Tandem Inter [4 + 2]/Intra [3 + 2] Cycloadditions of Nitroalkenes. Application to the Synthesis of Aminocarbasugars

by **Scott E. Denmark*** and **Martin Juhl**

Department of Chemistry, Roger Adams Laboratory, University of Illinois, 600 S. Mathews Avenue, Urbana, Illinois 61801, U.S.A. (e-mail: denmark@scs.uiuc.edu)

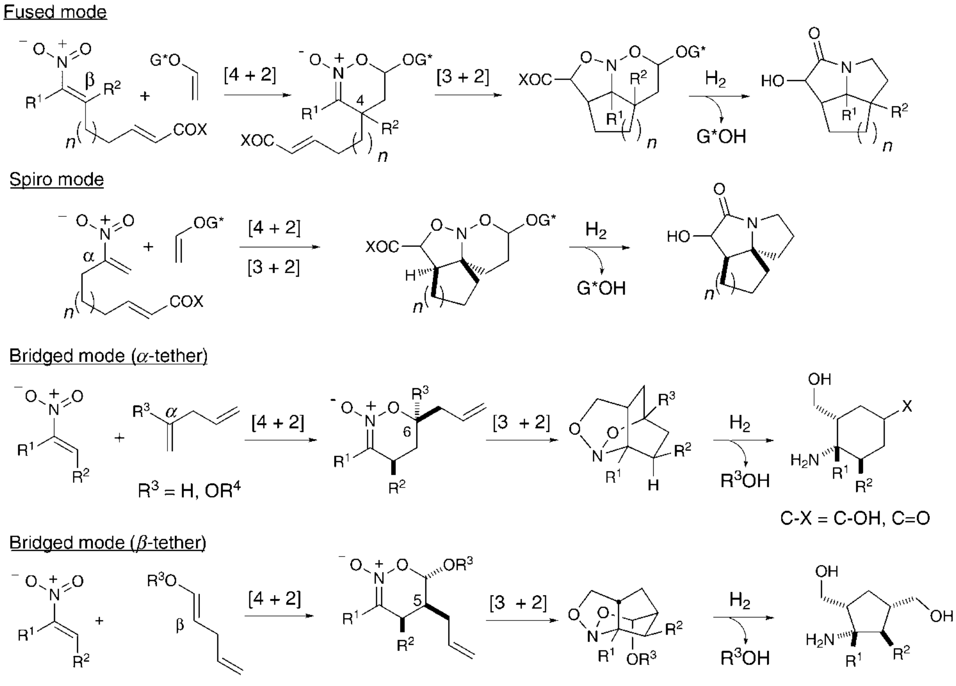
Dedicated to Professor *Dieter Seebach* on the happy occasion of his 65th birthday

The tandem inter [4 + 2]/intra [3 + 2] cycloaddition of nitroalkenes in the bridged mode was applied to the stereoselective synthesis of β-D-4-amino-2,4-dideoxycarbagulose, a representative aminocarbasugar. The synthesis required only five steps from known materials and delivered the protected aminocarbasugar (−)-**20** in excellent yield (see *Scheme 9*). The success of the synthetic sequence relies on *1*) the ability to incorporate O-substituents at the nitroalkene moiety, *2*) the identification of a suitably modified chiral dienophile, and in particular *3*) the development of specific experimental conditions and protocols that allow for the formation and isolation of the highly sensitive nitroso acetals. The reduction of the C(1) carbonyl group of (+)-**19** gave unexpected stereoselectivity, which could be rationalized by a conformational inversion of the substrate (see *Scheme 11*).

1. Introduction. – The *Diels–Alder* reaction has proven to be one of the most useful tools to create six-membered carbo- and heterocyclic ring systems with a high degree of regio-, stereo-, and enantiocontrol, by incorporating a wide variety of dienes and dienophiles [1]. Extensive studies from these laboratories beginning in 1986 have demonstrated the utility of nitroalkenes as the heterodiene components in inverse-electron-demand [4 + 2] cycloadditions [2]. Nitroalkenes are effective as 4π-components in *Lewis* acid promoted cycloadditions with cyclic and acyclic alkenes [3] as well as vinyl ethers to form a diversity of nitronates [4]. Although cyclic nitronates are stable intermediates that can be converted to a variety of useful derivatives, such as alcohols, ketones, oximes, and amines [3b], their greatest potential lies in their ability to undergo [3 + 2] cycloadditions [5]. The 1,3-dipolar cycloaddition reaction of nitronates was first reported by *Tartakovskii* and co-workers in 1964 [6] and has subsequently been studied by *Torssell* [7], *Carrie* and co-workers [8], *Seebach* and co-workers [9], and others [10].

The linking of these two pericyclic processes into a tandem sequence has been extremely fruitful. The tandem [4 + 2]/[3 + 2] cycloaddition of nitroalkenes in various combinations of inter- and intramolecular modes has been employed as a general approach for the synthesis of a variety of cyclic, N-containing systems. The class of tandem cycloaddition that has been most thoroughly investigated is the intermolecular [4 + 2]/intramolecular [3 + 2] sequence. In the inter [4 + 2]/intra [3 + 2] sequence, a wide variety of highly substituted nitroso acetals can be formed depending on the point of attachment of the dipolarophile. We have investigated three distinct subclasses (fused, spiro, and bridged) as illustrated in *Scheme 1*. The first subclass, termed the

Scheme 1

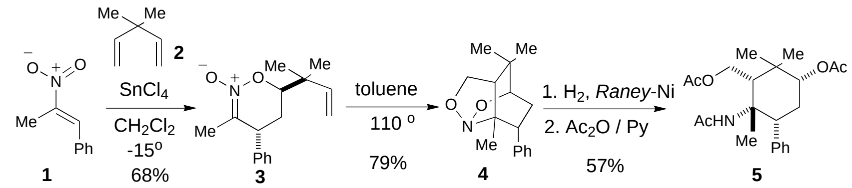


fused mode, involves tethering of an olefin or dipolarophile at the β-position of the nitroalkene. The intermediate nitronate, which results from an intermolecular $[4+2]$ cycloaddition, possesses the pendant olefin at the C(4) position. Subsequent intramolecular $[3+2]$ cycloaddition affords a fused, tricyclic nitroso acetal [11]. In the spiro mode, the dipolarophile is placed at the α-position of the nitroalkene, and tandem cycloaddition now affords a nitroso acetal having a spiro-fused skeleton [12]. The third subclass involves a construction entitled the bridged mode, in which the dipolarophile is attached at either C(5) or C(6) of the nitronate and, thus, must originally be part of the dienophile [13].

The bridged-mode process distinguishes itself from the fused- and spiro-mode processes in that the products are carbocycles: cyclohexanes in the case of the α-tether and cyclopentanes in the case of the β-tether. Although it might, at first glance, seem inappropriate to employ a heterodiene cycloaddition to prepare a carbocycle, the ability to install, in a stereo-defined manner, heteroatomic substituents in densely functionalized rings provides ample justification for developing this sequence.

2. Background. – Preliminary studies on the bridged-mode tandem $[4+2]/[3+2]$ cycloaddition employed [(1*E*)-2-nitroprop-1-enyl]benzene [14] (**1**) and 3,3-dimethylpenta-1,4-diene [15] (**2**) as the 4π- and 2π-components, respectively. As illustrated in *Scheme 2*, the $SnCl_4$-promoted $[4+2]$ cycloaddition provided the nitronate **3** as a single diastereoisomer (68% yield), which then underwent a thermal $[3+2]$ cycloaddition to

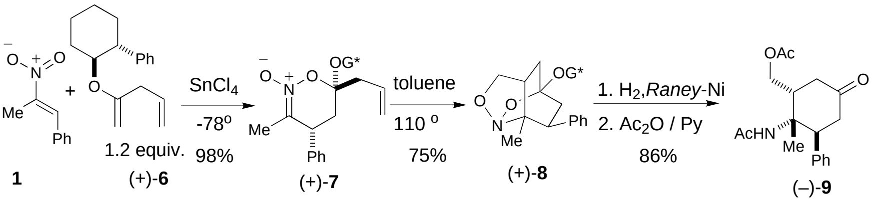
Scheme 2



give nitroso acetal **4** in 79% yield [13a]. Hydrogenation of **4** and peracetylation gave the highly functionalized cyclohexanemethanol triacetate **5**. The entire configuration of **5** was determined by X-ray crystallographic analysis. The crystal structure revealed that the [4 + 2] cycloaddition proceeded with *exo* selectivity (Ph and AcO groups *cis*). The facial selectivity in the thermal [3 + 2] cycloaddition was set by the configuration at the attachment point of the alkene tether, and the *endo* selectivity was due to the short tether length.

The generality of the process was demonstrated with a variety of nitroalkenes, dienophiles, and *Lewis* acids in the [4 + 2] cycloaddition reaction. The most important modification was to incorporate a stereocontrolling element in the reaction, so that the enantiomerically enriched products could be obtained. Attachment of a chiral auxiliary on the dienophile double bond showed very good stereocontrol through facial selectivity in the [4 + 2] cycloaddition. The $SnCl_4$-promoted cycloaddition of nitroalkene **1** with enantiomerically pure vinyl ether (+)-**6** afforded an excellent yield of the nitronate (+)-**7** (*Scheme 3*). The thermal intramolecular [3 + 2] reaction of nitronate (+)-**7** in refluxing anhydrous toluene gave 75% of the nitroso acetal (+)-**8**. Selective hydrogenolysis of the tricyclic nitroso acetal afforded (after subsequent acetylation) the protected cyclohexanone (−)-**9** in 86% yield and 99% ee [13a].

Scheme 3



This sequence clearly demonstrated the potential of the bridged-mode tandem cycloaddition to generate enantiomerically enriched and highly functionalized aminocyclohexanones. However, preliminary studies on the replacement of the phenyl group with a latent hydroxyl functionality (which would allow for the synthesis of 4-amino-2,4-dideoxycarbasugars) met with very limited success. Two problems were noted, *1*) poor diastereoselectivities with nitroalkenes bearing O-substituents at C(2) and *2*) the limited stability of nitronates bearing only a H-atom at C(3). Apparently, very subtle changes in structure have a dramatic effect on the outcome of the reaction.

The goal of the current study was to establish the structural and reaction conditions necessary to permit successful application of the tandem, bridge-mode [4 + 2]/[3 + 2] cycloaddition for the synthesis of aminocarbasugars. Carbasugars have attracted a great deal of interest as synthetic analogs of sugars [16]. While retaining the basic shape of the furanose or pyranose, they lack the anomeric linkage, and, therefore, may serve as effective inhibitors of enzymes that process the natural substrates [17]. Several aminocarbasugars occur in nature, *e.g.*, validamine [18] and valienamine [19] (*Fig. 1*) but most others are synthetic. Interestingly, among them, 4-amino-4-deoxy-5a-carbahexoses are notably rare [20]. Finally, the rare and unusual 2,4-diamino-2,4,6-trideoxygalactose (AAT) was recently found to be a component of a trisaccharide in the capsule of *Gram*-positive bacteria [21]. The 5a-carba analog of AAT (*Fig. 1*) may serve as a specific inhibitor of the cell-wall biosynthesis of these bacteria with obvious implications for the development of selective antibiotics.

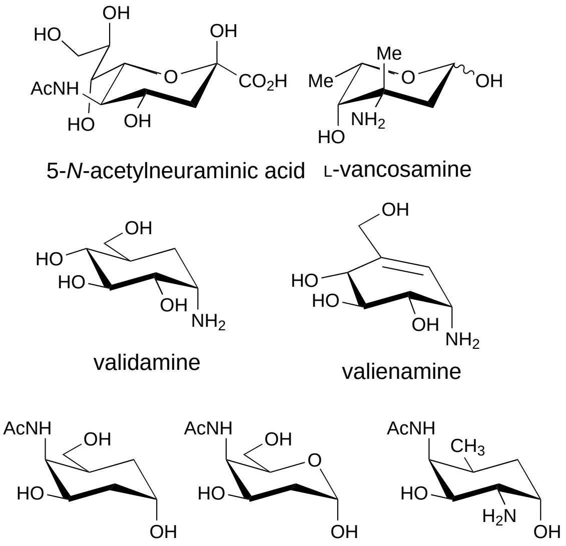
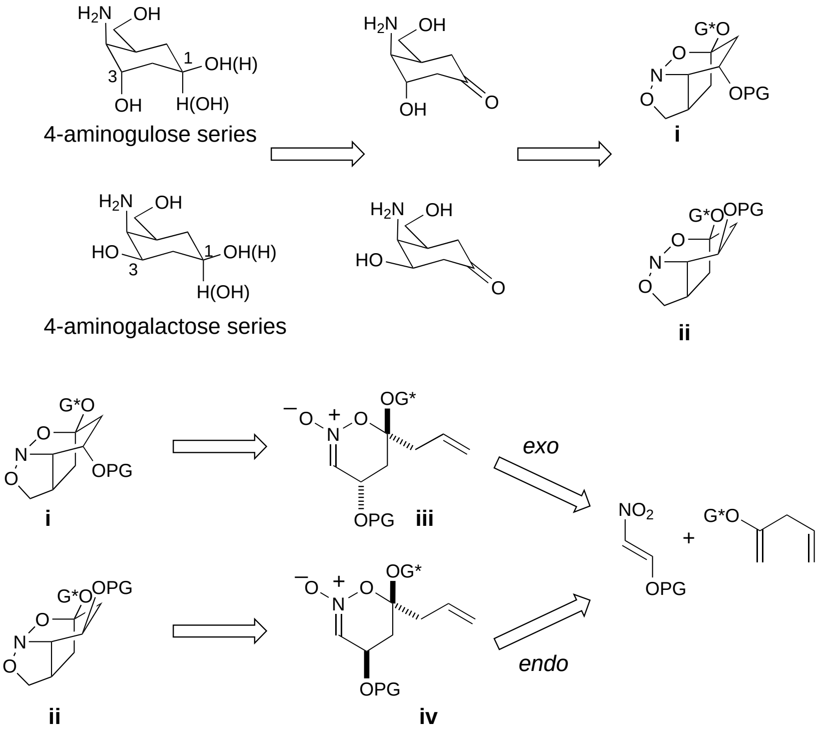


Fig. 1. *4-Aminogalactose/carbagalactose derivatives*

To accomplish this objective, a suitable nitroalkene would have to be identified along with appropriate choice of chiral auxiliary and *Lewis* acid to influence the regio-*exo*/*endo*- and facial stereocontrol [22]. As illustrated in the retrosynthetic analysis in *Scheme 4*, the stereogenic center at C(1) is controlled by selective reduction of the C(1) ketone, whereas the stereogenic center at C(3) arises from the configuration at C(4) of the nitronate, which is established by the facial selectivity of the [4 + 2] cycloaddition (to **iii** or **iv**). Of course, the overall absolute stereocontrol depends on the configuration of the auxiliary (G*) in combination with the choice of *Lewis* acid. We describe herein the successful implementation of this approach to the stereocontrolled synthesis of an aminocarbasugar.

Scheme 4



3. Results. – 3.1. *Preparation of Dienophiles.* To begin the survey of oxygenated nitroalkenes, we chose 1-(benzoyloxy)-2-nitroethene (**10a**) [23], which had served us well in earlier total-synthesis endeavors. We also decided to survey two chiral-auxiliary-modified dienes derived from *trans*-2-phenylcyclohexanol [13a] and *trans*-2-cumylcyclohexanol (=2-(1-methyl-1-phenylethyl)cyclohexanol) [24], which we had employed with good results previously. Both racemic and enantiomerically pure vinyl ether **13a** and enantiomerically pure vinyl ether (+)-**13b** were prepared by allylcupration of the corresponding alkoxyacetylenes **12a** and (+)-**12b** [25] in yields of 96 and 89%, respectively (*Scheme 5*)[1]. The use of allylmagnesium chloride was found to be necessary in the allylcupration; when the bromide was used in the reaction, the yield dropped significantly [26][2].

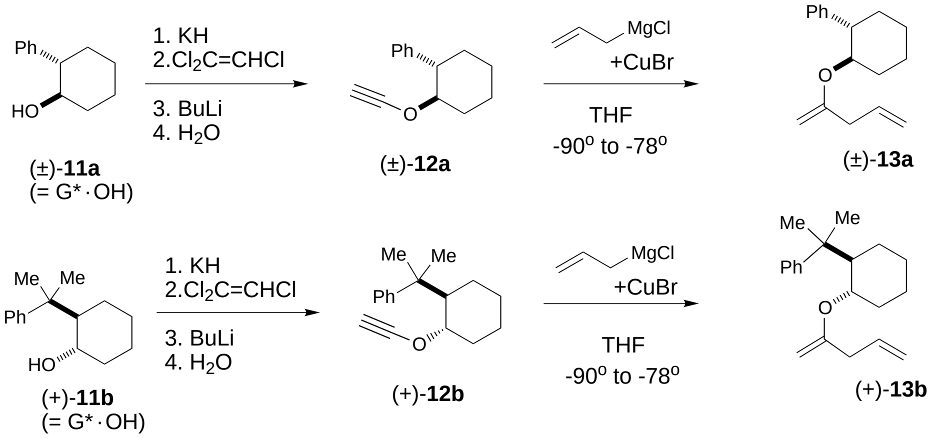
3.2. *[4+2] Cycloaddition.* In initial studies, *Lewis* acids were screened for selectivity in the system involving **10a** and vinyl ethers (±)-**13a** and (+)-**13b** (*Table 1*). Tin tetrachloride ($SnCl_4$) was the only *Lewis* acid that gave rise to product **14** formation. With either titanium dichlorodiisopropoxide or MAD (methylaluminium

---

[1] Enol ethers **13** are moisture sensitive and are prone to undergo isomerization to the corresponding penta-1,3-diene and, thus, should be stored at −25°.

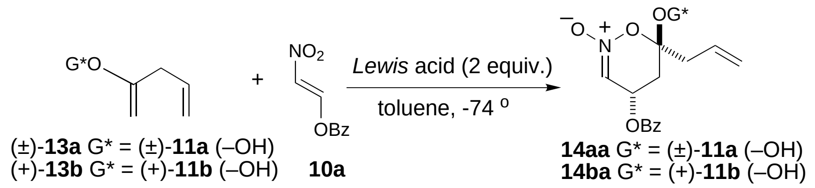
[2] Allylmagnesium bromide was used because of the problems associated with the preparation of allylmagnesium chloride in concentrations >0.3M [26].

Scheme 5



bis[2,6-di(*tert*-butyl)phenolate]), no product could be isolated from the reaction[3][4]). Attempts to thermally induce the [3+2] cycloaddition afforded a crude product in 60% yield, but the nitroso acetal could be isolated only in very low yield due to instability towards purification by silica-gel chromatography, even with Et_3N in the eluent.

Table 1. *Survey of* Lewis *Acids for [4+2] Cycloaddition with* **10a**



Lewis acid[a])	Dienophile[b])	Nitroalkene	Yield [%]	dr[c])
$SnCl_4$	(±)-**13a**	**10a**	78[d])	1.2 : 1
$TiCl_2(O^iPr)_2$	(±)-**13a**	**10a**	0	–
MAD[e])	(±)-**13a**	**10a**	0	–
MAPh[f])	(±)-**13a**	**10a**	0	–
$SnCl_4$	(+)-**13b**	**10a**	44	4.5 : 1

[a]) 2.0 equiv. [b]) 1.5 equiv.. [c]) Determined by ^{1}H-NMR analysis. [d]) Contaminated with **11a**. [e]) MAD = methylaluminium bis[2,6-di(*tert*-butyl)phenolate]. [f]) MAPh = methylaluminium bis[2,6-diphenylphenolate].

Whereas previous investigations revealed the stabilizing influence of substituents at C(3) of the nitronate [13a], this was not available to us in view of the target product structures. Thus, we turned our attention to other nitroalkenes to evaluate the

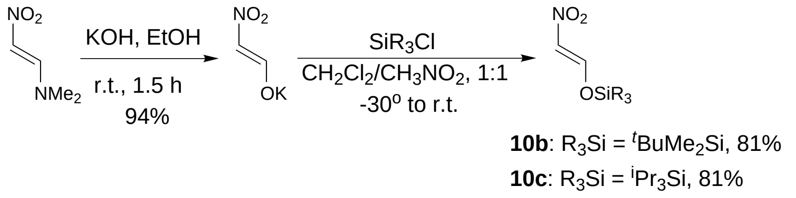
---

[3]) With MAD, the isomerized dienophile was identified by ^{1}H-NMR analysis of the crude product.

[4]) It was crucial to the isolation of the nitronates **14** that the reaction was quenched at −74° with 1M methanolic Et_3N solution and that 1% of Et_3N was present in the eluent for purification by silica-gel chromatography.

compatibility and stabilizing effect of different O-protecting groups. Trialkylsilyl groups have been used with success in earlier studies involving tandem [4 + 2]/[3 + 2] cycloadditions [27]. Nitro(silyloxy)alkenes **10b** and **10c** could be prepared by silylation of the potassium enolate of nitroacetaldehyde, itself available from hydrolysis of *N*,*N*-dimethyl-2-nitroethenamine (*Scheme 6*) [28]. The silylation was carried out with triisopropylsilyl chloride (TIPS-Cl) and (*tert*-butyl)dimethylsilyl chloride (TBS-Cl), with yields of 81% in both cases[5]).

Scheme 6



The results of [4 + 2] cycloaddition of **10b** and **10c** with (±)-**13a** and (+)-**13b** are collected in *Table 2*. As was the case with **10a,** only $SnCl_4$ led to product formation with both **10b** and **10c**. Cycloaddition with **10b** (TBS) proceeded with *exo* selectivity (with respect to OG*) as determined by X-ray crystallographic analysis of both the cyclohexanone (±)-**19** and the nitronate (−)-**14ab** (*vide infra*). The combination of **10b** and (±)-**13a** proved to be the most selective of those tried, giving a diastereoselectivity of 19 : 1. Surprisingly, the seemingly minor change in protective group from **10b** (TBS) to **10c** (TIPS) had a significant impact on the selectivity. Although both nitroalkenes reacted with *exo* preference, the selectivity of the reaction dropped from 19 : 1 to 2 : 1 for **10b** and **10c**, respectively. When the reaction was carried out with (+)-**13b**, the selectivity decreased even further to give a diastereomer ratio of 4.25 : 4.25 : 1[6]).

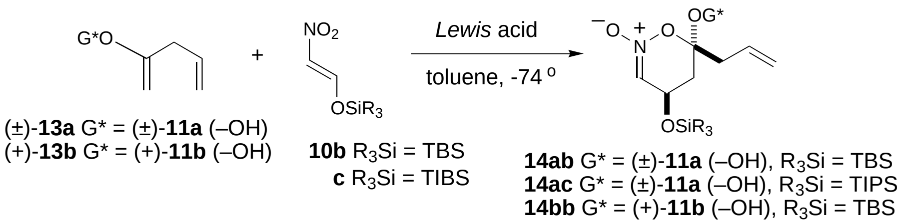
3.3. *[3 + 2] Cycloaddition.* The intramolecular [3 + 2] cycloaddition in the α-bridged mode with a nitronate **14** bearing only a H-atom at the C(3) position and a OG* substituent at the C(6) position is unprecedented. The nitroso acetals **15** were extremely acid sensitive and thus, to avoid decomposition, it was necessary to have an insoluble base present in the reaction mixture [13]. Moreover, purification of the nitroso acetals could not be performed with standard silica-gel column chromatography, even with base (0.5 – 1% of Et_3N) present in the eluent. The optimal purification procedure involved column chromatography on basic alumina (act. III) along with *ca.* 20 mg of $NaHCO_3$ present in all fraction tubes. In addition, ^1H-NMR data was obtained in (D_8)toluene with $NaHCO_3$ present. Only with these measures could reproducible yields be obtained and the optimal reaction conditions be determined (*Table 3*). The thermal [3 + 2] reaction was much faster than expected (*cf. Entry 1*); ^1H-NMR analysis of an aliquot taken after 4 h showed that the nitronate **14ab** was consumed and that

---

[5]) To obtain high yields of **10c**, the product must be purified by both *Schlenk* filtration and high-vacuum distillation to avoid decomposition.

[6]) Because none of the minor diastereoisomers was successfully taken on to aminocyclohexanones, it could not be determined whether the minor isomers resulted from a loss of *endo*/*exo* selectivity or facial selectivity.

Table 2. *Survey of* Lewis *Acids for [4+2] Cycloaddition with* **10b–c**



(±)-**13a** G* = (±)-**11a** (–OH)
(+)-**13b** G* = (+)-**11b** (–OH)

10b R_3Si = TBS
c R_3Si = TIBS

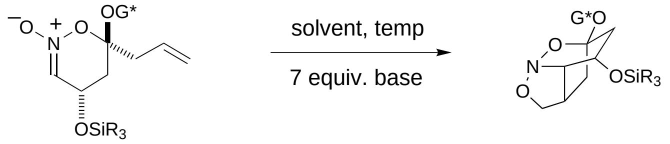
14ab G* = (±)-**11a** (–OH), R_3Si = TBS
14ac G* = (±)-**11a** (–OH), R_3Si = TIPS
14bb G* = (+)-**11b** (–OH), R_3Si = TBS

Lewis acid[a])	Dienophile[b])	Nitroalkene	Yield [%]	dr[c])
$SnCl_4$	(±)-**13a**	**10b**	57	19 : 1
$SnCl_4$	(±)-**13a**	**10c**	71	2 : 1
$TiCl_2(O^iPr)_2$	(±)-**13a**	**10c**	0	–
MAPh[d])	(±)-**13a**	**10c**	0[e])	–
$SnCl_4$	(+)-**13b**	**10c**	77	4.25 : 4.25 : 1

[a]) 2.0 equiv. [b]) 1.5 equiv. [c]) Determined by ^{1}H-NMR analysis. [d]) MAPh = methylaluminium bis[2,6-diphenylphenolate]. [e]) 24% of isomerized **13a** was isolated.

nitroso acetal **15ab** was present with little contamination. Apparently, the lack of a substituent at C(3) of the nitronate leads to faster [3+2] cycloaddition[7]). The TIPS-protected nitronate **14ac** reacted more slowly, but nitroso acetal **15ac** could be isolated in good yield after 18 h at 140°

Table 3. *Optimization of Conditions for [3+2] Cycloaddition with* **14**



14ab G* = (±)-**11a** (–OH), R_3Si = TBS
14ac G* = (±)-**11a** (–OH), R_3Si = TIPS

15ab G* = (±)-**11a** (–OH), R_3Si = TBS
15ac G* = (±)-**11a** (–OH), R_3Si = TIBS

Entry	Nitronate	R_3Si	Solvent	Temp. [°]	*Method*[a])	Base	Time [h]	Yield [%][b])
1	**14ab**	TBS	toluene	110	*A*	$NaHCO_3$	4.5	69[c])
2	**14ac**	TIPS	toluene	50	*A*	K_2CO_3	60	0 (20)[d])
3	**14ac**	TIPS	xylenes	140	*B*	$NaHCO_3$	18	49[c])
4	**14ac**	TIPS	$^tBuC_6H_5$	160	*B*	$NaHCO_3$	18	27[c])

Method A: the reaction mixture was placed in a preheated oil bath. *Method B:* syringe-pump addition of nitronate within 8 h into the refluxing reaction mixture, followed by stirring for an additional 10 h. [b]) Isolated yield. [c]) Purified by alumina chromatography (act. III, basic). [d]) Yield by ^{1}H-NMR analysis of the crude mixture.

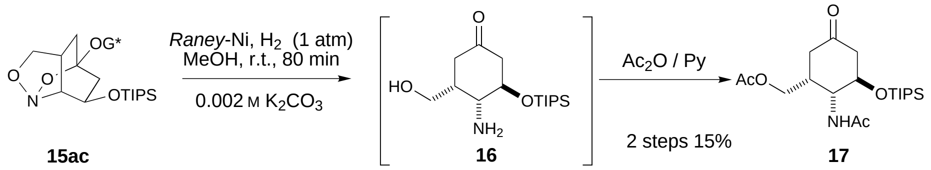
3.4. *Hydrogenolysis.* The nitroso acetal hydrogenolysis is a critical reaction whose success relies upon a delicate balance of three parameters (H_2 pressure, solvent, and amount of catalyst). The use of 1 atm of H_2 and MeOH as the solvent was dictated by

---

[7]) For example, the conversion of (+)-**7** to (+)-**8** (*Scheme 3*) required 26 h.

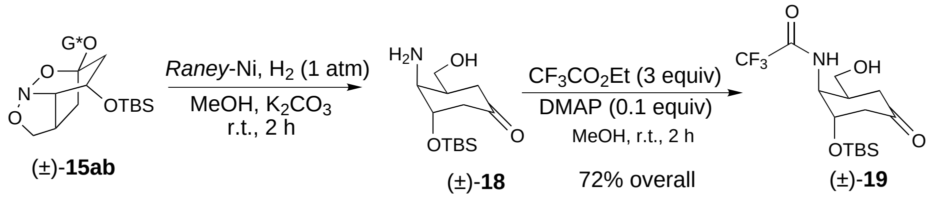
previous experience with this type of tricyclic nitroso acetals [13a]. These foregoing studies also revealed an important dependence of the rate of the nitroso acetal hydrogenation on the *Raney*-Ni loading. High loadings (*ca.* 17 equiv.) of *Raney*-Ni were required to obtain reasonable reaction times (1.3–4 h). The selective unmasking of nitroso acetal **15ac** to afford the corresponding ketone **16** could be achieved by stirring a methanolic suspension of commercially available *Raney*-Ni (W2) and nitroso acetal **15ac** under 1 atm of H_2 at room temperature for 1.5–2 h (*Scheme 7*). The crude product from the hydrogenation of nitroso acetal **15ac** was acetylated to give amino cyclohexanone **17** in 15% overall yield.

Scheme 7



The selective hydrogenation of nitroso acetal **15ab** was carried out under conditions similar to those described for **15ac,** but all attempts to acetylate the crude product from the hydrogenation failed[8]. It was discovered that the intermediate amino ketone (±)-**18** (*Scheme 8*) decomposed when the reaction mixture was concentrated *in vacuo*[9]. Thus, we needed to employ a method for protecting the amine that would be compatible with the use of MeOH as solvent. This was successfully accomplished by adding ethyl trifluoroacetate (together with *N*,*N*-dimethylpyridin-4-amine (DMAP)) to the crude MeOH solution of the amino ketone after removal of the Ni catalyst. In this way, protected cyclohexanone derivative (±)-**19** could be obtained in 72% overall yield (*Scheme 8*).

Scheme 8



The structure of (±)-**19** was confirmed by single-crystal X-ray analysis (*Fig. 2*)[10]. Analysis of ^{1}H-NMR coupling constants between H–C(3) and H–C(4) confirms that these H-atoms also occupy equatorial positions in solution, (*Fig. 3*). Thus, the

---

[8] The only compound isolated from the attempted hydrogenation/acetylation sequence of **15ac** was a partially reduced intermediate.

[9] The decomposition is probably due to imine polymerization by concentrating the amino ketone containing reaction mixture. It is also possible that this decomposition is catalyzed by Ni^{2+}.

[10] The crystallographic coordinates of (±)-**19** have been deposited with the *Cambridge Crystallographic Data Centre*, deposition No. CCDC-187303.

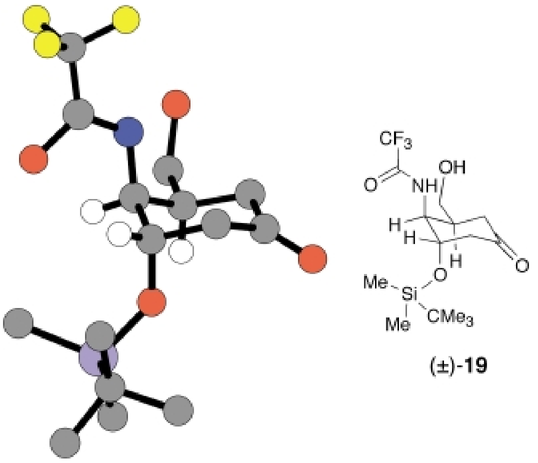
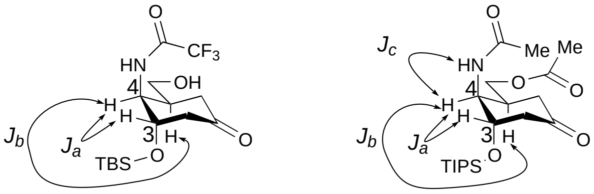


Fig. 2. *Chem-3D representation of X-ray crystal structure of* (±)-**19.** Most H-atoms are omitted for clarity. Red = O, blue = N, yellow = F, light blue = Si.



(±)-**19**
J_a = 4.7 Hz
J_b = 3.5 Hz

17
J_a = 4.7 Hz
J_b = 3.5 Hz
J_c = 7.9 Hz

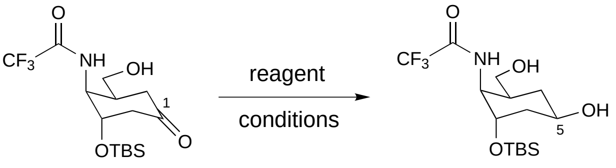
Fig. 3. *Selected* ^{1}*H-NMR data of* (±)-**19** *and* **17**

trifluoroacetamido and the TBSO groups at C(4) and C(3) must adopt axial positions in solution as well as in the solid state. By analogy, small coupling constants for H−C(3) and H−C(4) in the cyclohexanone **17** suggest that the acetamido and TIPSO groups also occupy axial positions.

3.5. *Cyclohexanone Reduction*. The selective reduction of (±)-**19** to the cyclohexanediol (±)-**20** was more challenging than expected. A variety of reagents and conditions were surveyed (*Table 4*). Disappointingly, of all the reagents initially tried, only the *Meerwein-Ponndorf-Verley* reduction (*Entries 2* and *3*) gave a favorable equatorial/axial ratio of the OH group at C(5). This reaction gave moderate to good selectivity, but longer reaction times and higher temperatures (conditions that should favor the thermodynamically preferred product) led to extensive decomposition. The use of Na in ammonia gave exclusively the unexpected axial product, although the chemical yield was very poor (*Entry 5*). We next considered the reduction of (±)-**19** to the epimeric cyclohexanediol with an axial hydroxy group, using *LS-Selectride* [29].

Here, again, the unexpected result was observed in the exclusive formation of the *equatorial alcohol* product (±)-**20**. The reduction was also extremely slow (*cf. Entries 9–11*; *Table 4*); complete consumption of the ketone at –78° required 7.5 equiv. of *LS-Selectride* over 48 h, to afford a 77% yield of (±)-**20**. Raising the temperature to –30° and stirring the reaction mixture for 8 h gave (±)-**20** in 55% yield, with no starting material remaining.

Table 4. *Optimization of Conditions for Reduction of* (±)-**19**



(±)-**19** (±)-**20**

Entry	Reagent	Conditions	Equatorial/axial	Conversion[a] [%]
1	$\mathrm{NaBH_4/CeCl_3}$	MeOH, –78°, 12 h	1 : 1.17	86
2	$\mathrm{Al(^{i}PrO)_3}$	^{i}PrOH, 50°, 1.5 h	4 : 1	100
3	$\mathrm{Al(^{i}PrO)_3}$	^{i}PrOH, 80°, 3 d	10 : 1	100[b]
4	$\mathrm{La_3(^{i}PrO)_9}$	^{i}PrOH, 80°, 3 d	–	dec.
5	Na[c]/$\mathrm{NH_3/^{i}PrOH}$	THF, –78°, 2 min	0 : 1	30
6	Na[d]/$\mathrm{NH_3/^{i}PrOH}$	THF, –78°, 2 min	0 : 1	100[e]
7	Na	$\mathrm{EtOH/Et_2O}$, 0°, 0.5 h	–	dec.
8	$\mathrm{SmI_2}$	$\mathrm{THF/H_2O}$, 0°, 0.5 h	1 : 1.09	100[f]
9	*LS-Selectride*	3.2 equiv. THF, –78°, 2.5 h	1 : 0	29[g] (61)[h]
10	*LS-Selectride*	3.5 equiv. THF, –78°, 12 h	1 : 0	37[g] (52)[h]
11	*LS-Selectride*	7.5 equiv. THF, –78°, 48 h	1 : 0	77[g]
12	*LS-Selectride*	8.0 equiv. THF, –30°, 8.0 h	1 : 0	55[g]

[a] Conversion based on ^{1}H-NMR intergration. [b] ^{1}H-NMR analysis showed extensive decomposition. [c] 10 equiv. of Na used. [d] 50 equiv. of Na added in three portions. [e] Isolated 20% of axial product. [f] Minor by-products observed. [g] Yield of isolated product. [h] (Recovered starting material).

The assignment of the configuration at C(5) of (±)-**20** was deduced from analysis of ^{1}H-NMR coupling constants (*Fig. 4*). The large coupling constants between H_a and H_c and H_e implied axial/axial coupling, which is possible only when the OH–C(5) is in the equatorial position. Additional structural evidence from chemical transformation was secured by treatment of (±)-**20** under *Mitsunobu* conditions (*Fig. 4*). None of the expected benzoate was obtained but rather the bicyclic compound **21**. This would be most unlikely if OH–C(5) were axial, because primary OH groups are know to react faster than secondary OH groups under *Mitsunobu* conditions [30][11]. Compound **21** could be formed by activation of the primary OH group followed by displacement of the activated phosphonium group with the OH–C(5) in a flipped chair conformation.

3.6. *Enantioselective Synthesis of a 4-Amino-2,4-dideoxycarbasugar*. On the basis of the high degree of selectivity observed in the [4 + 2] cycloaddition, the TBS-protected nitroalkene **10b** and the vinyl ether **13a** were chosen to prepare an enantiomerically

---

[11] For formation of a bicyclic tetrahydrofuran under *Mitsunobu* conditions, see [30c].

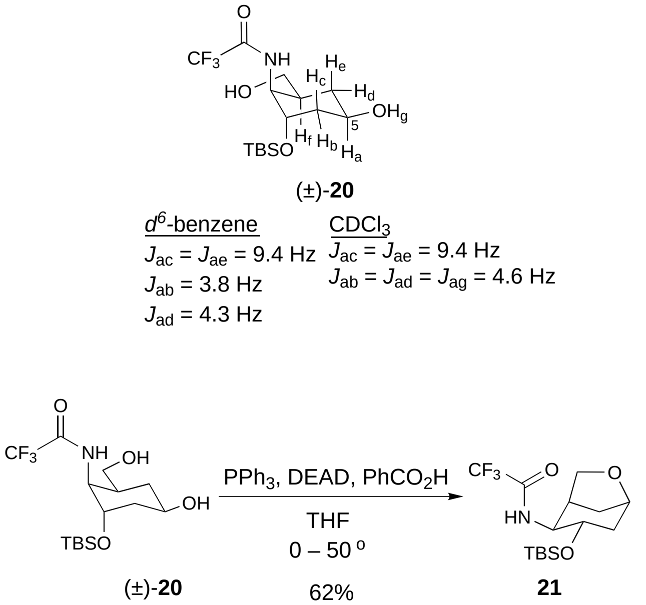


Fig. 4. *Structural assignment of reduction product* **20**

enriched aminocarbasugar. Given that a D-aminocarbasugar was desired, the correct enantiomer of *trans*-2-phenylcyclohexanol had to be chosen. This was done on the basis of the crystal structure of (±)-**8** [13a] (*Fig. 5*). The relative configuration between the chiral auxiliary and the nitroso acetal core can be determined by inspection. The configuration of the chiral auxiliary depicted is (1*S*,2*R*)-*trans*-2-phenylcyclohexanol ((±)-**11a**), which would lead to the L-aminocarbasugar **22**, derived from cyclohexanone (−)-**9** (*Fig. 6*). Thus, for the synthesis of D-aminocarbasugars, the (1*R*,2*S*)-*trans*-2-phenylcyclohexanol ((−)-**11a**) is required.

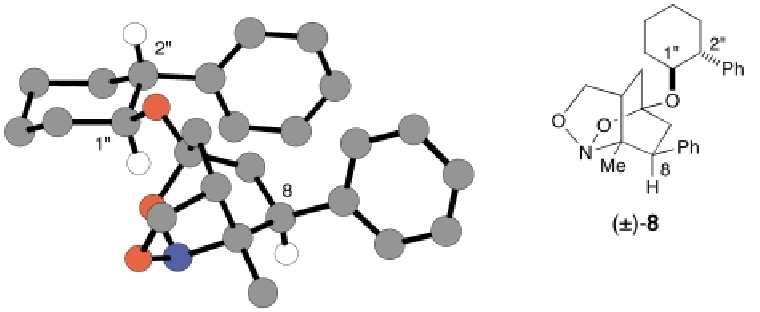


Fig. 5. *Chem-3D representation of the X-ray crystal structure of nitroso acetal* (±)-**8**. Most H-atoms are omitted for clarity. Red = O, blue = N.

The synthesis followed the optimal sequence established above and is outlined in *Scheme 9*. Gratifyingly, all of the yields and selectivities were higher than in the

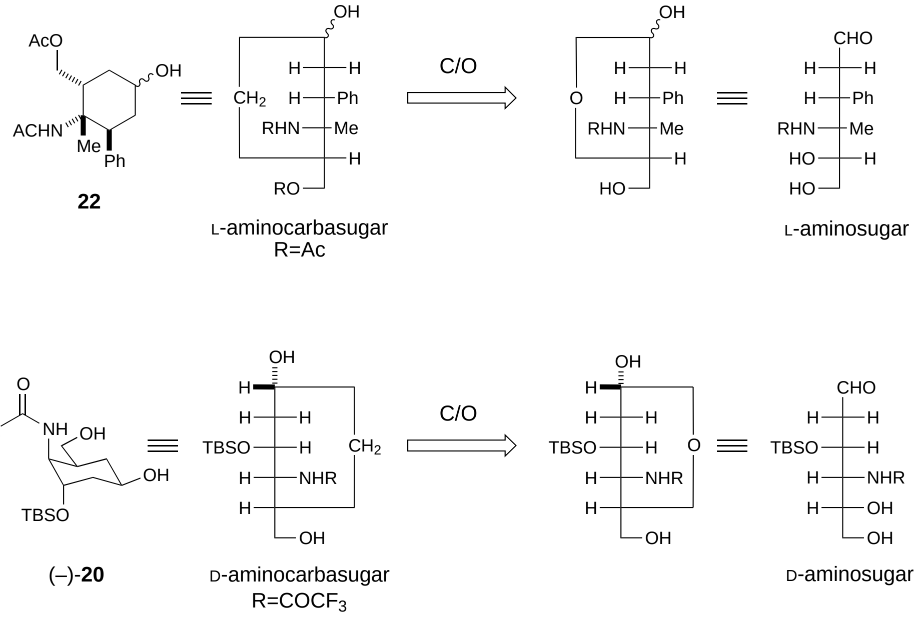
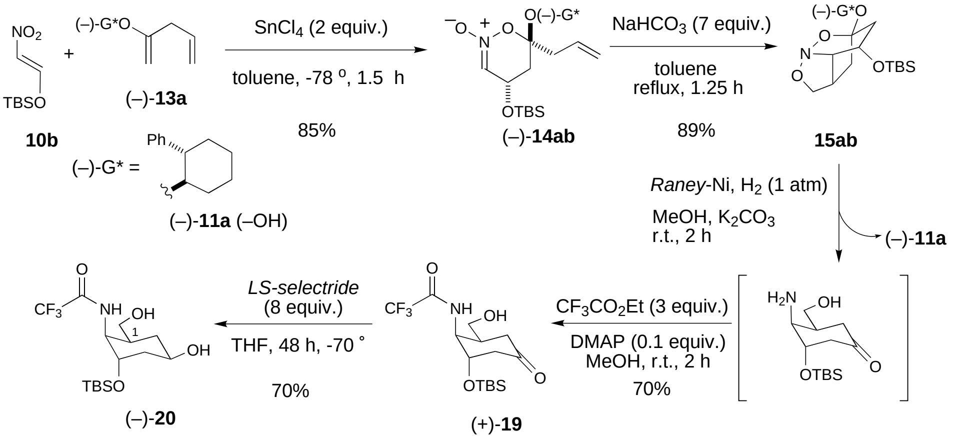


Fig. 6. Fischer *projections of aminocarbasugars* **22** *and* (−)-**20**

orienting experiments. The $SnCl_4$-promoted cycloaddition of nitroalkene **10b** with enantiomerically enriched dienophile (−)-**13a** produced the nitronate (−)-**14ab** in 85% yield. The [3+2] cycloaddition of nitronate (−)-**14ab** was carried out in refluxing anhydrous toluene with 7 equiv. of $NaHCO_3$ present to afford the nitroso acetal **15ab** in 89% yield. The selective hydrogenolysis of the highly strained tricyclic nitroso acetal proceeded under 1 atm of H_2 with 17 equiv. of *Raney*-Ni in MeOH. After trifluoroacetylation of the crude amino ketone, the target cyclohexanone (+)-**19** was isolated

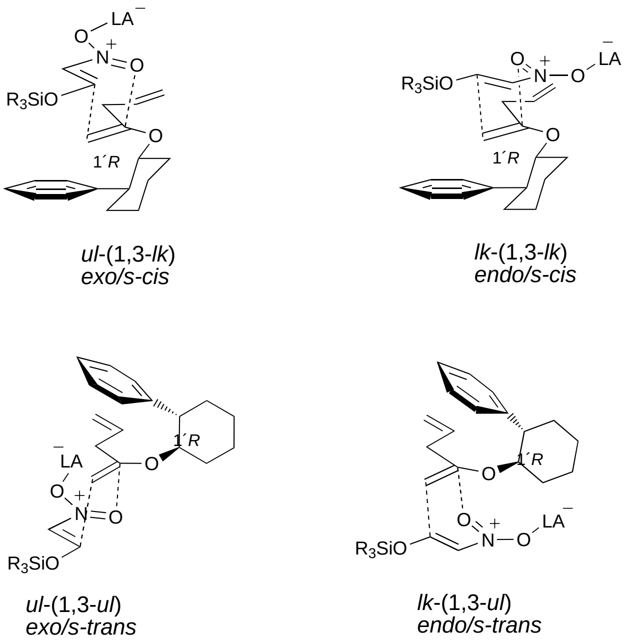
Scheme 9



in 70% yield. Selective reduction of (+)-**19** was carried out with 8 equiv. of *LS-Selectride* at −70° in THF for 48 h, to give the *β*-D-4-amino-2,4-dideoxycarbagulose ((−)-**20**) in 70% yield after recrystallization.

4. Discussion. – 4.1. *[4+2] Cycloaddition.* There are two stereochemical issues to consider in these inverse-electron-demand [4+2] cycloadditions(12). The first is the relative stereochemistry that describes the pairwise relationship between the enantiotopic faces of the diene and the diastereotopic faces of the dienophile. This is commonly referred to as *endo*/*exo* selectivity, though we have recommended the use of the *lk* (*like*) and *ul* (*unlike*) terms suggested by *Seebach* to more accurately describe the topical relationship of the *endo*/*exo* transition states. The second type of selectivity, called internal, becomes relevant when either the diene or the dienophile is chiral. In the case at hand, we employed chirally modified vinyl ethers, and, thus, the internal selectivity is defined as the pairwise relationship of the resident stereogenic center at the chiral unit with respect to the face of the dienophile that is engaged in cycloaddition. This type of selectivity is defined as (1,3-*lk*) and (1,3-*ul*). From computational analysis, it is known that there are two limiting ground-state conformations in vinyl ethers, the *s-cis* and the *s-trans* conformations around the GO*−C(2) bond. Which face of the vinyl ether is accessible depends on whether the vinyl ether is in the *s-cis* or *s-trans* conformation.

There are four possible transition-state structures as shown in *Fig. 7*. *Lewis* acids enhance the rates of these inverse-electron-demand cycloaddition reactions by



ul-(1,3-*lk*)
exo/s-cis

lk-(1,3-*lk*)
endo/s-cis

ul-(1,3-*ul*)
exo/s-trans

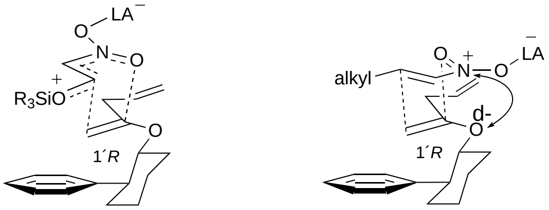
lk-(1,3-*ul*)
endo/s-trans

Fig. 7. *Four limiting transition-state structures for the [4+2] cycloaddition*

---

(12) For a thorough discussion of the stereochemical features of these cycloadditions, see [22b].

narrowing the FMO gap through the lowering of the $\mathrm{LUMO}_{(\mathrm{heterodiene})}$ by complexation. In addition, we have observed that the reaction selectivity has also been dramatically affected [22] [31]. With $SnCl_4$, the [4 + 2] reaction generally proceeds through a *ul*-type transition structure (*exo* with respect to the OR group in the vinyl ether). This has been proposed previously when groups capable of delocalizing electrons (*e.g.*, a phenyl group) are present in the *β*-position in the nitroalkene, (*Fig. 8*).



charge separation
exo (*ul*) favored

coulombic interaction
endo (*lk*) favored

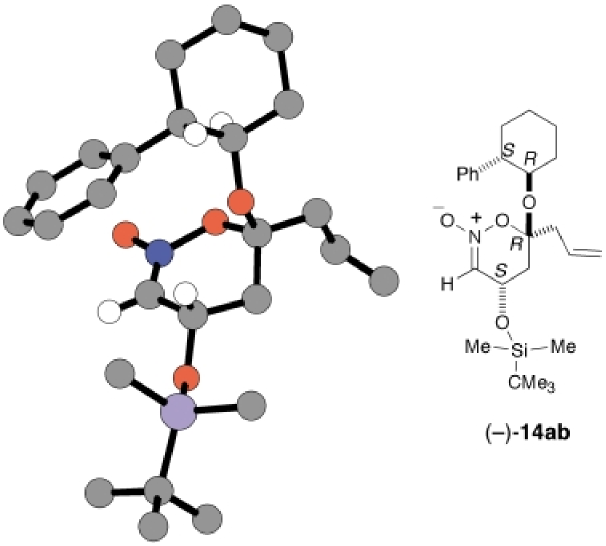
Fig. 8. *Electrostatic interactions in the* lk *and* ul *transition structures*

Both *Houk* and co-workers [32] and *Kahn* and *Hehre* [33] have suggested that coulombic interactions between the diene and dienophile in the transition structure control the relative (*exo*/*endo*) selectivity in *Diels–Alder* reactions. This model has been used to explain previous results with nitroalkenes and simple vinyl ethers or *β*-substituted vinyl ethers. Electrostatic interactions between the positively charged N-atom and the electron-rich O-atom in the vinyl ether would lead to the *l* (*endo*-derived) product. However, if an electron-delocalizing group, such as TBSO or TIPSO, were placed in the *β*-position of nitroalkene, it could change the electronic environment of the N-atom and delocalize the positive charge, thereby attenuating the coulombic interactions. The less sterically demanding *exo*-type approach could then be the controlling factor in the [4 + 2] cycloaddition. The significantly higher *exo* selectivity obtained with the TBSO-substituted nitroalkene **10b** compared to the TIPSO-substituted nitroalkene **10c** is difficult to explain in the absence of accurate transition-structure models. It is noteworthy that the *exo*-selective cycloaddition affords the *u* product, which leads to the D-4-amino-2,4-dideoxycarbagulose series. To access the D-4-amino-2,4-dideoxycarbagalactose series will require an *endo* cycloaddition promoted by a titanium- or aluminium-based *Lewis* acid.

To explain the origin of the internal selectivity imparted by the chiral auxiliary, we must understand how the phenyl group of the 2-phenylcyclohexyl unit shields the diastereofaces of the vinyl ether. As shown in *Figs. 7* and *8*, the phenyl group of the auxiliary blocks the *Si* face of the vinyl ether when it is in the *s-cis* conformation and blocks the *Re* face of the vinyl when it is in the *s-trans* conformation. The X-ray crystal structure of nitronate (−)-**14ab** (see below) unambiguously determined that the major product in the [4 + 2] cycloaddition was formed through an *ul*-(1,3-*lk*) (*exo*/*s-cis* type) transition-state structure. This means that the vinyl ether attacked from the *Re* face at C(2) to the *Si* face of the C(*β*) atom on the nitroalkene. There are no steric reasons for the reaction to proceed through an *s-cis* conformation of the vinyl ether, and *Houk* and co-workers have shown that simple vinyl ethers experience a conformational switch

[34]. In the ground state, the *s-trans* conformation is disfavored due to unfavorable lone pair/π-electron interactions. In the transition structure, on the other hand, the *s-trans* conformation is more favorable because of lone-pair stabilization of the developing positive charge. Indeed, earlier studies in this group have documented the conformational switch, but importantly also showed that it is *Lewis* acid dependent. For example, with MAD and $Ti^{i}PrO_2Cl_2$, vinyl ethers react through *s-trans* conformations, while, with $SnCl_4$, they prefer to react through an *s-cis* conformation [22b]. The stereochemical significance is reflected in the change in internal selectivity as a function of the *Lewis* acid. In this study, observed facial selectivity of the cycloaddtion between (−)-**13a** and **10b** indicates that the *Houk* conformational switch does not occur for these systems as well in the presence of $SnCl_4$.

4.2. *[3 + 2] Cycloaddition.* The rate of the thermal dipolar cycloaddition is related in part to the ease with which the nitronate can orient itself to a reactive conformation. It has been shown previously that the ground-state conformation of the nitronate is a half chair in which the alkoxy group (RO) at C(6) is placed in a pseudoaxial position to maximize the anomeric effect [13a]. This places the pendant dipolarophile in a pseudoequatorial position. This supposition has been confirmed in the solid state by the X-ray crystal structure of (−)-**14ab** (*Fig. 9*)[13].



(−)-14ab

Fig. 9. *Chem-3D representation of the X-ray crystal structure of* (−)-**14ab.** Most H-atoms are omitted for clarity. Red = O, blue = N, yellow = F, light blue = Si.

For the dipolarophile to position itself in a reactive orientation, the nitronate ring has to assume a high-energy, boat-like conformation wherein the dipolarophile is in a pseudoaxial position, (*Fig. 10*). As observed in previous investigations, this conformational reorientation is particularly unfavorable in the *trans*-nitronate because of the

---

[13] The crystallographic coordinates of (−)-**14ab** have been deposited with the *Cambridge Crystallographic Data Centre*, deposition No. CCDC-187304.

nonbonding interactions between the Me–C(3) and Ph–C(4), when changing from a dihedral angle (∠Me–C–C–Ph) of *ca.* 45° to 0°. This issue manifests itself in reaction conditions necessary for the [3 + 2] cycloaddition for the nitronate depicted in *Fig. 10*, namely 24 h in refluxing xylenes for the *trans*-nitronate compared to 11 h in refluxing benzene for the *cis* nitronate.

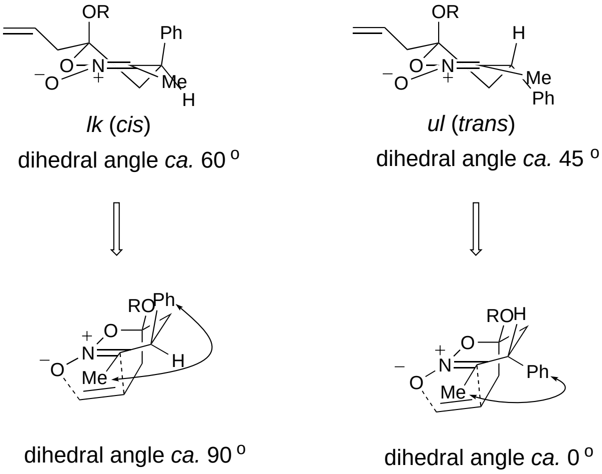


Fig. 10. *Transition-state structure for [3 + 2] cycloaddition*

In the case of *trans*-nitronate (–)-**14ab**, the reaction time was only 4.25 h in refluxing toluene to obtain complete conversion to **15ab**. This significant rate increase compared to the *trans*-nitronate in *Fig. 10* most likely arises from the lack of a substituent at C(3) in (–)-**14ab**. Two sterically related consequences of having a H-atom at this position are: *1*) reduced interactions between the dipole and the dipolarophile in the transition structure and *2*) reduced torsional interactions between a H-atom and a TBSO group, compared to a Me and a Ph group (*Fig. 11*).

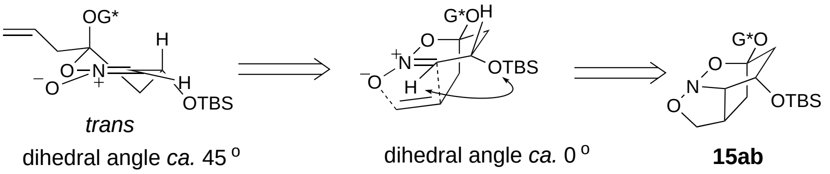
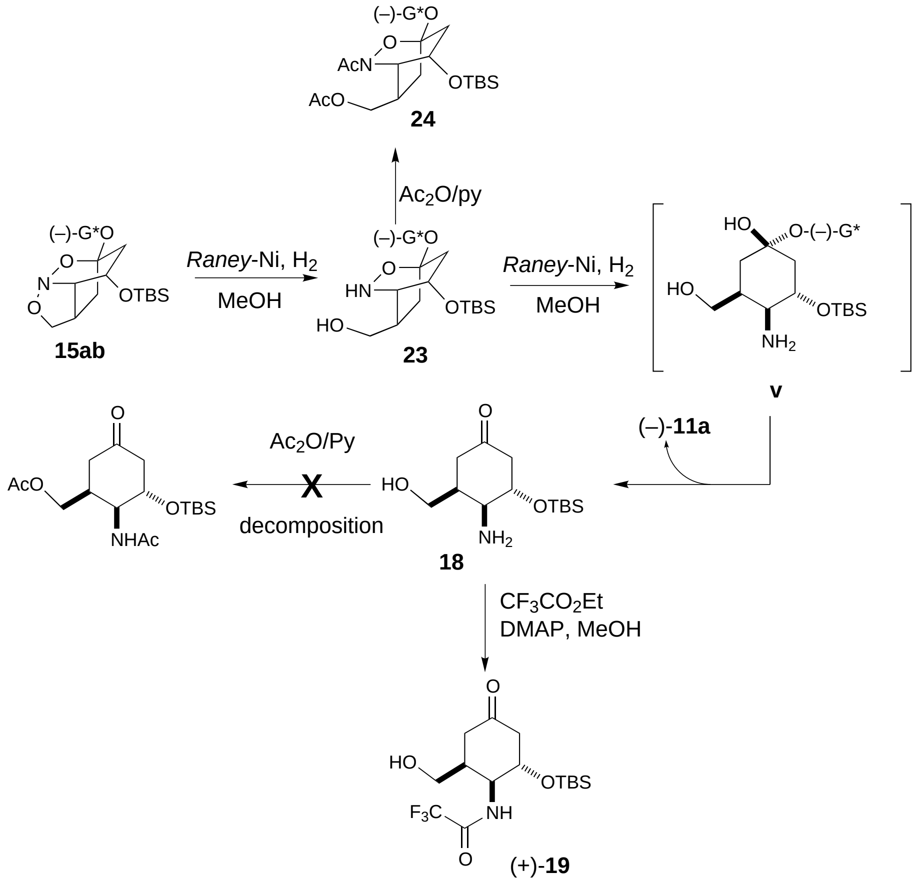


Fig. 11. *Transition-state structure for the [3 + 2] cycloaddition of* (–)-**14ab**

4.3. *Hydrogenation*. The selective hydrogenation of **15ab** to give cyclohexanone **18**, could be controlled by the amount of *Raney*-Ni used and the reaction time. The optimal conditions were *ca.* 17 equiv. of *Raney*-Ni under 1 atm of H_2 for 2–3 h. When 11 equiv. of *Raney*-Ni were used for 4.5 h partially hydrogenated product **24** was isolated after acetylation (*Scheme 10*). As in all previous studies, the isoxazolidine ring of the nitroso acetal was cleaved first (to give **23**), even when the other N–O bond of the 1,2-oxazine is longer.

Scheme 10



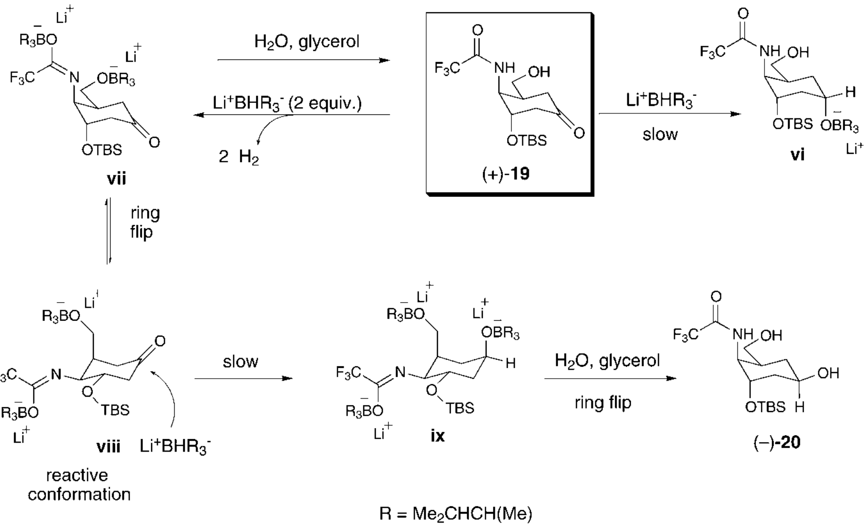
The instability of aminocyclohexanones **16** and **18** stands in contrast to the aminocyclohexanones from previous investigations (*cf. Scheme 3*). This increased instability is probably due to oligomerization as a consequence of the less sterically demanding environment around the amino group, which would be expected to accelerate intermolecular imine formation.

4.4. *Selective Ketone Reduction.* The selective reduction of cylcohexanone (+)-**19** to give alcohol (−)-**20** bearing an equatorially oriented OH group was very surprising. The bulky reducing agent *LS-Selectride* is well known to deliver hydride in an equatorial direction to generate axial alcohols [29]. This unexpected result could only be rationalized if the reactive conformation of the ketone (or ketone complex) were significantly different from the ground state. Thus, to pursue this possibility, we determined the ground-state conformation of **19** by a number of methods.

As described in *Sect. 3.5*, in both the solid (X-ray) and solution (^{1}H-NMR) states, the conformation of (±)-**19** is that in which both the CF_3CONH and TBSiO groups occupy axial positions with the hydroxymethyl group at C(1) in an equatorial orientation (*Fig. 2*). Further, an MM2 conformational search with MacroModel 7.0 showed that the axial/axial conformation of the CF_3CONH and silyloxy groups (Me_3SiO instead of TBSiO to minimize calculation time) in (±)-**19** was 18.3 kJ/mol lower in energy than the equatorial/equatorial conformation. The energy difference can be explained by steric interactions between the two bulky substituents (CF_3CONH and the TBSiO group) when both are placed in the equatorial positions as well as dipole interactions, which are minimized in the axial/axial conformation.

To rationalize the observed stereochemical outcome, we assume that *LS-Selectride* attacks (+)-**19** only from an equatorial direction on the well-accepted basis of steric-approach control. Direct reduction of (+)-**19** to give the expected axial alcohol (see **vi** in *Scheme 11*) must be very slow. Thus, there must be a conformational switch in the cyclohexanone ring prior to the hydride delivery to explain the equatorial OH group in (−)-**20.** The observation that the starting material is consumed after 1.5 h based on TLC analysis, but that prolonged exposure to H_2O regenerates (+)-**19,** gives an indication of a complex formed from (+)-**19** and *LS-Selectride.* As shown in *Scheme 11*, one could envision 2 equiv. of *LS-Selectride* reacting with the two most acidic protons in (+)-**19** thereby generating H_2 gas and complex **vii**, which is in equilibrium with the other chair conformation **viii**. This complexation must be faster than the delivery of hydride to the ketone, which would again generate reduction product **vi**. To explain the observed formation of the equatorial alcohol (−)-**20,** the reactive conformation must be **viii**. The delivery of hydride in expected equatorial direction leads to **ix.** The slow reduction (48 h), may in part be due to the low equilibrium concentration of **viii** and the slow rate of addition of hydride to a dianionic complex. Hydrolysis of **ix** then affords, after ring flipping, (−)-**20** in its more favorable conformation.

Scheme 11



We also note in passing that the dissolving metal reduction (Na/NH_3) also gave rise to an unexpected outcome in the preferential formation of the axial alcohol. This result appears contrary to the dogma that would predict the thermodynamically more favorable alcohol to be formed. However, the generation of the axial alcohol could arise as a result of internal chelation of the Na^+ cation between the ketyl radical anion and the TBSO O-atom, thus affording the product of thermodynamic control at the level of the ketyl radical [35]14).

5. Conclusions. – The feasibility of a bridged-mode tandem [4 + 2]/[3 + 2] cycloaddition sequence to form β-D-4-amino-2,4-dideoxycarbagulose was demonstrated. An appropriate combination of a nitro(silyloxy)alkene **10b** and chiral vinyl ether (−)-**13a** were found to give the tandem cycloaddition in high yield and with excellent stereoselectivity. The success of the synthetic route was highly dependent on the development of suitable experimental conditions due to the highly sensitive nature of the compounds along the path. The sequence is short (5 steps) and provides for ample structural modification. An unexpected reduction of the protected aminocyclohexanone provided the equatorial alcohol with *LS-Selectride*. Further investigations of more-complex dienes and dienophiles in the [4 + 2] cycloaddition is currently under investigation to explore the synthesis of more-complex aminocarbasugars.

We are grateful to the *National Institutes of Health* for generous financial support (R01 GM30938). *M. J.* thanks the *Fulbright Foundation* for a fellowship.

Experimental Part

General. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: hexane and CH_2Cl_2 ($CaCl_2$), AcOEt (K_2CO_3), Et_2O and ^{t}BuOMe ($CaSO_4$/$FeSO_4$). All solvents utilized in reactions were distilled from appropriate drying agents before use: THF and Et_2O (Na/benzophenone (= sodium oxidodiphenylmethyl), benzene (CaH_2), and CH_2Cl_2 (CaH_2 or P_2O_5). Butyllithium and allylmagnesium chloride were titrated according to the method of *Gilman* [36]. All reactions were conducted in flame-dried glassware under N_2. Brine refers to a sat. aq. NaCl soln. Bulb-to-bulb distillations were performed on a *Büchi GKR-50*-'Kugelrohr' apparatus, with air-bath temp. corresponding to boiling points. Anal. TLC: *Merck-60* glass-backed silica-gel plates with *F-254* indicator; visualization with UV light, I_2, ninhydrin, $Ce(SO_4)_2$/$Mo(NH_4)_3$/H_2SO_4, and phosphoromolybdic acid. Column (flash) chromatography (FC): 32 – 63 μm silica gel or alumina (neutral, act. IV, basic, act. III), *ca.* 150 mesh, 58 Å (*Aldrich*). All reaction temp. were measured as internal temp. with *Teflon*-coated thermocouples. M.p.: *Thomas – Hoover* capillary melting-point apparatus; corrected. IR Spectra: *Mattson Galaxy-FTIR-5000* spectrometer; $CHCl_3$ solns; in cm^{-1}; relative intensities: *s* (67 – 100%), *m* (33 – 67%), or *w* (0 – 33%). ^{1}H- and ^{13}C-NMR Spectra: *Varian Unity-400* (400 MHz ^{1}H, 100 MHz ^{13}C), *– 500* (500 MHz ^{1}H, 125.7 MHz ^{13}C), and *Varian Unity-Inova-500* (500 MHz ^{1}H, 125.7 MHz ^{13}C) spectrometers; $CDCl_3$, (D_6)benzene, (D_8)toluene, (D_6)acetone, or CD_3OD solns. with the deuterated solvent as an internal reference; chemical shift δ in ppm, coupling constants *J* in Hz; assignment of ^{13}C resonances were supported by HMQC and/or APT; in ^{13}C-NMR spectra, all peaks for which coupling constants are reported are *q* due to C,F-coupling. MS: *Varian MAT-CH-5* spectrometer, fast atom bombardment (FAB) ionization technique; in *m/z*. Combustion analyses were performed by the University of Illinois Microanalytical Laboratory.

Preparations According to the Literature. (1*R*,2*S*)-2-Phenylcyclohexanol ((−)-**11a**) [37], (1*S*,2*R*)-2-cumylcyclohexanol ((+)-**11b**) [24], {[(1*R*,2*S*)-2-phenylcyclohexyl]oxy}ethyne ((−)-**12a**) [22a], {[(1*S*,2*R*)-2-(1-methyl-1-phenylethyl)cyclohexyl]oxy}ethyne ((+)-**12b**) [13a], 2-{[(1*R*,2*S*)-2-phenylcyclohexyl]oxy}penta-1,4-diene ((−)-**13a**) [13a], 2-{[(1*S*,2*R*)-2-(1-methyl-1-phenylethyl)cyclohexyl]oxy}penta-1,4-diene ((+)-**13b**) [13a], potassium nitroacetaldehyde [28], 2-(benzoyloxy)-1-nitroethene (**10a**) [23].

*(1*E*)-1-{[(*tert*-Butyl)dimethylsilyl]oxy}-2-nitroethene* (**10b**). To a cold (− 26°, internal temp.) suspension of potassium 2-nitroethen-1-olate (3.76 g, 29.6 mmol) in CH_2Cl_2/$MeNO_2$ 1 : 1 (300 ml) was added dropwise a soln.

---

14) This analysis finds compelling precedent in the work of *Eschenmoser* and co-workers [35].

of (*tert*-butyl)dimethylsilyl chloride (4.46 g, 29.6 mmol) in CH_2Cl_2 (50 ml). The mixture was allowed to warm to r.t. over 3 h, during which time the white-grey soln. turned slightly yellow. The salts were filtered off with a *Schlenk* filtration apparatus, and the solvents were evaporated. The crude product was purified by distillation: 3.89 g (81%) of **10b** [38]. Light yellow liquid, which turned solid at – 25° in the drybox freezer. B.p. 77 – 78°/0.15 Torr. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.13 (*d*, J = 10.5, 1 H); 7.03 (*d*, J = 10.5, 1 H); 0.94 (*s*, ^{t}BuSi); 0.29 (*s*, Me_2Si).

(1E)-1-Nitro-2-[(triisopropylsilyl)oxy]ethene (**10c**). To a cold (– 30°) suspension of potassium 2-nitroethen-1-olate (1.00 g, 7.87 mmol) in CH_2Cl_2/$MeNO_2$ 1 : 1 (100 ml) was added dropwise a soln. of triisopropylsilyl chloride (1.73 ml, 8.06 mmol, 1.0 equiv.) in CH_2Cl_2 (40 ml). The mixture was allowed to warm to r.t. over 4 h. The salts were filtered off, and the solvents were evaporated. The crude product was purified by 'Kugelrohr' distillation and subjected to high vacuum (0.3 – 0.4 Torr) for 12 h at r.t. to give 0.50 g (81%) of **10c**. Light yellow liquid. B.p. 120 – 150° (air-bath temp.)/0.3 – 0.4 Torr. ^{1}H-NMR (400 MHz, $CDCl_3$): 8.20 (*d*, J = 10.5, 1 H); 7.05 (*d*, J = 10.5, 1 H); 1.2 – 1.3 (*m*, $(Me_2C\mathit{H})_3Si$); 1.10 (*d*, J = 7.1, $(\mathit{Me}_2CH)_3Si$). ^{13}C NMR (100 MHz, $CDCl_3$): 158.30; 128.43; 17.55 $(\mathit{Me}_2CH)_3Si$); 11.84 ($(Me_2\mathit{C}H)_3Si$).

(4S,6R)-4-{[(tert-Butyl)dimethylsilyl]oxy}-5,6-dihydro-6-{[(1′R,2′S)-2′-phenylcyclohexyl]oxy}-6-(prop-2″-enyl)-4H-1,2-oxazine 2-Oxide ((–)-**14ab**). $SnCl_4$ (4.76 ml, 40.7 mmol, 2.0 equiv.) was added dropwise to a cold (– 74°) soln. of **10b** (4.14 g, 20.4 mmol) in toluene (500 ml), and the mixture was stirred for 5 min. A cold (– 74°) soln. of (–)**-13a** (7.40 g, 30.5 mmol, 1.5 equiv.) in toluene (100 ml) was added *via* cannula. The yellow-brown mixture was stirred for 1.5 h at – 74° and then quenched at – 74° with 1M Et_3N in MeOH (173 ml, 173 mmol, 8.5 equiv.). The mixture was stirred for 15 min at – 74°, then poured into Et_2O (3 l) and sat. aq. $NaHCO_3$ soln. (400 ml). The org. phase was washed with sat. aq. $NaHCO_3$ soln. (3 × 400 ml), and the aq. phases were back-extracted with Et_2O (300 ml). The combined org. phase was washed with brine (400 ml), dried (Na_2SO_4), and evaporated and the yellow oil purified by FC (silica, hexane/AcOEt/Et_3N 90 : 9 : 1): 8.37 g (92%) of (–)-**14ab**. Recrystallization (hexane/AcOEt 5 : 1) gave 7.73 g (85%) of a single stereoisomer of anal. pure (–)-**14ab**. Colorless crystals. M.p. 114 – 116° (hexane/AcOEt 5 : 1). R_f (hexane/AcOEt/Et_3N 4 : 1 : 0.05) 0.44. $[\alpha]_D$ = – 156.6° ($CDCl_3$, c = 2.78). IR ($CHCl_3$): 3008*m*, 2933*s*, 2859*s*, 1633*s*, 1492*w*, 1463*w*, 1450*w*, 1371*w*, 1253*m*, 1120*s*, 1078*s*, 1006*s*, 836*s*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.32 (*t*, J = 7.35, 2 H_o); 7.24 – 7.18 (*m*, 2 H_m, H_p); 5.75 (*ddt*, J = 17.09, 10.13, 7.08, H–C(2″)); 5.18 (*dd*, J = 10.13, 1.8, 1 H–C(3″)); 5.15 (*dd*, J = 17.09, 1.8, 1 H–C(3″)); 5.04 (*dd*, J = 2.31, 0.98, 1 H–C(3)); 4.19 (*dt*, J = 10.01, 4.28, H–C(1′)); 3.73 (*ddd*, J = 10.25, 7.08, 2.32, H–C(4)); 2.64 – 2.54 (*m*, 2 H–C(1″)); 2.54 – 2.48 (*m*, H–C(2′)); 2.26 (*d*, J = 10.25, 1 H–C(6′)); 1.98 (*ddd*, J = 13.18, 7.08, 1.1, 1 H–C(5)); 1.85 (br. *s*, 1 H–C(5′)); 1.82 (br. *s*, 1 H–C(3′)); 1.75, (*d*, J = 12.57, 1 H–C(4′)); 1.59 (*dq*, J = 12.70, 4.15, 1 H–C(3′)); 1.51 – 1.37 (*m*, 1 H–C(5), 1 H–C(5′), 1 H–C(6′)); 1.31 (*m*, 1 H–C(4′)); 0.82 (*s*, ^{t}BuSi); 0.01 (*s*, 1 MeSi); 0.00 (*s*, 1 MeSi). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 144.53 (C_{ipso}); 131.42 (C(2″)); 128.39 (C_o)); 127.48 (C_m)); 126.24 (C_p); 119.80 (C(3″)); 113.79 (C(3)); 105.48 (C(6)); 75.19 (C(1′)); 62.15 (C(4)); 52.10 (C(2′)); 42.69 (C(1″)); 35.74 (C(5)); 35.57 (C(6′)); 34.60 (C(5′)); 25.81 (C(4′)); 25.55 (Me_3CSi); 25.05 (C(3′)); 17.74 ($Me_3\mathit{C}Si$); – 4.65 (MeSi); – 4.83 (MeSi). FAB-MS (pos.): 446.2 ($[M+1]^+$). Anal. Calc. for $C_{25}H_{39}NO_4Si$ (445.63): C 67.38, H 8.82, N 3.14; found: C 67.42, H 9.09, N 3.30.

(1R,6S,7S,8S)-8-{[(tert-Butyl)dimethylsilyl]oxy}-1-{[(1′R,2′S)-2′-phenylcyclohexyl]oxy}-2,4-dioxa-3-azatricyclo[4.3.1.0$^{3.7}$]decane (**15ab**). A soln. of nitronate (–)-**14ab** (1.5 g, 3.38 mmol, 1 equiv.) in toluene (350 ml) was placed in a flask (1 l) containing vacuum-dried (0.1 Torr, 1 h) $NaHCO_3$ (1.99 g, 23.6 mmol, 7 equiv.). The flask was lowered into a 118° oil bath, and the contents were stirred for 1 h under reflux. The solvent was evaporated and the residue purified by FC (basic alumina (act. III), hexane/AcOEt 9 : 1; the tubes for collecting fractions contained *ca.* 50 mg of $NaHCO_3$) to yield 1.33 g (89%) of **15ab**. White foam. R_f (hexane/AcOEt 4 : 1, basic alumina) 0.76. IR ($CHCl_3$): 3060*w*, 3060*w*, 2929*s*, 2886*s*, 2856*s*, 2273*w*, 1602*w*, 1492*w*, 1492*m*, 1450*s*, 1359*s*, 1321*s*, 1257*s*. FAB-MS (pos.): 446.2 ($[M+1]^+$). ^{1}H-NMR (500 MHz, (D_8)toluene): 7.27 (*t*, J = 7.00, 2 H_m); 7.21 – 7.17 (*m*, 2 $H_{o,}$ H_p)); 4.31 (*ddd*, J = 9.28, 4.27, 1.95, H–C(8)); 3.71 (*m*, CH_2(5), H–C(1′)); 3.03 (*t*, J = 4.03, H–C(7)); 2.62 (*m*, 1 H–C(6′)); 2.53 (*ddd*, J = 3.66, 10.13, 12.82, H–C(2′)); 2.47 (*m*, H–C(6)); 1.99 (*dd*, J = 13.18, 9.77, 1 H–C(10)); 1.86 (*m*, 1 H–C(3′)); 1.81 – 1.73 (*m*, 1 H–C(5′), 1 H–C(9)); 1.72 – 1.65 (*m*, 1 H–C(10), 1 H–C(4′)); 1.64 – 1.54 (*m*, 1 H–C(6′), H–C(3′)); 1.41 (*qt*, J = 13.20, 3.5, 1 H–C(5′)); 1.24 (*qt*, J = 12.8, 3.54, 1 H–C(4′)); 0.96 (*s*, ^{t}BuSi); 0.01 (*s*, 1 MeSi); 0.00 (*s*, 1 MeSi). ^{13}C-NMR (125.7 MHz, (D_8)toluene): 144.85 (C_{ipso}); 128.99 (C_m); 128.03 (C_o); 126.54 (C_p); 96.66 (C(1)); 77.87, 76.65 (C(5), C(1′)); 68.35 (C(8)); 63.75 (C(7)); 51.28 (C(6)); 41.06 (C(10)); 36.42 (C(6′)); 34.50 (C(2′)); 32.30 (C(3′)); 26.20, 25.84 (C(5'), C(9)); 25.80 (Me_3CSi); 25.50 (C(4′)); 18.00 ($Me_3\mathit{C}Si$); – 4.60 (MeSi); – 4.80 (MeSi).

(3S,4S,5S)-3-{[(tert-Butyl)dimethylsilyl]oxy}-5-(hydroxymethyl)-4-(2,2,2-trifluoroacetamido)cyclohexanone ((+)-**19**). A soln. of **15ab** (800 mg, 1.80 mmol, 1 equiv.) in MeOH (60 ml) was added to a flask (100 ml) containing K_2CO_3 (16.6 mg, 0.12 mmol) and *Raney*-Ni (2.09 g, 30.5 mmol, 17 equiv.), which had been washed

with anh. MeOH (5 × 50 ml) prior to use. The mixture was vigorously stirred under H_2 (1 atm) for 2.5 h. The *Raney*-Ni was filtered off and washed with MeOH (10 × 50 ml) and the combined org. phase concentrated to a volume of 60 ml of MeOH at 0°. The MeOH soln. of the amino ketone was then transferred to a 2-neck flask. *N,N*-Dimethylpyridine-4-amine (12.7 mg, 0.104 mmol, 0.1 equiv.) and ethyl trifluoroacetate (0.37 ml, 3.12 mmol, 3 equiv.) were added. The resulting mixture was stirred for 2 h and then evaporated to leave a slightly yellow-green oil. Purification of the oil by FC (hexane/AcOEt 70 : 30) and subsequent recrystallization from CH_2Cl_2 afforded 465 mg (70%) of anal. pure (+)-**19**. M.p. 91 – 92° (CH_2Cl_2). R_f (hexane/AcOEt 2 : 3) 0.47. $[\alpha]_D = 5.3$ ($CHCl_3$, $c = 1.61$). IR: 3615*w*, 3434*m*, 3357*w*, 3010*w*, 2954*s*, 2931*s*, 2886*m*, 2858*m*, 1722*s*, 1536*m*, 1471*m*, 1361*m*, 1338*m*, 1257*s*, 1230*m*, 1170*s*, 1112*m*, 1031*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.86 (br. *s*, NH); 4.69 (*dt*, *J* = 4.7, 3.5, H–C(3)); 4.12 (*q*, *J* = 4.7, H–C(4)); 3.97 (*ddd*, *J* = 10.74, 3.76, 2.56, 1 H, C*H*$_2$OH); 3.82 (*ddd*, *J* = 10.74, 5.25, 3.78, 1 H, C*H*$_2$OH); 2.75 (*m*, H–C(5)); 2.62 (*m*, 1 H–C(2), 1 H–C(6)); 2.41 (*m*, 1 H–C(2), 1 H–C(6)); 2.01 (*t*, *J* = 3.78, OH); 0.89 (*s*, ^{t}BuSi); 0.14 (*s*, 1 MeSi); 0.12 (*s*, 1 MeSi). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 207.66 (C(1)); 158.48 (*q*, *J* = 37.28, C=O); 115.95 (*q*, *J* = 288.15, CF_3); 69.17 (C(3)); 64.69 (CH_2OH); 55.87 (C(4)); 45.41 (C(6)); 39.83(C(2)); 35.46 (C(5)); 25.81 (*Me*$_3$CSi); 18.04 (Me$_3$*C*Si); – 4.70 (MeSi); – 4.84 (MeSi). FAB-MS (pos.): 370.1 ($[M+1]^+$). Anal. calc. for $C_{15}H_{26}F_3NO_4Si$ (369.45): C 48.76, H 7.09, N 3.80; found: C 48.88, H 7.31, N 3.93.

*(1*S*,2*S*,3*S*,5*R*)-3-{[(*tert*-Butyl)dimethylsilyl]oxy}-5-hydroxy-2-(2,2,2-trifluoroacetamido)cyclohexanemethanol* ((–)-**20**). A cold (– 74°) soln. of 1M *LS-Selectride* in THF (8.0 ml, 8 equiv.) in THF (15 ml) was transferred *via* cannula into a cold (– 74°) soln. of (+)-**19** in THF (30 ml), and the soln. was stirred for 48 h at – 74°. The reaction was quenched at – 74° with glycerol/buffer (pH 7) 1 : 1 (20 ml). Then the mixture was warmed to r.t. and stirred for 2 h further. The mixture was poured into sat. aq. $NaHCO_3$ soln. (120 ml) and extracted with AcOEt (4 × 80 ml). The combined org. phases were washed with brine (80 ml), dried (Na_2SO_4), and evaporated. Purification of the residue by gradient column chromatography (silica gel, hexane/AcOEt 4 : 1 (250 ml), 3 : 2 (250 ml), 1 : 1 (250 ml), and 2 : 3 (250 ml)) afforded 292 mg (79%) of a transparent oil that crystallized upon cooling to – 78°. Recrystallization from $CHCl_3$ yielded 259 mg (70%) of (–)-**20**. Colorless powder. M.p. 60 – 61° ($CHCl_3$). R_f (hexane/AcOEt 2 : 3) 0.20. $[\alpha]_D = -14.1$ (MeOH, $c = 4.73$). IR ($CHCl_3$): 3627*w*, 3432*w*, 3342*w*, 3029*w* (br.), 2956*m*, 2931*m*, 2886*w*, 2859*m*, 2360*w*, 2341*w*, 1722*s*, 1542*m*, 1471*w*, 1257*m*, 1230*m*, 1176*s*, 1120*m*, 1097*m*. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.01 (br. *s*, NH); 4.27 (*m*, H–C(3)); 4.13 (*tq*, *J* = 9.40, 4.64, H–C(5)); 3.96 (*m*, H–C(2)); 3.75 – 3.63 (*m*, C*H*$_2$OH); 2.52 (br. *s*, CH$_2$O*H*); 2.36 (*m*, H–C(1)); 1.93 – 1.80 (*m*, H_e–C(4), H_e–C(6), HO–C(5)); 1.55 (*ddd*, *J* = 12.82, 9.64, 2.44, H_a–C(6)); 1.44 (*q*, *J* = 11.51, H_a–C(4)); 0.91 (*s*, ^{t}BuSi); 0.14 (*s*, MeSi); 0.12 (*s*, MeSi). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 158.19 (*q*, *J* = 37.28, *C*OCF$_3$); 116.00 (*q*, *J* = 288.15, CO*C*F$_3$); 67.56 (C(3)); 65.35 (C(5)); 64.08 (CH_2OH); 53.97 (C(2)); 38.30 (C(6)); 34.96 (C(1)); 33.06 (C(4)); 25.56 (*Me*$_3$CSi); 17.76 (Me$_3$*C*Si); – 5.00 (MeSi), – 5.15 (MeSi). FAB-MS (pos.): 372.1 ($[M+1]^+$). Anal. calc. for $C_{15}H_{28}F_3NO_4Si$ (371.47): C 48.50, H 7.60, N 3.77; found: C 48.21, H 7.63, N 3.84.

*(4*S**,6*R**)-5,6-Dihydro-6-{[(1′*R**,2′*S**)-2′-phenylcyclohexyl]oxy}-6-(prop-2″-enyl)-4-[(triisopropylsilyl)oxy]-4*H*-1,2-oxazine 2-Oxide* (**14ac**). $SnCl_4$ (0.38 ml, 3.28 mmol, 2.0 equiv.) was added dropwise to a cold (– 74°) soln. of **10c** (402 mg, 1.64 mmol) in toluene (40 ml), and the mixture was stirred for 5 min. A cold (– 74°) soln. of (±)-**13a** (583 mg, 2.41 mmol, 1.5 equiv.) in toluene (10 ml) was added *via* cannula. The yellow-brown mixture was stirred for 1.5 h at – 74° and then quenched at – 74° with 1M Et_3N in MeOH (16 ml, 16 mmol, 9.8 equiv.). The mixture was stirred for 5 min and then poured into Et_2O (350 ml) and sat. aq. $NaHCO_3$ soln. (100 ml). The aq. phase was back-extracted with Et_2O (3 × 75 ml). The combined org. phase was washed with brine (75 ml), dried (Na_2SO_4), and evaporated and the residue purified by radial chromatography with a chromatotron (silica gel, hexane/AcOEt/Et_3N 90 : 9 : 1): 441 mg (55%) of one diastereoisomer of **14ac** and 126 mg (16%) of another diastereoisomer contaminated with impurities. Major diastereoisomer: R_f (hexane/AcOEt/Et_3N 4 : 1 : 0.05)0.49. ^{1}H-NMR (500 MHz, $CDCl_3$): 7.34 (*t*, *J* = 6.99, 2 H_m); 7.29 – 7.21 (*m*, 2 H_o, H_p); 5.75 (*ddt*, *J* = 17.00, 10.00, 7.50, H–C(8)); 5.18 (*m*, 2 H–C(3″), H–C(3)); 4.20 (*dt*, *J* = 10.00, 4.00, H–C(1′)); 3.90 (*ddd*, *J* = 9.50, 7.00, 2.50, H–C(4)); 2.64 (*dd*, *J* = 14.50, 7.50, 1 H–C(1″)); 2.55 (*dd*, *J* = 9.00, 7.50, 1 H–C(1″)); 2.54 – 2.42 (*m*, H–C(2′)); 2.26 (*d*, *J* = 9.5, 1 H–C(6′)); 2.06 (*dd*, *J* = 13.00, 6.50, 1 H–C(5)); 1.85 (br. *s*, 1 H–C(5′)); 1.82 (br. *s*, 1 H–C(3′)); 1.74 (*d*, *J* = 12.50, 1 H–C(4′)); 1.62 – 1.35 (*m*, 1 H–C(3′), 1 H–C(5), 1 H–C(5′), 1 H–C(6′), (Me$_2$C*H*$_3$Si); 1.31 (*m*, 1 H–C(4′)); 1.01 (*d*, 18 H, (*Me*$_2$CH)$_3$Si). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 144.48; 131.51; 128.40; 127.38; 126.13; 119.72; 113.91; 105.47 (C(1)); 75.07 (C(1′)); 62.24 (C(4)); 52.10 (C(2′)); 42.65 (C(1″)); 36.03 (C(5)); 35.55 (C(6′)); 34.77 (C(5′)); 25.82 (C(4′)); 25.05 (C(3′)); 17.91 (*Me*$_2$CH)$_3$Si); 17.86 (*Me*$_2$CH)$_3$Si); 11.96 ((Me$_2$*C*H)$_3$Si).

*(1*R**,6*S**,7*S**,8*S**)-1-{[(1′*R**,2′*S**)-2′-Phenylcyclohexyl]oxy}-8-[(triisopropylsilyl)oxy]-2,4-dioxa-3-azatricyclo[4.3.1.0$^{3.7}$]decane* (**15ac**). A soln. of the major diastereoisomer of **14ac** (220 mg, 0.45 mmol) in toluene

(10 ml) was added dropwise *via* syringe pump within 8 h to a flask (100 ml) containing vacuum-dried (0.1 Torr, 1 h) $NaHCO_3$ (265 mg, 3.16 mmol, 7 equiv.) in xylenes (40 ml) under reflux. After complete addition, the mixture was stirred for an additional 10 h, then cooled to r.t., filtered through a cotton plug into a flask (250 ml) containing $NaHCO_3$ (50 mg), and then evaporated. The residue was purified by FC (basic alumina (act. III), hexane/^{t}BuOMe 4 : 1; all fraction tubes contained *ca.* 50 mg of $NaHCO_3$): 107 mg (49%) of **15ac**. Colorless foam. R_f (hexane/AcOEt 4 : 1, basic alumina) 0.78. ^{1}H-NMR (500 MHz, (D_8)toluene): 7.30 – 7.10 (*m*, 5 arom. H); 4.45 (*dd*, *J* = 9.00, 4.50, H–C(8)); 3.75 (*m*, CH_2(5), H–C(1′)); 3.19 (*t*, *J* = 4.00, H–C(8)); 2.68 (*m*, 1 H–C(6′)); 2.58 – 2.52 (*m*, H–C(2′), H–C(6)); 2.05 (*dd*, *J* = 13.50, 9.50, 1 H–C(10)); 1.86 (*m*, 1 H–C(3′)); 1.81 – 1.55 (*m*, 1 H–C(9), 1 H–C(3′), 1 H–C(4′), 1 H–C(5′), 1 H–C(8), 1 H–C(6′)); 1.41 – 1.35 (*m*, 1 H–C(5′)); 1.26 – 1.22 (*m*, 1 H–C(4′′)); 1.06 (*d*, *J* = 7.00, (*Me*$_2$CH)$_3$Si); 0.98 (*sept.*, *J* = 7.00, (Me_2C*H*)$_3$Si).

(3R*,4R*,5R*)-5-[(Acetyloxy)methyl]-4-(2,2,2-trifluoroacetamido)-3-(triisopropylsilyloxy)cyclohexanone (**17**). A soln. of **15ac** (160 mg, 0.328 mmol, 1 equiv.) in MeOH (10 ml) was added to K_2CO_3 (5 mg, 0.036 mmol) and *Raney*-Ni (327 mg, 5.58 mmol, 17 equiv.), which had been washed with anh. MeOH (3 × 10 ml) prior to use. The mixture was vigorously stirred under H_2 (1 atm) for 80 min. The *Raney*-Ni was washed with MeOH (10 × 50 ml) and the combined org. phase evaporated. The amino ketone **16** was then dissolved in Ac_2O (10 ml) and pyridine (15 ml), and the soln. was stirred at r.t. for 14 h. AcOEt (100 ml) was added, the mixture washed with sat. aq. $NaHCO_3$ soln. (4 × 30 ml) and brine (30 ml), the org. phase dried (Na_2SO_4) and evaporated, and the residue purified by FC (hexane/AcOEt 70 : 30): 24 mg (15%) of **17**. ^{1}H-NMR ($CDCl_3$, 500 MHz): 6.14 (*d*, *J* = 7.93, NH); 4.45 (*q*, *J* = 3.65, H–C(3)); 4.33 (*dt*, *J* = 7.93, 3.90, H–(4)); 4.09 (*dd*, *J* = 7.29, 11.80, 1 H, OCH_2–C(5)); 3.99 (*dd*, *J* = 11.15, 6.00, 1 H, OCH_2–C(5)); 2.99 – 2.91 (*m*, H–C(5)); 2.60 (*dd*, *J* = 14.79, 3.22, H_e–C(6)); 2.45 (*d*, *J* = 14.79, H_a–C(6)); 2.39 (*dd*, *J* = 15.01, 4.72, H_e–C(4)); 2.18 (*dd*, *J* = 15.01, 13.29, H_a–C(4)); 2.04 (*s*, 1 COMe)); 2.03 (*s*, 1 COMe); 1.08 – 1.02 (*m*, (*Me*$_2$C*H*)$_3$Si). ^{13}C-NMR (125.7 MHz, $CDCl_3$): 207.21 (C(1)); 170.86 (*C*OMe); 170.35 (*C*OMe); 70.80 (C(3)); 64.69 (O*C*H$_2$–C(5)); 50.27 (C(4)); 45.21 (C(6)); 39.45 (C(2)); 33.64 (C(5)); 23.33 (CO*Me*); 20.76 (CO*Me*); 17.88 ((*Me*$_2$CH)$_3$Si); 11.98 ((Me_2*C*H)$_3$Si).

(4S*,6R*)-4-(Benzoyloxy)-5,6-dihydro-6-{[(1′R*,2′S*)-2′-phenylcyclohexyl]oxy}-6-(prop-2′′-enyl)-4H-1,2-oxazine 2-Oxide (**14aa**). $SnCl_4$ (0.19 ml, 1.6 mmol, 2.0 equiv.) was added dropwise to a cold (– 78°) soln. of **10a** (154.6 mg, 0.80 mmol; dried at 0.1 Torr for 1.5 h) in toluene (20 ml), and the mixture was stirred for 5 min. A cold (– 78°) soln. of (±)-**13a** (291 mg, 1.20 mmol, 1.5 equiv.) in toluene (5 ml) was added *via* cannula. The yellow-brown mixture was stirred for 25 min at – 78° and then quenched at – 78° with 1M Et_3N in MeOH (7.5 ml, 7.5 mmol, 9.4 equiv.). The mixture was stirred for 5 – 10 min and then poured into ^{t}BuOMe (200 ml) and sat. aq. $NaHCO_3$ soln. (50 ml). The aq. phase was extracted with ^{t}BuOMe (2 × 75 ml). The combined org. phase was washed with brine (2 × 75 ml), dried (Na_2SO_4), filtered through a plug of *Celite*, and evaporated. Purification of the residue by radial chromatography (silica gel, hexane/AcOEt/Et_3N 90 : 9 : 1) afforded 203 mg (58%) and 69.3 mg (20%) of two diastereomeric nitronates **14aa1** and **14aa2**, resp., both contaminated with chiral auxiliary (±)-**11a**.

Data of **14aa1**: ^{1}H-NMR (500 MHz, $CDCl_3$): 7.96 (*d*, *J* = 8.06, 2 H_o(Bz)); 7.59 (*t*, *J* = 7.45, H_p(Ph)); 7.45 (*t*, *J* = 8.06, 2 H_m(Bz)); 7.38 (*t*, *J* = 7.45, 2 H_m(Ph)); 7.32 (*d*, *J* = 6.96, 2 H_o(Ph)); 7.25 (*t*, *J* = 7.32, H_p(Bz)); 5.79 (*ddt*, *J* = 17.02, 10.25, 7.08, H–C(2′′)); 5.19 (*dd*, *J* = 10.25, 1.01, 1 H–C(3′′)); 5.17 (*dd*, *J* = 17.02, 1.01, 1 H–C(3′′)); 5.16 (*d*, *J* = 2.56, H–C(3)); 5.11 (*ddd*, *J* = 10.13, 4.76, 2.56, H–C(4)); 4.19 (*dt*, *J* = 10.25, 4.00, H–C(1′)); 2.70 – 2.57 (*m*, CH_2(1′′), H–C(2′)); 2.39 (*dd*, *J* = 13.06, 7.32, 1 H); 2.28 (*dd*, *J* = 12.21, 3.30, 1 H); 1.93 – 1.84 (*m*, 2 H); 1.82 – 1.75 (*m*, 1 H); 1.73 – 1.63 (*m*, 2 H); 1.60 – 1.28 (*m*, 3 H).

Data of **14aa2**: ^{1}H-NMR (500 MHz, $CDCl_3$): 8.03 (*dd*, *J* = 8.42, 1.34, 2 H_o(Bz)); 7.62 (*dt*, *J* = 7.45, 1.34, 1 H); 7.47 (*t*, *J* = 7.75, 2 H); 7.40 – 7.22 (*m*, 7 H); 6.51 (*dd*, *J* = 2.81, 0.98, H–C(3)); 5.96 (*ddd*, *J* = 10.13, 7.32, 2.81, H–C(4)); 5.25 – 5.14 (*m*, H–C(2′′)); 4.95 (*d*, *J* = 10.13, 1 H–C(3′′)); 4.73 (*d*, *J* = 17.09, 1 H–C(3′′)); 3.87 (*dt*, *J* = 10.01, 4.64, H–C(1′)); 2.72 – 1.31 (*m*, 12 H).

4-(Benzoyloxy)-5,6-dihydro-6-{[(1′S,2′R)-2′-(1-methyl-1-phenylethyl)cyclohexyl]oxy}-6-(prop-2′′enyl)-4H-1,2-oxazine 2-Oxide (**14ba**). $SnCl_4$ (0.09 ml, 0.80 mmol, 2.0 equiv.) was added dropwise to a cold (– 74°) soln. of **10a** (77.26 mg, 0.40 mmol, 1 equiv.) in toluene (10 ml), and the mixture was stirred for 5 min. A cold (– 74°) soln. of (+)-**13b** (341 mg, 1.2 mmol, 3 equiv.) in toluene (2.5 ml) was added *via* cannula. The yellow-brown mixture was stirred for 3 h at – 74° and then quenched at – 74° with 1M Et_3N in MeOH (4 ml, 4 mmol, 10 equiv.). The mixture was stirred for 5 – 10 min and then poured into Et_2O (200 ml) and sat. aq. $NaHCO_3$ solution (50 ml). The aq. phase was extracted with Et_2O (3 × 75 ml), the combined org. phase washed with brine (75 ml), dried (Na_2SO_4), filtered through a plug of *Celite*, and evaporated. ^{1}H-NMR: diastereoisomer ratio 9 : 2. Purification of the residue by FC (silica gel, hexane/AcOEt/Et_3N 83.3 : 16 : 0.6) afforded 45 mg (24%) of **14ba1** and 38 mg of another diastereoisomer **14ba2** contaminated with an unidentified by-product. **14ba1**: ^{1}H-NMR (500 MHz, $CDCl_3$): 8.01 (*dd*, *J* = 8.30, 1.22, 2 H_o(Bz)); 7.61 (*tt*, *J* = 7.57, 1.22, H_p(Bz)); 7.47 (*t*, *J* = 7.81, 2 H_m(Bz));

7.35 (*dd*, $J = 8.55$, 1.46, 2 H_m(Ph)); 7.29 (*t*, $J = 8.30$, 2 H_o(Ph)); 7.04 (*t*, $J = 7.08$, H_p(Ph)); 6.43 (*d*, $J = 2.44$, H–C(3)); 5.75 (*dddd*, $J = 16.80$, 10.40, 9.20, 5.60, 1 H–C(2″)); 5.21 (*d*, $J = 9.77$, 1 H–C(3″)); 5.17 (*d*, $J = 17.09$, 1 H–C(3″)); 5.03 (*ddd*, $J = 10.50$, 7.81, 2.93, H–C(4)); 3.88 (*dt*, $J = 9.28$, 3.66, H–C(1′)); 2.78 (*dd*, $J = 14.16$, 5.37, 1 H); 2.41 (*dd*, $J = 11.94$, 3.42, 1 H); 2.18 (*dd*, $J = 14.16$, 3.30, 1 H); 1.85 (*d*, $J = 10.01$, 1 H); 1.83 (*d*, $J = 10.01$, 1 H); 1.76 – 1.68 (*m*, 3 H); 1.38 (*s*, 1 Me); 1.36 – 1.14 (*m*, 7 H).

*8-(Benzoyloxy)-1-{[(1′*S*,2′*R*)-2′-(1-methyl-1-phenylethyl)cyclohexyl]oxy}-2,4-dioxa-3-azatricyclo[4.3.1.*$0^{3.7}$*]-decane* (**15ba1**). A soln. of nitronate **14ba1** (45 mg, 0.094 mmol, 1 equiv.) in xylenes (5 ml) was added dropwise *via* syringe pump within 1 h to NaHCO$_3$ (55.4 mg, 0.66 mmol, 7 equiv.) and 40 ml of xylenes under reflux. After complete addition, the mixture was stirred for an additional 1 h and then cooled to r.t. The mixture was filtered through a cotton plug into a flask containing 50 mg of NaHCO$_3$ and was evaporated. The residue was purified by FC (basic alumina (act. III), hexane/^{t}BuOMe 1:1; all fraction tubes contained *ca.* 50 mg of NaHCO$_3$): 6.9 mg (15%) of **15ba1**. White foam. ^{1}H-NMR (500 MHz, (D$_8$)toluene): 7.99 (*d*, $J = 8.42$, 2 H_o(Bz)); 7.31 (*t*, $J = 8.42$, 1 H_p(Bz)); 7.20 – 7.16 (*m*, 2 H_m(Bz)); 7.12 – 7.01 (*m*, 5 H); 5.59 (br. *d*, $J = 11.60$, H–C(8)); 3.72 (*dt*, $J = 9.40$, 3.91, H–C(1′)); 3.59 (*d*, $J = 6.84$, H–C(5)); 3.54 (*t*, $J = 5.75$, 1 H–C(5)); 3.13 (*t*, $J = 3.91$, H–C(7)); 2.22 (*ddd*, $J = 13.67$, 10.01, 3.54, 1 H); 2.16 (*dt*, $J = 9.64$, 4.3, 1 H); 2.02 (br. *d*, $J = 13.18$, 1 H); 1.92 (*ddd*, $J = 11.96$, 8.67, 3.30, 1 H); 1.71 (*dd*, $J = 13.31$, 9.89, 1 H); 1.52 (*s*, 1 Me); 1.45 – 1.30 (*m*, 4 H); 1.28 (*s*, 1 Me); 1.27 – 1.22 (*m*, 1 H); 1.06 – 0.86 (*m*, 2 H).

REFERENCES

[1] W. Oppolzer, in 'Comprehensive Organic Synthesis', Vol. 5, Ed. L. A. Paquette, Pergamon, Oxford, 1991, p. 315; H. Waldmann, *Synthesis* **1994**, 535; H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007; D. A. Evans, J. A. Johnson, in 'Comprehensive Asymmetric Catalysis', Vol. III, Eds. E. N. Jacobsen, A. Pfaltz, and H. Yamamoto, Springer Verlag, Heidelberg, 1999, p. 1177; E. J. Corey, *Angew. Chem., Int. Ed.* **2002**, *40*, 1651; K. C. Nicolaou, *Angew. Chem., Int. Ed.* **2002**, *40*, 1650.

[2] S. E. Denmark, M. S. Dappen, C. J. Cramer, *J. Am. Chem. Soc.* **1986**, *108*, 1306; S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137.

[3] a) S. E. Denmark, B. S. Kesler, Y.-C. Moon, *J. Org. Chem.* **1992**, *57*, 4912; b) S. E. Denmark, C. J. Cramer, J. Sternberg, *Helv. Chim. Acta* **1986**, *69*, 1971; c) S. E. Denmark, Y.-C. Moon, C. J. Cramer, M. S. Dappen, C. B. W. Senanayake, *Tetrahedron* **1990**, *46*, 7383.

[4] S. E. Denmark, C.-Y. Moon, C. B. W. Senanayake, *J. Am. Chem. Soc.* **1990**, *112*, 311; S. E. Denmark, C. B. W. Senanayake, *J. Org. Chem.* **1993**, *58*, 1853.

[5] S. E. Denmark, J. J. Cottell, in 'The Chemistry of Heterocyclic Compounds: Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products', Eds: A. Padwa and W. H. Pearson, Wiley-Interscience, New York, 2002; p. 83; V. F. Rudchenko, *Chem. Rev.* **1993**, *93*, 725; E. Breuer, H. G. Aurich, A. Nielsen, 'Nitrones, Nitronates and Nitroxides', Wiley, New York, 1990, p. 105.

[6] V. A. Tartakovskii, I. E. Chlenov, S. S. Smagin, S. S. Novikov, *Izv. Akad. Nuak SSSR, Ser. Khim. (Engl. Transl.)* **1964**, 583; V. A. Tartakovskii, *Izv. Akad. Nuak SSSR, Ser. Khim (Engl. Transl.)* **1984**, 5147.

[7] K. B. G. Torsell, 'Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis, VCH, New York, 1988; Chapt. 4.

[8] R. Grée, F. Tonnard, R. Carrié, *Bull. Soc. Chim. Fr.* **1975**, 1325; R. Grée, F. Tonnard, R. Carrié, *Tetrahedron* **1976**, *32*, 675; R. Grée, R. Carrié, *J. Am. Chem. Soc.* **1977**, *99*, 6667; R. Grée, R. Carrié, *J. Heterocycl. Chem.* **1977**, *14*, 965.

[9] E. W. Colvin, D. Seebach, *J. Chem. Soc., Chem. Commun* **1978**, 689; D. Seebach, M. A. Brook, *Helv. Chim. Acta* **1985**, *68*, 319; M. A. Brook, D. Seebach, *Can. J. Chem.* **1987**, *65*, 836; D. Seebach, I. M. Lyapkalo, R. Dahinden, *Helv. Chim. Acta* **1999**, *82*, 1829.

[10] P. Righi, E. Marotta, A. Landuzzi, G. Rosini, *J. Am. Chem. Soc.* **1996**, *118*, 9446; P. Righi, E. Marotta, G. Rosini, *Chem.–Eur. J.* **1998**, *4*, 2501; M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, M. A. Silva, *Chem. Commun.* **1998**, 459.

[11] S. E. Denmark, A. Thorarensen, D. S. Middleton, *J. Am. Chem. Soc.* **1996**, *118*, 8266; S. E. Denmark, E. A. Martinborough, *J. Am. Chem. Soc.* **1999**, *121*, 3046; S. E. Denmark, A. R. Hurd, *J. Org. Chem.* **2000**, *65*, 2875; S. E. Denmark, J. J. Cottell, *J. Org. Chem.* **2001**, *66*, 4276.

[12] S. E. Denmark, D. S. Middleton, *J. Org. Chem.* **1998**, *63*, 1604.

[13] a) S. E. Denmark, V. Guagnano, J. A. Dixon, A. Stolle, *J. Org. Chem.* **1997**, *62*, 4610; b) E. S. Denmark, J. A. Dixon, *J. Org. Chem.* **1998**, *63*, 6167.

[14] S. E. Denmark, B. S. Kesler, Y.-C. Moon, *J. Org. Chem.* **1992**, *57*, 4912.

[15] P. Eilbracht, M. Acker, W. Trotzauer, *Chem. Ber.* **1983**, *116*, 238.

[16] R. Schauer, *Adv. Carbohydr. Chem. Biochem.* **1982**, *40*, 131; T. Suami, in 'Carbohydrates Synthetic Methods and Applications in Medicinal Chemistry', Eds. H. Ogura, A. Hasegawa, and T. Suami, VCH Publishers, New York, 1992; Chapt. 9.

[17] G. E. McCaslan, S. Furuta, L. J. Durham, *J. Org. Chem.* **1968**, *33*, 2841.

[18] S. Horii, T. Iwasa, E. Mizuta, Y. Kameda, *J. Antibiot.* **1971**, *24*, 59.

[19] Y. Kameda, S. Horii, *J. Chem. Soc., Chem. Commun.* **1972**, 746.

[20] S. Ogawa, T. Taki, A. Isaka, *Carbohydr. Res.* **1989**, *191*, 154; G. Fronza, C. Fuganti, G. Pedrocchi-Fantoni, *J. Carbohydr. Chem.* **1989**, *8*, 85.

[21] H. Baumann, A. O. Tzianabos, J. R. Brisson, D. L. Kasper, H. Jennings, *J. Biochem.* **1992**, *31*, 4081; A. O. Tzianabos, A. B. Onderdonk, B. Rosner, R. L. Cisneros, D. L. Kasper, *Science (Washington, D.C.),* **1993**, *262*, 416; D. L. Kasper, A. Weintraub, A. A. Lindberg, J. Lönngren, *J. Bacteriol.* **1983**, *53*, 991.

[22] a) S. E. Denmark, M. A. Schnute, C. B. Senanayake, *J. Org. Chem.* **1993**, *58*, 1859; b) S. E. Denmark, M. J. Seierstad, *J. Org. Chem.* **1999**, *64*, 1610.

[23] S. E. Denmark, A. Thorarensen, *J. Org. Chem.* **1994**, *59*, 5672.

[24] S. E. Denmark, A. Thorarensen, *J. Org. Chem.* **1996**, *61*, 6727.

[25] H. Sörensen, A. E. Greene, *Tetrahedron Lett.* **1990**, *31*, 7597; N. A. Porter, P. Dussault, R. A. Breyer, J. Kaplan, J. Morelli, *J. Chem. Res. Toxicol.* **1990**, *3*, 236.

[26] A. E. Hill, W. A. Boyd, H. Desai, A. Darki, L. Bivens, *J. Organomet. Chem.* **1996**, *514*, 1; J. R. Jennings, *J. Organomet. Chem.* **1987**, *325*, 25.

[27] S. E. Denmark, A. R. Hurd, H. J. Sacha, *J. Org. Chem.* **1997**, *62*, 1668; S. E. Denmark, J. J. Cottell, *J. Org. Chem.* **2001**, *66*, 4276.

[28] K. K. Babievskii, V. M. Belikov, N. A. Tikhonov, *Bull. Acad. Sci. USSR (Engl. Transl.)* **1970**, 1161.

[29] H. C. Brown, S. Krishnamurthy, *J. Am. Chem. Soc.* **1976**, *98*, 3383; J. D. Brown, M. A. Foley, L. D. Comins, *J. Am. Chem. Soc.* **1988**, *110*, 7445.

[30] O. Mitsunobu, J. Kumura, Y. Fujisawa, *Bull. Chem. Soc. Jpn.* **1972**, *45*, 245; S. Shimokawa, J. Kimura, O. Mitsunobu, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3357; Y. Torisawa, H. Okabe, S. Ikegami, *Chem. Lett.* **1984**, 1555.

[31] S. E. Denmark, J. A. Dixon, *J. Org. Chem.* **1998**, *63*, 6178.

[32] R. J. Loncharich, T. R. Schwartz, K. N. Houk, *J. Am. Chem. Soc.* **1987**, *109*, 14; D. M. Birney, K. N. Houk, *J. Am. Chem. Soc.* **1990**, *112*, 4127; see also S. Yamabe, T. Dai, T. Minato, *J. Am. Chem. Soc.* **1995**, *117*, 10994.

[33] S. D. Kahn, W. J. Hehre, *J. Am. Chem. Soc.* **1987**, *109*, 663.

[34] J. Liu, S. Niwayama, Y. You, K. N. Houk, *J. Org. Chem.* **1998**, *63*, 1064.

[35] F. Jaisli, D. Sternbach, M. Shibuya, A. Eschenmoser, *Angew. Chem.* **1979**, *91*, 673.

[36] H. Gilman, *J. Am. Chem. Soc.* **1944**, *66*, 1515.

[37] S. B. King, K. B. Sharpless, *Tetrahedron Lett.* **1994**, *35*, 5611.

[38] H. Sacha, Postdoctoral Report, University of Illinois, 1995.

Received June 10, 2002