of Tosylhydrazones 4 to Azoalkanes 5. Ketals **2** were smoothly hydrolyzed to ketones **3** at ambient temperature within 12 h by stirring them in a H_2SO_4/SiO_2 slurry.[15] ^1H and ^{13}C NMR analysis, which also included NOE experiments for derivative **3a**, established the structures and confirmed that no scrambling of the stereolabeled olefin functionality had occurred.

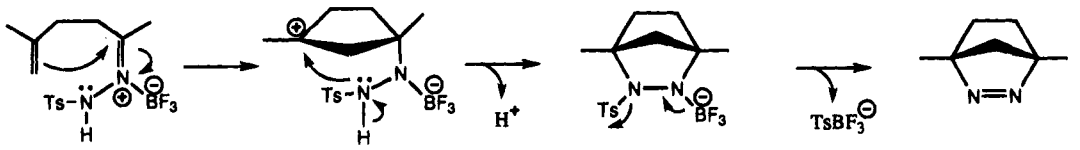
Tosylhydrazones **4** were obtained as mixtures of *syn* and *anti* isomers in nearly quantitative yields by acid-catalyzed (glacial acetic acid) reaction of tosylhydrazine and the appropriate ketone **3**.[7a,b] The diastereomeric ratio was strongly dependent on the reaction conditions and on the alkyl substituent α to the keto group (see Table 2). The *syn*/*anti* configuration of the tosylhydrazone functionality in **4** was assigned by comparison with the literature spectral data of the parent 5-methyl-5-hexen-2-one tosylhydrazone.[7b]

For the BF_3-catalyzed cyclization of tosylhydrazones **4** to azoalkanes **5**, solubility problems required optimization of the usual reaction conditions.[7a,b] Thus, reflux in 1,1,1-trichloroethane (Table 2) proved to be the most appropriate condition to afford the pure azoalkanes in acceptable yields after flash chromatography and Kugelrohr distillation.

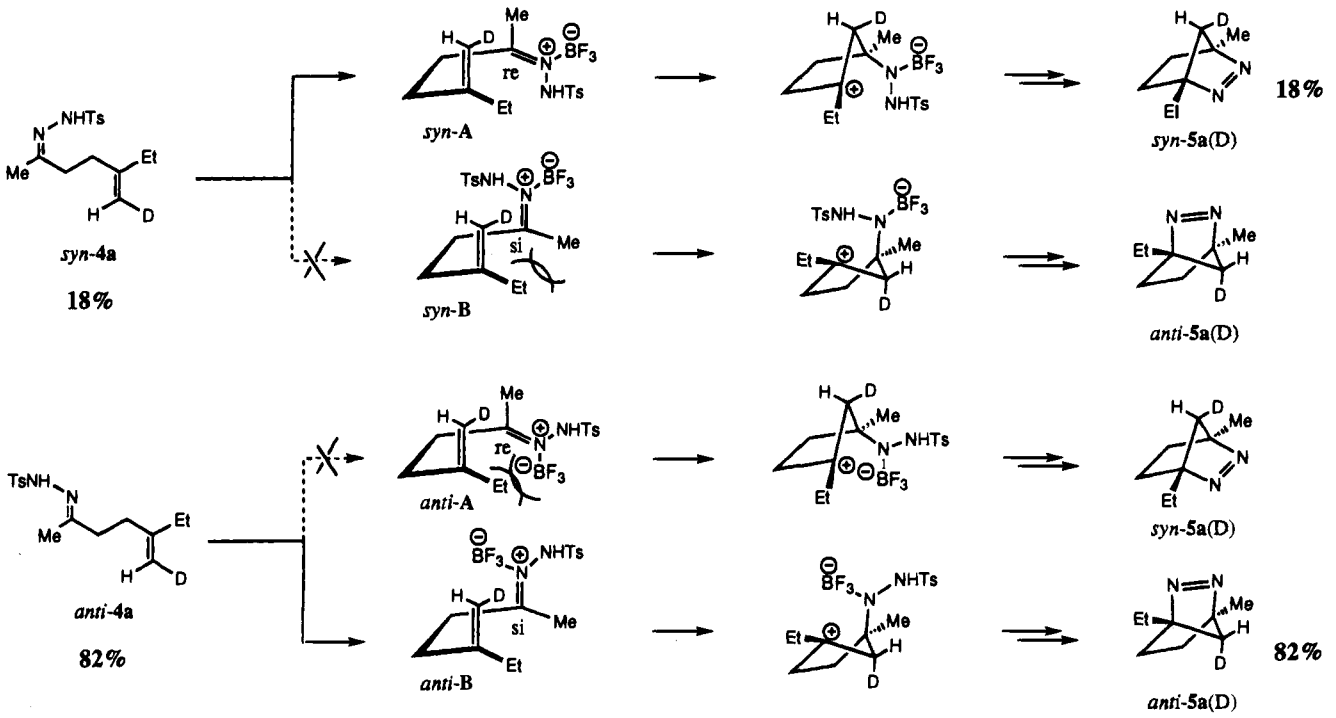
(14) (a) Alexakis, A.; Commercon, A.; Villieras, J.; Normant, J. F. *Tetrahedron Lett.* **1976**, *27*, 2313–2316. (b) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888–3901. (c) Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 98–102.

(15) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63–65.

Scheme 2



Scheme 3



In the deuterium-labeled azoalkanes **5a–c** the high-field proton (δ 0.35–0.42) was assigned to 7-H_a and the low-field proton (δ 0.60–0.68) to 7-H_s. This stereochemical assignment was confirmed for azoalkane **5a** on the basis of the characteristic W coupling (J = 2.45 and 2.30 Hz) only for 7-H_s at δ 0.62. Finally, NOE experiments on the azoalkane **5a** corroborated the proposed stereochemistry. Thus, the cyclization of tosylhydrazones **4** to azoalkanes **5** is strictly stereoselective; for example, in the case of **4a**(D), the *E*-isomer with *anti* hydrazone configuration affords the *anti*-**5a**(D) azoalkane, while the (*E*)-*syn*-**4a**(D) diastereomer gives *syn*-**5a**(D) (Table 2; entry 1). The reverse applies to (*Z*)-*anti*- and (*Z*)-*syn*-**4a**(D) isomers, which lead to the respective *syn*- and *anti*-**5a**(D) azoalkanes (Table 2; entry 2).

Mechanistic Considerations

Wilson and co-workers[7a,b] proposed carbocation addition of the tosylhydrazone–BF_3 complex to the olefin, followed by proton loss during the cyclization. The elimination of the tosyl borate ion in the final step is a well-documented process.[16] Due to the fact that azoalkane formation is inhibited when the olefin moiety does not bear a methyl group (the latter stabilizes the developing positive charge), a stepwise addition mechanism was recognized (Scheme 2). This cyclization mechanism predicts that only one azoalkane diastereomer is expected from a particular tosylhydrazone. Nevertheless, in all cases mixtures of diastereomeric azoalkanes were obtained from stereolabeled tosylhydrazones **4** (Table 2). Moreover, the outlined cyclization in the simplified mechanism, cf. Scheme 2, applies only to the *syn*-configurated tosylhydrazones and *not* to the thermodynamically favored *anti* diastereomers! Therefore, the mechanism in Scheme 2 must be expanded to account for our stereochemical results. A more elaborate mechanism is displayed in Scheme 3, in which both the *syn* and *anti* diastereomers of the hydrazone functionality are explicitly considered.

Contrary to the unsubstituted case, for the stereolabeled tosylhydrazones it matters whether the nucleophilic attack of the stereolabeled olefin moiety on the iminium bond takes place from above (*re* attack) or below (*si* attack) the C=N plane. The stereochemical label, as illustrated for the deuterium-labeled pair *syn,anti*-**4a** (Scheme 3), allows differentiation of the resulting cyclopentyl cations in that the stereolabel and the tosylhydrazone moiety are either on different sides or on the same side of the cyclopentene ring. However, the ultimate stereochemical outcome is further complicated by the conformational flexibility of the employed acyclic tosylhydrazones. With rotation about the C-2/C-3 bond while the olefinic functionality is kept stationary,[17] the orthogonal and the parallel arrangements *syn*-**A** and *syn*-**B** are possible for the *syn*-**4a** isomer and correspondingly the *anti*-**A** and *anti*-**B** for the *anti*-**4a** isomer. These represent respectively *re* and *si* attack, and after cyclization, proton loss, and elimination of tosyl borate ion, the azoalkane diastereomers *syn*- and *anti*-**5a**(D) stereolabeled at C-7 are obtained.

Thus, by starting from an 18:82 *syn/anti* mixture of the deuterium *E*-labeled tosylhydrazone (*E*)-**4a**(D), cyclization

(16) (a) Cacchi, S.; Caglioti, L.; Paolucci, G. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2323–2324. (b) Caglioti, L. *Tetrahedron* **1966**, *22*, 487–493. (c) Hutchins, R. O.; Natale, N. R. *J. Org. Chem.* **1978**, *43*, 2299–2301.

(17) Alternatively, one can rotate the olefin moiety around the C-4/C-5 bond while holding the tosylhydrazone group stationary; however, this operation would generate the enantiomer of the parallel conformer.

occurs for the *syn* tosylhydrazone (18%) from the orthogonally arranged conformer *syn*-**A** to afford the *syn*-**5a**(D) azoalkane in 18% yield. The *anti* tosylhydrazone (82%) reacts from the parallelly arranged conformer *anti*-**B** to lead thereby to the azoalkane *anti*-**5a**(D) in 82% yield (Table 2; entry 1). The fact that the deuterium *Z*-labeled tosylhydrazone (*Z*)-**4a**(D) gave the reverse diastereomeric ratio of these azoalkanes, i.e., *anti*/*syn*-**5a**(D) = 18:82 (Table 2; entry 2), corroborates the stereochemical analysis above. Therefore, irrespective of the deuterium-labeled olefin stereochemistry, the diastereoselectivity in this cyclization is dictated by the tosylhydrazone geometry since for the *syn* tosylhydrazone product formation occurs from the orthogonal conformer *syn*-**A**, whereas for the *anti* tosylhydrazone it occurs from the parallel conformer *anti*-**B**. Indeed, this happenstance holds for all deuterium-labeled tosylhydrazones, namely, (*Z*)-**4b**(D) and (*Z*)-**4c**(D), cf. entries 3 and 4 in Table 2, although for the latter the diastereomeric excess (*anti*/*syn* = 57:43) in the initial tosylhydrazone is very low.

It is difficult to assess the steric effects of the substituents in the highly ordered conformers. Clearly, complex and subtle steric features dictate whether the orthogonal or the parallel conformation **A** or **B** (Scheme 3) is preferred in the crucial stereoselective cyclization step. An attempt to provide mechanistic insight through semiempirical computations[18] failed because the structures appear to be too complex. Thus, in view of the computational problems,[19] we cannot quantify the steric repulsion between an alkyl (ethyl, *tert*-butyl) and an *N*-tosyl group (*syn*-**A**) as between an alkyl (ethyl, *tert*-butyl) and a methyl group (*syn*-**B**); in the former the tosyl group can evade steric hindrance by appropriate rotations and thereby reduce its steric demand. The same holds true for the steric repulsion between an alkyl (ethyl, *tert*-butyl) group and the complexed N−BF_3 moiety (*anti*-**A**) compared to that between an alkyl (ethyl, *tert*-butyl) and a methyl group (*anti*-**B**). It is our qualitative guess that the steric demand of the complexed N−BF_3 moiety appears to be larger than that of the methyl group, but due to the complexity of the molecules, calculations more elaborate than AM1 will be required to provide an answer.

In conclusion, 1,4-dialkylated 2,3-diazabicyclo[2.2.1]hept-2-enes with stereolabels at the C-7 position were prepared for the first time via the highly diastereoselective intramolecular cyclization of stereolabeled γ,δ-unsaturated tosylhydrazones under acidic conditions. The diastereoselectivity of the cyclization process derives from the *syn*/*anti* stereochemistry of the tosylhydrazone functionality, whereby a delicate balance of the transition state energies of the orthogonal and parallel conformers for the *syn* and *anti* diastereomers of the tosylhydrazones dictates the stereochemical outcome in the final stereolabeled azoalkane.

Experimental Section

Instrumentation and General Aspects. Solvents were purified according to standard procedures. TLC was performed on Polygram SIL G UV (40 × 80 mm), Macherey & Nagel. Silica gel was used for column (63−230 μm) and flash (32−64 μm) chromatography, both from Woelm. IR spectra were recorded on a Perkin-Elmer Model 1420 instrument. ^{1}H (^{13}C) NMR spectra were obtained at 250 (62.9) MHz on a Bruker AC 250 or at 200 (50.3) MHz on a Bruker AC 200 instrument with $CDCl_3$ [δ 7.24 (77.0)] or C_6D_6 [δ 7.16 (128)] as internal standards. UV spectra were recorded on a Hitachi U 3200 spectrophotometer. Gas chromatographic analyses were conducted on a Vega 6000 Series capillary GC instrument from Carlo Erba, equipped with a flame ionization detector (FID) and a Shimadzu C-R 6A electronic integrator. A wide-bore capillary column (30-m RTX 1) with an internal diameter of 0.53 mm and a film thickness of 1.5 μm was used. Combustion analyses were performed by the Microanalytical Division of the Institute for Inorganic Chemistry, University of Würzburg. Due to the similarity of the spectral properties of the deuterium-labeled isomers and the unsubstituted ones, only one combustion analysis was made for the whole series. Cu^{I}Br (Fluka) and LiBr (Riedel-de-Haen) were dried at 130 °C and 0.01 Torr for 6 h and stored under an argon gas atmosphere. 2,4-Pentanedione and propargyl chloride were obtained from commercial sources and used as received. 3,5-Heptanedione,[9] 5-hexyn-2-one,[10] and 6-heptyn-3-one[20] were prepared according to the known procedures.

4-(2-Methyl-1,3-dioxolan-2-yl)but-1-yne (1a)[11] was prepared from 5-hexyn-2-one (15.1 g, 158 mmol) and ethylene glycol (9.79 g, 158 mmol) by following the known procedure to yield 19.8 g (90%) as a colorless liquid after distillation: bp 64−68 °C at 14 Torr; IR (neat) 3320, 3020, 2990, 2960, 2910, 2620, 2140, 1460, 1395, 1160; ^{1}H NMR ($CDCl_3$) δ 1.25 (s, 3H, 1-H), 1.85 (pseudo (ps) t, J = 7.4 Hz, 2H, 3-H), 1.88 (t, J = 2.6 Hz, 1H, 6-H), 2.20 (ps td, J = 7.4, 2.6 Hz, 2H, 4-H), 3.81−3.93 (m, 4H, 7,7′-H); ^{13}C NMR ($CDCl_3$) δ 13.2 (t, C-4), 23.8 (q, C-1), 37.9 (t, C-3), 64.7 (t, C-7,7′), 67.9 (d, C-6), 84.3 (d, J_{CCH} = 40 Hz, C-5), 109.0 (s, C-2).

4-(2-Ethyl-1,3-dioxolan-2-yl)but-1-yne (1b) was obtained on distillation as a colorless liquid (38.6 g, 90%) from 6-heptyn-3-one (30.8 g, 280 mmol) and ethylene glycol (17.4 g, 280 mmol), analogous to the procedure for **1a**: bp 74−78 °C at 14 Torr: IR (neat) 3320, 3000, 2960, 2900, 2120, 1470, 1450, 1370, 1220, 1160; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, J = 7.5 Hz, 3H, 1-H), 1.58 (q, J = 7.5 Hz, 2H, 2-H), 1.85 (ps t, J = 7.45 Hz, 2H, 4-H), 1.89 (t, J = 2.7 Hz, 1H, 7-H), 2.21 (ps td, J = 7.45, 2.7 Hz, 2H, 5-H), 3.90 (br s, 4H, 8,8′-H); ^{13}C NMR ($CDCl_3$) δ 7.96 (q, C-1), 13.0 (t, C-5), 29.9 (t, C-2), 35.5 (t, C-4), 65.0 (t, C-8,8′), 67.8 (d, C-7), 84.4 (d, J_{CCH} = 40 Hz, C-6), 110.9 (s, C-3). Anal. Calcd for $C_9H_{14}O_2$ (154.2): C, 70.10; H, 9.15. Found: C, 70.07; H, 9.46.

1-Deuterio-4-(2-methyl-1,3-dioxolan-2-yl)but-1-yne [1a(D)]. To a refluxed solution of ethylmagnesium bromide (12.0 g, 90.0 mmol) in 50 mL of dry THF was added over a 15-min period alkyne **1a** (11.9 g, 84.9 mmol) in 20 mL of dry THF. The reaction mixture was refluxed for 4 h and treated with D_2O (1.80 g, 90.0 mmol) at 0 °C. After drying over $MgSO_4$ and removing the solvent at 25 °C and 20 Torr, the liquid residue was distilled in vacuo to yield 9.97 g (83%) of a colorless liquid: bp 64−66 °C at 14 Torr; IR (neat) 3000, 2970, 2950, 2895, 2600, 1480, 1450, 1380, 1150, 950; ^{1}H NMR ($CDCl_3$) δ 1.26 (s, 3H, 1-H), 1.85 (m_c, 2H, 3-H), 2.21 (m_c, 2H, 4-H), 3.82−3.94 (m, 4H, 7,7′-H); ^{13}C NMR ($CDCl_3$) δ 13.5 (t, C-4), 24.2 (q, C-1), 38.3 (t, C-3), 65.1 (t, C-7,7′), 68.0 (t, J_{CD} = 26 Hz, C-6), 84.2 (t, J_{CCD} = 7.6 Hz, C-5), 109.3 (s, C-2).

1-Deuterio-4-(2-ethyl-1,3-dioxolan-2-yl)but-1-yne [1b(D)] was obtained on distillation as a colorless liquid (6.79 g, 68%), in a procedure analogous to the one for **1a**(D): bp 77−79 °C at 14 Torr; IR (neat) 3010, 2980, 2620, 1480, 1460, 1380, 1220, 1160, 1085; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.5 Hz, 3H, 1-H), 1.62 (q, J = 7.5 Hz, 2H, 2−H), 1.88 (ps t, J = 7.45 Hz, 2H, 5-H), 2.25 (ps t, J = 7.45 Hz, 2H, 4-H), 3.93 (br s, 4H, 8,8′-H); ^{13}C NMR ($CDCl_3$) δ 67.8 (t, J_{CD} = 26 Hz, C-7), 83.9 (t, J_{CCD} = 7.6 Hz, C-6).

General Procedure for the Preparation of the Ketals 2. Under an argon gas atmosphere 2.1 equiv of the appropriate Grignard reagent in THF was cooled down to −60 °C and 1.05 equiv of lithium bromide and copper(I) bromide were added carefully. The white-gray suspension was stirred for 1 h at −60 °C, 1.0 equiv of the alkyne **1** was added, and the mixture was allowed to warm up to 0 °C. After 1 h of stirring

(18) The AM1 method was used; cf.: Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.;Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909. The VAMP program was used and run on a Silicon Graphics Iris Indigo workstation: Rauhut, G.; Alex, A.; Chandrasekhar, J.; Steinke, T.; Clark, T. *VAMP 5.0*; Universität Erlangen: Erlangen, FRG, 1993.

(19) AM1 calculations were conducted on the *syn*-**A**, *syn*-**B**, *anti*-**A**, and *anti*-**B** geometries (Scheme 3). The trajectory computations revealed that only the *syn*-**A** and *syn*-**B** structures converged, of which the *syn*-**A** conformation is preferred, as observed experimentally. For the other two, namely, *anti*-**A** and *anti*-**B**, unfortunately, the calculations did not converge, so that we cannot come to definitive theoretical conclusions in regard to the preferred conformational arrangement; nevertheless, the experimental results clearly speak for the *syn*-**A** and *anti*-**B** structures as the preferred geometries.

(20) Bohlmann, F.; Jastrow, H.; Ertingshausen, G.; Kramer, D. *Chem. Ber.* **1964**, *97*, 801−808.

at 0 °C, the dark-green reaction mixture of the cuprate was treated with aqueous NH_4Cl, which contained 10% sodium cyanide, or with D_2O, followed by NH_4Cl. The colorless, aqueous layer was extracted with methyl *tert*-butyl ether (3 × 70 mL), and the combined organic layers were washed with aqueous NH_4Cl (2 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL). After drying over $MgSO_4$ and removing of the solvent at 25 °C and 20 Torr, the liquid residue was distilled in vacuo to obtain the olefins **2**. The residue of the distillation was taken up in methanol (30 mL), whereby crystals appeared, which were collected, washed with cold methanol (10 mL), and dried in vacuo (20 °C at 14 Torr) to afford the dimers $(\mathbf{2})_2$.

3-Methylene-5-(2-methyl-1,3-dioxolan-2-yl)pentane (2a). From alkyne **1a** (6.00 g, 42.8 mmol), ethylmagnesium bromide (12.0 g, 90.0 mmol), lithium bromide (3.91 g, 45.0 mmol), and copper(I) bromide (6.45 g, 45.0 mmol) in 250 mL of dry THF was obtained 6.01 g (83%) of **2a** as a colorless liquid according to the general procedure: bp 82–84 °C at 14 Torr; IR (neat) 3080, 2960, 2940, 2880, 1640, 1620, 1450, 1375, 1250, 1220; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.4 Hz, 3H, 7-H), 1.34 (s, 3H, 1-H), 1.78 (m_c, 2H, 3-H), 2.04 (q, J = 7.4 Hz, 2H, 6-H), 2.12 (m_c, 2H, 4-H), 3.95 (m, 4H, 9,9′-H), 4.71 (t, J = 1.1 Hz, 2H, 8-H); ^{13}C NMR ($CDCl_3$) δ 12.4 (q, C-7), 23.8 (q, C-1), 29.1 (t, C-6), 30.5 (t, C-4), 37.5 (t, C-3), 64.7 (t, C-9,9′), 107.3 (t, C-8), 110.0 (s, C-2), 151.3 (s, C-5).

5,8-Diethyl-2,11-bis(1,3-dioxolan-2-yl)-(*E*,*E*)-dodeca-5,7-diene [$(\mathbf{2a})_2$] was obtained from the above distillation residue as long, colorless needles (600 mg, 8%) after recrystallization, mp (MeOH) 68–69 °C; IR (KBr) 3060, 3000, 2970, 2920, 1625, 1490, 1395, 1275, 1255, 1220; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.56 Hz, 6H, 15,17-H), 1.27 (s, 6H, 1,12-H), 1.66–1.73 (m_c, 4H, 3,10-H), 2.07–2.15 (m, 8H, 4,9,14,16-H), 3.83–3.94 (m, 8H, 13,13′,18,18′-H), 5.92 (s, 2H, 6,7-H); ^{13}C NMR ($CDCl_3$) δ 13.2 (q, C-15,17), 23.5 (t, C-14,16), 23.8 (q, C-1,12), 31.4 (t, C-4,9), 37.9 (t, C-3,10), 64.6 (t, C-13,13′,18,18′), 109.9 (s, C-2,11), 119.5 (d, C-6,7), 142.1 (s, C-5,8). Anal. Calcd for $C_{20}H_{34}O_4$ (338.5): C, 70.97; H, 10.12. Found: C, 70.59; H, 10.46.

(*E*)-3-(Deuteriomethylene)-5-(2-methyl-1,3-dioxolan-2-yl)pentane [(*E*)-2a(D)] was prepared analogous to **2a** by treatment with D_2O instead of H_2O to afford a colorless liquid (6.61 g, 77%): bp 82–84 °C at 14 Torr; IR (neat) 2260 (CD); ^{1}H NMR ($CDCl_3$) δ 4.70 (br s, 1H, 8-H_Z); ^{13}C NMR ($CDCl_3$) δ 107.7 (dt, J_{CD} = 24 Hz, C-8). Recrystallization of the distillation residue from methanol afforded $(\mathbf{2a})_2$ (685 mg, 8%).

(*Z*)-3-(Deuteriomethylene)-5-(2-methyl-1,3-dioxolan-2-yl)pentane [(*Z*)-2a(D)]. From alkyne **1a**(D) (12.0 g, 85.0 mmol), ethylmagnesium bromide (24.0 g, 180 mmol), lithium bromide (7.82 g, 90.0 mmol), and copper(I) bromide (12.9 g, 90.0 mmol) in 300 mL of dry THF was obtained 11.7 g (81%) of (*Z*)-**2a**(D) as a colorless liquid according to the general procedure: bp 82–84 °C at 14 Torr; IR (neat) 2240 (CD); ^{1}H NMR ($CDCl_3$) δ 4.70 (br s, 1H, 8-H_E); ^{13}C NMR ($CDCl_3$) δ 107.0 (dt, J_{CD} = 24 Hz, C-8). Anal. Calcd for $C_{10}H_{17}DO_2$ (171.3): C, 70.13; H, 10.71. Found: C, 69.88; H, 10.63.

6,7-Dideuterio-5,8-diethyl-2,11-bis(1,3-dioxolan-2-yl)-(*E*,*E*)-dodeca-5,7-diene [2a(D)]$_2$. Recrystallization of the above distillation residue from methanol yielded [**2a**(D)]$_2$ as colorless needles (1.16 g, 8%): mp (MeOH) 68–69 °C; IR (KBr) 2230 (CD); ^{1}H NMR ($CDCl_3$) no olefinic resonances; ^{13}C NMR ($CDCl_3$) δ 119.3 (t, J_{CD} = 24 Hz, C-6,7).

(*Z*)-3-(Deuteriomethylene)-2,2-dimethyl-5-(2-methyl-1,3-dioxolan-2-yl)pentane [(*Z*)-2b(D)]. From alkyne **1a** (8.00 g, 57.1 mmol), *tert*-butylmagnesium chloride (14.9 g, 127 mmol), lithium bromide (5.51 g, 63.5 mmol), and copper(I) bromide (9.11 g, 63.5 mmol) in 300 mL of dry THF was obtained on treatment with D_2O 8.08 g (80%) of (*Z*)-**2b**(D), together with the regioisomer **2b′** (18%), as a colorless liquid: bp 95–100 °C at 14 Torr; IR (neat) 3080, 2980, 2920, 2890, 2240, 1620, 1485, 1470, 1385, 1370; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H, 7,7′,7″-H), 1.33 (s, 3H, 1-H), 1.61–1.81 (m_c, 2H, 3-H), 2.00–2.17 (m_c, 2H, 4-H), 3.85–4.00 (m, 4H, 9,9′-H), 4.63 (t, J = 1.4 Hz, 1H, 8-H_E); ^{13}C NMR ($CDCl_3$) δ 23.8 (q, C-1), 25.4 (t, C-4), 29.3 (q, C-7,7′,7″), 36.3 (s, C-6), 38.9 (t, C-3), 64.6 (t, C-9,9′), 105.6 (dt, J_{CD} = 24 Hz, C-8), 110.0 (s, C-2), 157.7 (s, C-5). Anal. Calcd for $C_{12}H_{21}DO_2$ (199.3): C, 72.32; H, 11.00. Found: C, 72.56; H, 11.27.

(*E*)-3-(Deuteriomethylene)-2,2-dimethyl-5-(2-methyl-1,3-dioxolan-2-yl)pentane [(*E*)-2b(D)]. From alkyne **1a**(D) (7.00 g, 49.6 mmol), *tert*-butylmagnesium chloride (12.9 g, 111 mmol), lithium bromide (4.78 g, 55.0 mmol), and copper(I) bromide (7.89 g, 55.0 mmol) in 250 mL of dry THF was obtained 5.57 g (85%) of (*E*)-**2b**(D) according to the general procedure, together with the regioisomer **2b′** (18%), as a colorless liquid: bp 95–100 °C at 14 Torr; IR (neat) 3110, 2990, 2900, 2220, 1625, 1490, 1475, 1385, 1375, 1260; ^{1}H NMR ($CDCl_3$) δ 4.81 (t, J = 0.7 Hz, 1H, 8-H_Z); ^{13}C NMR ($CDCl_3$) δ 105.6 (dt, J_{CD} = 24 Hz, C-8).

(*E*)-3-(Deuteriomethylene)-5-(2-ethyl-1,3-dioxolan-2-yl)pentane [(*E*)-2c(D)]. From alkyne **1b** (7.00 g, 45.4 mmol), ethylmagnesium bromide (13.4 g, 100 mmol), lithium bromide (4.34 g, 50.0 mmol), and copper(I) bromide (7.17 g, 50.0 mmol) in 250 mL of dry THF was obtained 6.36 g (76%) of (*E*)-**2c**(D) according to the general procedure by treatment with D_2O: colorless liquid, bp 90–91 °C at 14 Torr.- IR (neat) 3060, 2990, 2960, 2900, 2270, 1635, 1470, 1385, 1365, 1345; ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.5 Hz, 3H, 1-H), 1.00 (t, J = 7.45 Hz, 3H, 8-H), 1.63 (q, J = 7.5 Hz, 2H, 2-H), 1.68–1.76 (m_c, 2H, 4-H), 1.96–2.10 (m_c, 4H, 5,7-H), 3.93 (br s, 4H, 10,10′-H), 4.67 (t, J = 0.95 Hz, 1H, 9-H_Z); ^{13}C NMR ($CDCl_3$) δ 8.11 (q, C-1), 12.3 (q, C-8), 29.0 (t, C-7), 29.9 (t, C-2), 30.2 (t, C-5), 35.0 (t, C-4), 65.0 (t, C-10,10′), 106.9 (dt, J_{CD} = 24 Hz, C-9), 111.9 (s, C-3), 151.3 (s, C-7). Anal. Calcd for $C_{11}H_{19}DO_2$ (185.3): C, 71.31; H, 10.99. Found: C, 71.51; H, 11.19.

6,9-Diethyl-3,12-bis(1,3-dioxolan-2-yl)-(*E*,*E*)-tetradeca-6,8-diene [(2c)$_2$]. Recrystallization of the above distillation residue gave 470 mg (6%) of $(\mathbf{2c})_2$ as colorless needles: mp (MeOH) 51–52 °C; IR (KBr) 3050, 2980, 2950, 2910, 2880, 1615, 1470, 1460, 1355, 1205; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J = 7.32 Hz, 6H, 1,14-H), 0.99 (t, J = 7.45 Hz, 6H, 16,18-H), 1.64 (q, J = 7.32 Hz, 4H, 2,13-H), 1.69–1.77 (m_c, 4H, 4,11-H), 2.09–2.21 (m_c, 8H, 5,10,15,17-H), 3.94 (br s, 8H, 19,19′,20,20′-H), 5.97 (s, 2H, 7,8-H); ^{13}C NMR ($CDCl_3$) δ 8.10 (q, C-1,14), 13.3 (q, C-16,18), 23.6 (t, C-15,17), 29.9 (t, C-2,13), 31.3 (t, C-5,10), 35.5 (t, C-4,11), 65.0 (t, C-19,19′,20,20′), 111.9 (s, C-3,12), 119.6 (d, C-7,8), 142.3 (s, C-6,9). Anal. Calcd for $C_{22}H_{38}O_4$ (366.5): C, 72.09; H, 10.45. Found: C, 71.94; H, 10.64.

(*Z*)-3-(Deuteriomethylene)-5-(2-ethyl-1,3-dioxolan-2-yl)pentane [(*Z*)-2c(D)] was prepared analogously to (*E*)-**2c**(D) from alkyne **1b**(D) (6.73 g, 43.3 mmol) by treatment with aqueous NH_4Cl to afford 5.00 g (62%) as a colorless liquid: bp 90–91 °C at 14 Torr; IR (neat) 2220 (CD); ^{1}H NMR ($CDCl_3$) δ 4.66 (t, J = 0.75 Hz, 1H, 9-H_E); ^{13}C NMR ($CDCl_3$) δ 106.9 (dt, J_{CD} = 24 Hz, C-9).

7,8-Dideuterio-6,9-diethyl-3,12-bis(1,3-dioxolan-2-yl)-(*E*,*E*)-tetradeca-6,8-diene [2c(D)]$_2$ was obtained by recrystallization of the above distillation residue as colorless needles (83.0 mg, 1%): mp (MeOH) 51–52 °C; IR (KBr) 2980, 2950, 2910, 2880, 2250, 1610, 1470, 1370, 1210, 1150; ^{1}H NMR ($CDCl_3$) no olefinic resonances; ^{13}C NMR ($CDCl_3$) δ 119.5 (t, J_{CD} = 24 Hz, C-7,8).

General Procedure for the Preparation of Ketones 3. The ketals (10.0 mmol) were added to a suspension[15] of silica gel (63–230 μm, 25.0 g) in 20% aqueous sulfuric acid (2.50 g) and CH_2Cl_2 (60 mL) and stirred for 12 h at room temperature (ca. 20 °C). After neutralization with potassium carbonate, the solid material was collected by suction filtration, washed with CH_2Cl_2 (1 × 100 mL), and discarded. From the combined filtrates the solvent was evaporated (25 °C, 20 Torr), and distillation of the residual oil gave pure ketones **3**.

5-Methylene-2-heptanone (3a)[21] was obtained as a colorless liquid (4.35 g, 98%) from **2a** (6.01 g, 35.2 mmol): bp 63–65 °C at 14 Torr; IR (neat) 3080, 2960, 2930, 2900, 2880, 1715, 1645, 1460, 1360, 1160; ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3H, 7-H), 1.98 (q, J = 7.4 Hz, 2H, 6-H), 2.11 (s, 3H, 1-H), 2.25 (ps t, J = 8.05, 7.12 Hz, 2H, 4-H), 2.54 (ps t, J = 8.05,7.12 Hz, 2H, 3-H), 4.66 (br d, J = 13.4 Hz, 2H, 8-H); ^{13}C NMR ($CDCl_3$) δ 12.3 (q, C-7), 29.1 (t, C-6), 29.9 (t, C-4), 29.9 (q, C-1), 42.0 (t, C-3), 107.9 (t, C-8), 150.0 (s, C-5), 208.5 (s, C-2).

(*E*)-5-(Deuteriomethylene)-2-heptanone [(*E*)-3a(D)] was obtained as a colorless liquid (4.52 g, 98%): bp 63–65 °C at 14 Torr; IR (neat) 2260 (CD); ^{1}H NMR ($CDCl_3$) δ 4.61 (br s, 1H, 8-H_Z); ^{13}C NMR ($CDCl_3$) δ 107.6 (dt, J_{CD} = 24 Hz, C-8).

(*Z*)-5-(Deuteriomethylene)-2-heptanone [(*Z*)-3a(D)] was also obtained as a colorless liquid (6.76 g, 96%): bp 63–65 °C at 14 Torr;

(21) Kollmeyer, W. D. *U.S. Patent* US 4439225; *Chem. Abstr.* **1984**, *101*, 7026a.

IR (neat) 2260 (CD); ^{1}H NMR ($CDCl_3$) δ 4.68 (t, J = 0.77 Hz, 1H, 8-H_E); ^{13}C NMR ($CDCl_3$) δ 107.6 (dt, J_{CD} = 24 Hz, C-8).

(*Z*)-5-(Deuteriomethylene)-6,6-dimethyl-2-heptanone [(*Z*)-3b(D)] was obtained as a colorless liquid (6.01 g, 97%): bp 73−75 °C at 14 Torr; IR (neat) 3420, 3060, 2960, 2900, 2860, 2280, 1710, 1610, 1475, 1465; ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9H, 7,7′,7″-H), 2.14 (s, 3H, 1-H), 2.20−2.37 (m_c, 2H, 4-H), 2.50−2.65 (m_c, 2H, 3-H), 4.56 (t, J = 1.5 Hz, 1H, 8-H_E); ^{13}C NMR ($CDCl_3$) δ 24.9 (t, C-4), 29.2 (q, C-7,7′,7″), 29.9 (q, C-1), 36.3 (s, C-6), 43.1 (t, C-3), 105.7 (dt, J_{CD} = 24 Hz, C-8), 156.6 (s, C-5), 208.6 (s, C-2). Anal. Calcd for $C_{10}H_{17}DO$ (155.3): C, 77.36; H, 11.81. Found: C, 76.92; H, 12.05.

(*E*)-5-(Deuteriomethylene)-6,6-dimethyl-2-heptanone [(*E*)-3b(D)] was obtained as a colorless liquid (3.83 g, 98%): bp 73−75 °C at 14 Torr; IR (neat) 3430, 3110, 2990, 2940, 2900, 2230, 1735, 1630, 1440, 1430; ^{1}H NMR ($CDCl_3$) δ 4.82 (dt, J = 0.9 Hz, 1H, 8-H_Z); ^{13}C NMR ($CDCl_3$) δ 105.7 (t, J_{CD} = 24 Hz, C-8).

(*E*)-6-(Deuteriomethylene)-3-octanone [(*E*)-3c(D)] was obtained as a colorless liquid (4.31 g, 91%): bp 69−71 °C at 14 Torr; IR (neat) 3440, 3060, 3000, 2960, 2930, 2270, 1730, 1640, 1475, 1430; ^{1}H NMR ($CDCl_3$) δ 1.00 (t, J = 7.42 Hz, 3H, 8-H), 1.03 (t, J = 7.32 Hz, 3H, 1-H), 2.00 (q, J = 7.42 Hz, 2H, 7-H), 2.22−2.30 (m_c, 2H, 5-H), 2.43 (q, J = 7.32 Hz, 2H, 2-H), 2.49−2.57 (m_c, 2H, 4-H), 4.62 (t, J = 1.02 Hz, 1H, 9-H_Z); ^{13}C NMR ($CDCl_3$) δ 7.74 (q, C-1), 12.2 (q, C-8), 28.9 (t, C-7), 29.9 (t, C-5), 35.9 (t, C-2), 40.6 (t, C-4), 107.4 (dt, J_{CD} = 24 Hz, C-9), 150.1 (s, C-6), 211.0 (s, C-3). Anal. Calcd for $C_9H_{15}DO$ (141.2): C, 76.54; H, 11.24. Found: C, 76.23; H, 10.98.

(*Z*)-6-Deuteriomethylene-3-octanone [(*Z*)-3c(D)] was obtained as a colorless liquid (2.80 g, 75%): bp 69−71 °C at 14 Torr; IR (neat) 3080, 3010, 2980, 2920, 2240, 1735, 1645, 1475, 1430, 1395; ^{1}H NMR ($CDCl_3$) δ 4.68 (br s, 1H, 9-H_E); ^{13}C NMR ($CDCl_3$) δ 107.4 (dt, J_{CD} = 24 Hz, C-9).

General Procedure for the Preparation of Tosylhydrazones 4. The ketones (10.0 mmol) were added to a suspension of 1.05 equiv of tosylhydrazine in 30 mL of petroleum ether (30−50 °C) which contained one drop of glacial acetic acid.[7b] After 24 h of stirring at room temperature (ca. 20 °C), the precipitate was collected by suction filtration, washed with cold petroleum ether (70 mL), dried in vacuo (20 °C, 14 Torr), and recrystallized from methanol at −20 °C. The material was used in the subsequent cyclizations to the azoalkanes without further purification. Analytical samples were obtained by dissolution in CH_2Cl_2 (5 mL), filtration through SiO_2, and subsequent recrystallization from methanol.

5-Methylene-2-heptanone tosylhydrazone (4a), 3.70 g (87%), was obtained as a mixture of *syn* and *anti* isomers (18:82): colorless powder, mp (MeOH) 78−79 °C; IR (KBr) 3240, 3080, 3060, 3040, 2980, 2880, 2590, 1625, 1600, 1495; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.4 Hz, 3H, 7-H), 1.74 (s, 3H, 1-H), 1.86−1.95 (m_c, 2H, 6-H), 2.10−2.16 (m_c, 2H, 4-H), 2.28−2.35 (m_c, 2H, 3-H), 2.40 (s, 3H, 13-H), 4.57 [br d, J = 8.14 Hz, 1.64H (*anti*), 8-H], 4.65 [br d, J = 21.4 Hz, 0.36H (*syn*), 8-H], 7.28 (d, J = 8.16 Hz, 2H, 11,11′-H), 7.53 (br s, 1H, NH), 7.82 (d, J = 8.16 Hz, 2H, 10,10′-H); ^{13}C NMR ($CDCl_3$) δ 12.1 (q, C-7), 15.5 (q, C-1), 21.5 (q, C-13), 28.5 (t, C-6), 32.2 (t, C-4), 36.9 (t, C-3), 108.0 (t, C-8), 128.0 (d, C-11,11′), 129.3 (d, C-10,10′), 135.4 (s, C-12), 143.8 (s, C-9), 149.9 (s, C-5), 157.8 (s, C-2).

(*E*)-5-(Deuteriomethylene)-2-heptanone tosylhydrazone [(*E*)-4a-(D)], 9.50 g (91%), was obtained as a mixture of *syn* and *anti* isomers (18:82): colorless powder, mp (MeOH) 78−79 °C; IR (KBr) 2260 (CD); ^{1}H NMR ($CDCl_3$) δ 4.54 [br s, 0.82H (*anti*), 8-H_Z], 4.59 [br s, 0.18H (*syn*), 8-H_Z], 7.67 (br s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 107.8 (dt, J_{CD} = 24 Hz, C-8). Anal. Calcd for $C_{15}H_{21}DN_2O_2S$ (295.4): C, 60.98; H, 7.57; N, 9.48. Found: C, 60.52; H, 7.58; N, 9.56.

(*Z*)-5-(Deuteriomethylene)-2-heptanone tosylhydrazone [(*Z*)-4a-(D)], 4.96 g (86%), was obtained as a mixture of *syn* and *anti* isomers (18:82): colorless powder, mp (MeOH) 78−79 °C; IR (KBr) 2260 (CD); ^{1}H NMR ($CDCl_3$) δ 4.58 [br s, 0.82H (*anti*), 8-H_E], 4.68 [br s, 0.18H (*syn*), 8-H_E]; ^{13}C NMR ($CDCl_3$) δ 107.8 (dt, J_{CD} = 24 Hz, C-8). Anal. Calcd for $C_{15}H_{21}DN_2O_2S$ (295.4): C, 60.98; H, 7.57; N, 9.48. Found: C, 60.64; H, 7.37; N, 9.46.

(*Z*)-5-(Deuteriomethylene)-6,6-dimethyl-2-heptanone tosylhydrazone [(*Z*)-4b(D)], 5.64 g (97%), was obtained as a mixture of *syn* and *anti* isomers (16:84): colorless powder, mp (MeOH) 87−88 °C; IR (KBr) 3240, 3080, 3040, 2980, 2920, 2880, 2280, 1645, 1620, 1605; ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 9H, 7,7′,7″-H), 1.76 (s, 3H, 1-H), 2.10−2.16 (m_c, 2H, 4-H), 2.20−2.36 (m_c, 2H, 3-H), 2.40 (s, 3H, 13-H), 4.52 [br s, 0.84H (*anti*), 8-H_E], 4.56 [br s, 0.16H (*syn*), 8-H_E], 7.28 (d, J = 8.16 Hz, 2H, 11,11′-H), 7.60 (br s, 1H, NH), 7.84 (d, J = 8.16 Hz, 2H, 10,10′-H); ^{13}C NMR ($CDCl_3$) δ 15.8 (q, C-1), 21.6 (q, C-13), 27.1 (t, C-4), 29.2 (q, C-7,7′,7″), 36.4 (s, C-6), 38.1 (t, C-3), 105.4 (dt, J_{CD} = 24 Hz, C-8), 128.2 (d, C-11,11′), 129.5 (d, C-10,10′), 135.4 (s, C-12), 143.9 (s, C-9), 156.4 (s, C-5), 158.2 (s, C-2). Anal. Calcd for $C_{17}H_{25}DN_2O_2S$ (323.5): C, 63.12; H, 8.16; N, 8.66. Found: C, 63.54; H, 8.30; N, 8.59.

(*E*)-5-(Deuteriomethylene)-6,6-dimethyl-2-heptanone tosylhydrazone [(*E*)-4b(D)], 7.17 g (92%), was obtained as a mixture of *syn* and *anti* isomers (16:84): colorless powder, mp (MeOH) 87−88 °C; IR (KBr) 3240, 3100, 3050, 2980, 2920, 2880, 2240, 1645, 1620, 1605; ^{1}H NMR ($CDCl_3$) δ 4.75 [br s, 0.84H (*anti*), 8-H_Z], 4.83 [br s, 0.16H (*syn*), 8-H_Z]; ^{13}C NMR ($CDCl_3$) δ 105.4 (dt, J_{CD} = 24 Hz, C-8).

(*E*)-6-(Deuteriomethylene)-3-octanone tosylhydrazone [(*E*)-4c-(D)], 9.20 g (99%), was obtained as a mixture of *syn* and *anti* isomers (50:50): colorless, waxy solid, mp (MeOH) 36−37 °C; IR (neat) 3260, 3080, 3050, 3000, 2970, 2910, 2280, 1645, 1620, 1350; ^{1}H NMR ($CDCl_3$) δ 0.90−1.03 (m_c, 6H, 1,8-H), 1.92 (qd, J = 7.4, 1.33 Hz, 2H, 7-H), 2.05−2.37 (m, 6H, 2,4,5-H), 2.40 (s, 3H, 14-H), 4.54 [br s, 0.5H (*anti*), 9-H_Z], 4.58 [br s, 0.5H (*syn*), 9-H_Z], 7.27 (d, J = 8.16 Hz, 2H, 12,12′-H), 7.60 (br s, 1H, NH), 7.83 (d, J = 8.16 Hz, 2H, 11,11′-H); ^{13}C NMR ($CDCl_3$) for *anti* isomer, δ 9.38 (q, *anti*, C-1), 12.1 (q, *anti*, C-8), 21.4 (q, *anti*, C-14), 22.6 (t, *anti*, C-2), 29.6 (t, *anti*, C-7), 32.0 (t, *anti*, C-5), 34.3 (t, *anti*, C-4); for *syn* isomer, 10.2 (q, *syn*, C-1), 12.0 (q, *syn*, C-8), 21.4 (q, *syn*, C-14), 28.0 (t, *syn*, C-2), 28.5, 28.6 (t, *syn*, C-5,7), 30.8 (t, *syn*, C-4); for *anti* and *syn* isomers, 107.4, 107.9 (dt, *anti*, *syn*, J_{CD} = 24 Hz, C-9), 127.9, 128.0 (d, *anti*, *syn*, C-12,12′), 129.2, 129.3 (d, *anti*, *syn*, C-11,11′), 135.0, 135.1 (s, *anti*, *syn*, C-13), 143.6, 143.7 (s, *anti*, *syn*, C-10), 149.3, 150.1 (s, *anti*, *syn*, C-6), 162.2, 162.4 (s, *anti*, *syn*, C-3).

(*Z*)-6-(Deuteriomethylene)-3-octanone tosylhydrazone [(*Z*)-4c(D)], 6.05 g (99%), was obtained as a mixture of *syn* and *anti* isomers (43:57) by refluxing for 12 h in petroleum ether (30−50 °C): colorless, waxy solid, mp (MeOH) 36−37 °C; IR (neat) 3260, 3100, 3070, 3010, 2970, 2910, 2260, 1645, 1620, 1350; ^{1}H NMR ($CDCl_3$) δ 4.59 [br s, 0.57H (*anti*), 9-H_E], 4.65 [br s, 0.43H (*syn*), 9-H_E]; ^{13}C NMR ($CDCl_3$) δ 107.4, 107.9 (dt, J_{CD} = 24 Hz, C-9). Anal. Calcd for $C_{16}H_{23}DN_2O_2S$ (309.5): C, 62.10; H, 7.74; N, 9.05. Found: C, 62.48; H, 8.03; N, 8.80.

General Procedure for the Preparation of Azoalkanes 5. Under reflux, to a solution of 1.30 equiv of BF_3·OEt_2 in a given solvent (30 mL) was added over a 4-h period the particular tosylhydrazone (10.0 mmol) dissolved in the same solvent (250 mL). The reaction mixture was maintained at reflux for 2 h, and 1 M aqueous K_2CO_3 (100 mL) was added. The organic layer was separated, washed with brine (3 × 50 mL), dried over $MgSO_4$, and concentrated by removal of the solvent by distillation.[7b] The brownish-red residue was prepurified by column chromatography on silica gel with petroleum ether (30−50 °C)/methylene chloride/methyl acetate (10:10:1) as eluent, and analytical samples were obtained by Kugelrohr distillation. All azoalkanes purified according to this procedure had a purity >99% (KGC analysis).

1-Ethyl-4-methyl-2,3-diazabicyclo[2.2.1]hept-2-ene (5a). From tosylhydrazone **4a** (5.00 g, 16.9 mmol) and BF_3·OEt_2 (3.12 g, 22.0 mmol) in 470 mL absolute cyclohexane was obtained **5a** as a colorless liquid (172 mg, 7%) according to the general procedure: bp 100 °C at 14 Torr; R_f = 0.32 (10:10:1 petroleum ether/methylene chloride/methyl acetate); IR (CCl_4) 2960, 2940, 2870, 1500, 1455, 1380, 1305, 1280, 1240, 1200; UV (*n*-pentane) λ_{max} (log ϵ) 348 nm (2.373); ^{1}H NMR (C_6D_6) δ 0.41 (d, J = 9.96 Hz, 1H, 7-H_a), 0.62 (d ps t, J = 9.96, 2.45, 2.30 Hz, 1H, 7-H_s), 0.74−0.83 (m, 2H, 5,6-H_n), 0.94−1.08 (m, 2H, 5,6-H_x), 1.01 (t, J = 7.52 Hz, 3H, 9-H), 1.61 (s, 3H, 10-H), 1.80−2.24 (m_c, 2H, 8-H); ^{13}C NMR (C_6D_6) δ 10.1 (q, C-9), 17.2 (q, C-10), 24.5 (t, C-8), 27.0 (t, C-5), 28.9 (t, C-6), 47.5 (t, C-7), 83.8 (s, C-4), 89.0 (s, C-1).

***syn/anti*-7-Deuterio-1-ethyl-4-methyl-2,3-diazabicyclo[2.2.1]hept-2-ene [*syn/anti*-5a(D)].** From tosylhydrazone (*E*)-**4a**(D) (5.00 g, 16.9 mmol) and BF_3·OEt_2 (3.12 g, 22.0 mmol) in 470 mL of absolute benzene was obtained 620 mg (26%) of 18:82 *syn/anti*-**5a**(D) as a colorless liquid: bp 100 °C at 14 Torr; IR (CCl_4) 2240 (CD); UV (*n*-pentane)

λ_{max} (log ϵ) 348 nm (2.382); ^{1}H NMR (C_6D_6) δ 0.40 (t, J = 1.35 Hz, 0.18H, 7-H_a), 0.60 (br s, 0.82H, 7-H_s); ^{13}C NMR (C_6D_6) δ 47.2 (dt, J_{CD} = 21 Hz, C-7); ^{2}H NMR ($CFCl_3$) δ 0.50 (d, J = 1.46 Hz, 0.81D, 7-D_a), 0.63 (d, J = 1.42 Hz, 0.19D, 7-D_s).

From the tosylhydrazone (*Z*)-**4a**(D) (3.00 g, 10.1 mmol) and BF_3·OEt_2 (1.86 g, 13.1 mmol) in 280 mL of absolute benzene was obtained 320 mg (23%) of 82:18 *syn/anti*-**5a**(D) as a colorless liquid: bp 100 °C at 14 Torr; IR (CCl_4) 2220 (CD); UV (*n*-pentane) λ_{max} (log ϵ) 348 nm (2.401); ^{1}H NMR (C_6D_6) δ 0.40 (t, J = 1.35 Hz, 0.82H, 7-H_a), 0.60 (br s, 0.18H, 7-H_s); ^{13}C NMR (C_6D_6) δ 47.2 (dt, J_{CD} = 21 Hz, C-7); ^{2}H NMR ($CFCl_3$) δ 0.52 (d, J = 1.46 Hz, 0.18D, 7-D_a), 0.64 (d, J = 1.42 Hz, 0.82D, 7-D_s). Anal. Calcd for $C_8H_{13}DN_2$ (139.2): C, 69.02; H, 10.27; N, 20.12. Found: C, 69.04; H, 10.15; N, 19.78.

***syn/anti*-7-Deuterio-1-(1,1′-dimethylethyl)-4-methyl-2,3-diazabicyclo[2.2.1]hept-2-ene [*syn/anti*-5b(D)].** From tosylhydrazone (*Z*)-**4b**(D) (3.00 g, 9.27 mmol) and BF_3·OEt_2 (1.72 g, 12.1 mmol) in 260 mL of absolute 1,1,1-trichloroethane was obtained 475 mg (37%) of 16:84 *syn/anti*-**5b**(D) in long colorless needles: mp 42−42.5 °C; R_f = 0.43 (10:10:1 petroleum ether/methylene chloride/methyl acetate); IR (CCl_4) 2970, 2930, 2910, 2870, 2200, 1470, 1460, 1380, 1320, 1260; ^{1}H NMR (C_6D_6) δ 0.42 (br s, 0.16H, 7-H_a), 0.62 (br s, 0.84H, 7-H_s), 0.71−0.93 (m, 2H, 5,6-H_n), 0.97−1.20 (m, 2H, 5,6-H_x), 1.10 (s, 9H, 9,9′,9″-H), 1.63 (s, 3H, 10-H); ^{13}C NMR (C_6D_6) δ 17.1 (q, C-9), 23.2 (t, C-5), 26.7 (q, C-9,9′,9″), 29.3 (t, C-6), 31.5 (s, C-8), 44.7 (dt, J_{CD} = 21 Hz, C-7), 83.8 (s, C-4), 95.7 (s, C-1). Anal. Calcd. for $C_{10}H_{17}DN_2$ (167.3): C, 71.81; H, 10.96; N, 16.70: Found: C, 71.80; H, 10.88; N, 16.59.

***syn/anti*-7-Deuterio-1,4-diethyl-2,3-diazabicyclo[2.2.1]hept-2-ene [*syn/anti*-5c(D)].** From tosylhydrazone (*Z*)-**4c**(D) (4.50 g, 14.5 mmol) and BF_3·OEt_2 (2.68 g, 18.9 mmol) in 380 mL of absolute 1,1,1-trichloroethane was obtained 580 mg (26%) of 57:43 *syn/anti*-**5c**(D) as a colorless oil: bp 130 °C and 14 Torr; R_f = 0.29 (10:10:1 petroleum ether/methylene chloride/methyl acetate); IR (CCl_4) 2970, 2940, 2900, 2880, 2220, 1470, 1460, 1370, 1320, 1260; UV (CCl_4) λ_{max} (log ϵ) 349 nm (2.350); ^{1}H NMR (C_6D_6) δ 0.35 (ps t, J = 1.40 Hz, 0.57H, 7-H_a), 0.68 (br s, 0.43H, 7-H_s), 0.73−0.82 (m, 2H, 5,6-H_n), 0.98−1.07 (m, 2H, 5,6-H_x), 1.03 (t, J = 7.52 Hz, 6H, 9,9′-H), 1.84−2.27 (m_c, 4H, 8,8′-H); ^{13}C NMR (C_6D_6) δ 10.1 (q, C-9,9′), 24.6 (t, C-8,8′), 26.6 (t, C-5,6), 44.5 (dt, J_{CD} = 21 Hz, C-7), 88.5 (s, C-1,4). Anal. Calcd for $C_9H_{15}DN_2$ (153.3): C, 70.54; H, 10.65; N, 18.28. Found: C, 70.43; H, 10.29; N, 17.96.

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