

distances to other hydrogens being considerably longer than the sum of the van der Waals radii. As a result, the tetramethylammonium cation shows little distortion and is essentially tetrahedral.

The bond distances and angles found for the $\text{H}_2\text{N}-\text{C}(\text{C}-\text{H}_3)=\text{CH}-\text{CN}$ part of the adduct agree well with those predicted from the known structures of the similar molecules, CH_3CN , $\text{NC}-\text{CN}$, $\text{CH}_2=\text{CH}_2$, CH_3CHO , H_2NCHO , and CH_3COCN .³⁶

The infrared and Raman spectra of the $\text{N}(\text{CH}_3)_4\text{F}-\text{H}_2\text{NC}(\text{C}-\text{H}_3)\text{CHCN}$ adduct are given in Figure 5. The sizes of the molecules involved, the low crystal symmetry, and the large unit cell make detailed assignments difficult. However, the following vibrations can be readily assigned: $\nu(\text{C}\equiv\text{N})$, 2173; $\nu(\text{C}=\text{C})$, 1582; $\nu_{\text{as}}(\text{NC}_4)$, 958, 942; $\nu_{\text{s}}(\text{NC}_4)$, 758; $\delta_{\text{as}}(\text{NC}_4)$, 469 cm^{-1} . The intense and narrow $\text{C}\equiv\text{N}$ stretching vibration at 2173–2180 cm^{-1} is very useful for checking for the presence of the nitrile adduct in $\text{N}(\text{CH}_3)_4\text{F}$ that has been handled in CH_3CN .

Conclusion

Contrary to the general belief that $\text{N}(\text{CH}_3)_4\text{F}$ cannot be obtained anhydrous and that removal of water results in decomposition,³ it was shown in this study that $\text{N}(\text{CH}_3)_4\text{F}$ with a water content of ≤ 0.06 wt % can be prepared with relative ease. This synthesis of anhydrous $\text{N}(\text{CH}_3)_4\text{F}$ provides a relatively cheap source of highly soluble fluoride containing a chemically very inert

counteranion. Thus, anhydrous $\text{N}(\text{CH}_3)_4\text{F}$ might become an attractive substitute for the more expensive and less inert fluoride ion source, $(\text{TAS})\text{F}$, $[(\text{CH}_3)_2\text{N}]_3\text{S}^+\text{F}_2\text{Si}(\text{CH}_3)_3^-$. A characterization of anhydrous $\text{N}(\text{CH}_3)_4\text{F}$ also revealed that the properties of the "naked" fluoride ion in solution are poorly understood and that some of the properties previously attributed to the fluoride ion are due to other anions, such as HF_2^- . Furthermore, it was shown that certain solvents, such as CH_3CN or partially chlorinated hydrocarbons, which in the past have been preferred for fluoride ion reactions,^{37,38} undergo chemical reactions with F^- . Finally, a novel 1:1 adduct of $\text{N}(\text{CH}_3)_4\text{F}$ with a dimer of CH_3CN was isolated from CH_3CN solution, and its crystal structure was determined.

Acknowledgment. We thank Dr. Carl Schack for helpful discussions and the preparation of a sample of $\text{SiF}(\text{CH}_3)_3$. The work at Rocketdyne was financially supported by the Air Force Astronautics Laboratory and the Army Research Office.

Supplementary Material Available: Tables A–G listing final atomic coordinates, hydrogen atom positions, N–H and C–H bond distances, hydrogen bond distances, final temperature factors, and mode descriptions for the $\text{N}(\text{CH}_3)_4^+$ cation, respectively (6 pages); observed and calculated structure factors (5 pages). Ordering information is given on any current masthead page.

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[3 + 3]-Carbocyclizations of Nitroallylic Esters and Enamines with Stereoselective Formation of up to Six New Stereogenic Centers

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Abstract: Enamines (**1**) from open-chain and cyclic ketones react with 2-nitro-2-propen-1-yl acetates and pivalates (nitroallylic esters **2**) to give, after aqueous workup, 4-nitrocyclohexanones (Schemes I–IV; products **3–18**). Monocyclic as well as bicyclic [4.3.1], [3.3.1], and [3.2.1] systems may be prepared. With appropriate substitution of the educt structures, up to five stereogenic centers are formed in this [3 + 3]-carbocyclization. One diastereoisomer usually prevails (60% to >95% selectivity). With enamines from (*S*)-2-(methoxymethyl)pyrrolidine (prolinol methyl ether) and cyclic ketones, enantiomerically pure compounds are obtained (see **8** and **15–18** in Scheme VI). The configuration and conformation of the products are assigned by extensive use of NMR spectroscopy. An additional stereogenic center may be formed by stereoselective borohydride reduction of the keto group in the nitrocyclohexanones, and Baeyer–Villiger oxidation introduces another functional group (see the hydroxydimethylnitrocyclooctanecarboxylic acid derivatives **23** in Scheme VII). The mechanism of the complex sequence of reactions, leading to the observed products, is discussed (Schemes VIII, X, XI). The structures of the products and intermediates, which can be trapped under certain conditions (Scheme IX), as well as previous investigations of single steps of the in situ reaction sequence involved in the carbocyclization are used to arrive at a tentative proposal for the steric course of these steps: (i) intermolecular coupling of the trigonal centers of enamine and nitroolefin with preferred relative topology like, (ii) intramolecular coupling of the trigonal centers in an intermediate olefinic enamine, (iii) protonation of a nitronate anion moiety, and (iv) protonation of an enamine (in the case of the monocyclic products).

(A) Introduction

Due to their special reactivity³ and ease of functional-group interchange,⁴ aliphatic nitrocompounds have acquired an important

position as intermediates in organic synthesis. Among the most commonly encountered reactions are the nitroaldol addition and condensation⁵ and the Michael addition of either nitroalkanes to enones or of nucleophiles to nitroolefins.⁶ Also Diels–Alder

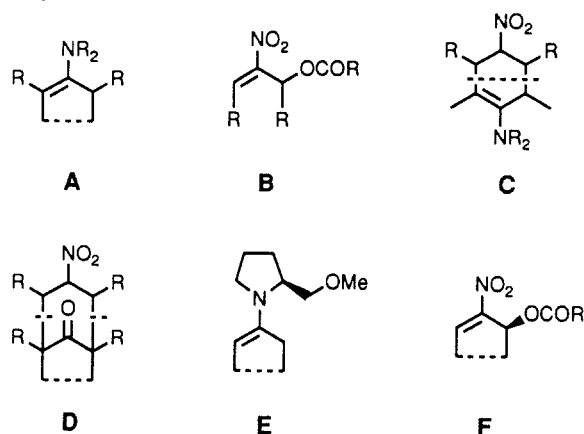
(1) Most of the results described here are taken from the dissertation of M. Missbach, ETH-Nr. 9152, Eidgenössische Technische Hochschule, 1990.

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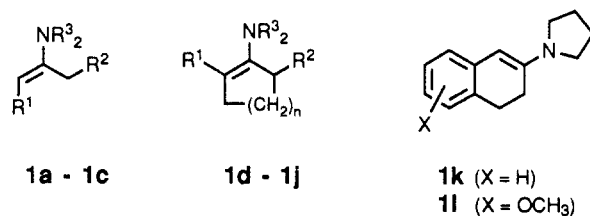
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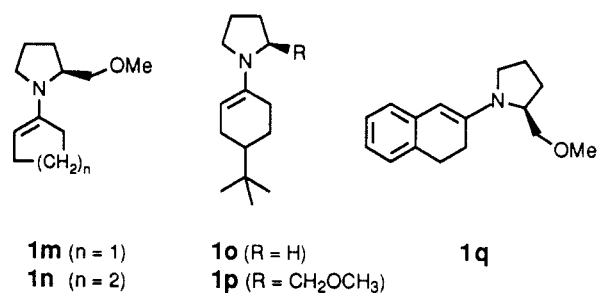
Scheme I. [3 + 3]-Carbocyclizations with Enamines and Nitroallyl Carboxylates

reactions involving nitroolefins (see refs 16,17) and the use of nitroallylic esters as multiple-coupling reagents⁷ have to be mentioned. In such reactions, carbo- and heterocyclic⁸ products may result from acyclic precursors. Furthermore, the nitro group delivers a pattern of substitution and/or functionality not readily accessible by other means. Thus, the regioselectivity of the Diels-Alder addition can be reversed by employing a nitro-substituted component,⁹ and Michael additions with formation of 1,4-dicarbonyl functionality lead to cyclohexanes different from those obtained via Robinson annulations.^{3,10} In the list of references¹¹⁻¹⁸ we have collected those carbocyclizations known to use in which the nitro group is involved in *both* carbon-carbon bond-forming steps on the way leading from two precursor molecules to a ring.

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Scheme II. The Enamines

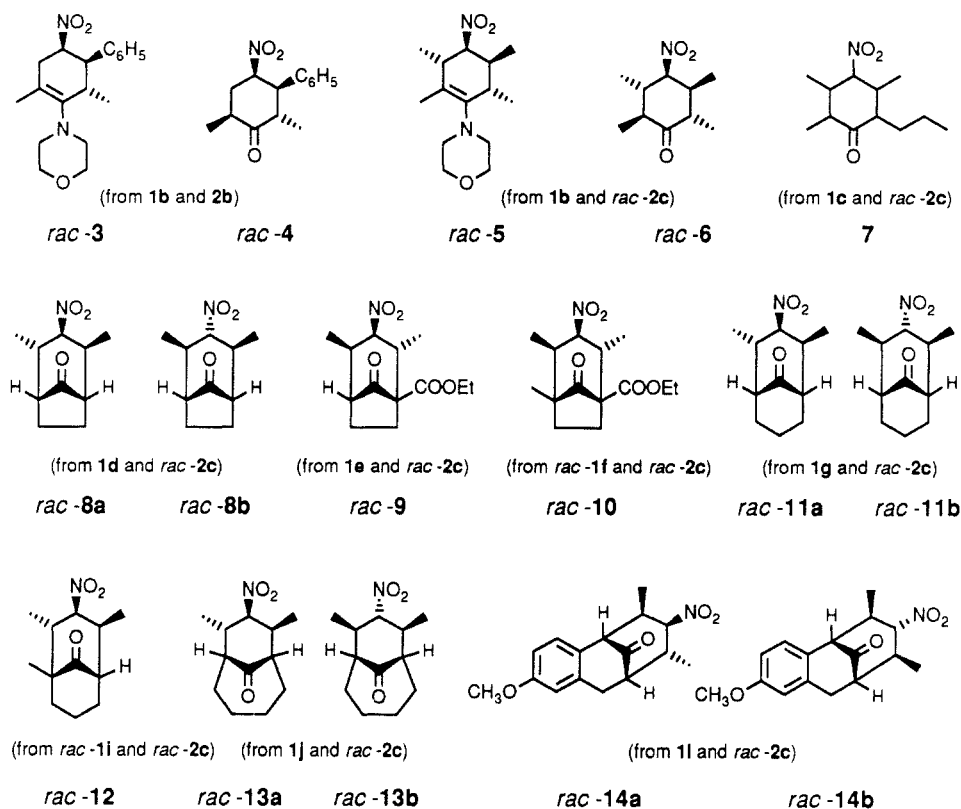
	R ¹	R ²	R ₂ ³	n
1a	CH ₃	CH ₃	-(CH ₂) ₄ -	-
1b	CH ₃	CH ₃	-(CH ₂) ₂ -O-(CH ₂) ₂ -	-
1c	CH ₃	C ₃ H ₇	-(CH ₂) ₄ -	-
1d	H	H	-(CH ₂) ₄ -	1
1e	COOC ₂ H ₅	H	-(CH ₂) ₄ -	1
<i>rac</i> - 1f	COOC ₂ H ₅	CH ₃	-(CH ₂) ₄ -	1
1g	H	H	-(CH ₂) ₄ -	2
1h	H	H	-(CH ₂) ₂ -O-(CH ₂) ₂ -	2
<i>rac</i> - 1i	H	CH ₃	-(CH ₂) ₄ -	2
1j	H	H	-(CH ₂) ₄ -	3

**Scheme III.** The Nitroallylic Esters

	R ¹	R ²	R ³
E-2a	H	C ₄ H ₉	CO ⁱ C ₄ H ₉
E-2b	H	C ₆ H ₅	CO ⁱ C ₄ H ₉
(E+Z)-rac-2c	CH ₃	CH ₃	COCH ₃
E-(S)(+)-2c	CH ₃	CH ₃	COCH ₃
E-(R)(-)-2d	CH ₃	CH ₃	CO ⁱ C ₄ H ₉
(S)(-)-2e		-(CH ₂) ₃ -	COCH ₃
(R)(+)-2f		-(CH ₂) ₃ -	CO ⁱ C ₄ H ₉
(R)(+)-2g		-(CH ₂) ₃ -	CH ₂ OCH ₃

Except for one special case¹⁹ we have not found [3 + 3]-carbocyclizations with nitrocompounds. Indeed, this type of cyclization has seldom been realized at all in the construction of

(19) The formation of six-membered rings from trinitrobenzene precursors has been reported: Strauss, M.; Torres, R. *J. Org. Chem.* **1989**, *54*, 756 and references therein.

Scheme IV. Products of [3 + 3]-Carbocyclizations with Racemic and/or Achiral Components^a

^a The yields of crude (% c) and purified (% p) product and the diastereoselectivities (% d) are as follows: **rac-3** (p 50, d >95); **rac-4** (p 60, d >95); **rac-5** (p 45, d >90); **rac-6** (c 70, d 85); **rac-7** (c 64, 4 diastereoisomers); **rac-8** (p 57, d 80); **rac-9** (c 50, p 22, d 66); **rac-10** (c 18, p 12, d 70); **rac-11** (p 58, d 66); **rac-12** (c 34, p 23, d 87); **rac-13** (p 60, d 58); **rac-14** (c 52, d 55).

six-membered rings. Leading references²⁰⁻²⁸ to the various transformations employed for [3 + 3]-carbocyclization show that most examples involve a double alkylation of cyclic enamines with 1,3-bis-electrophilic (a¹,a³)²⁹ reagents to give a bicyclo[3.3.1]-nonane skeleton.²⁰⁻²⁴ Another, rather well-established²⁵ principle

is the combination of a Michael addition with a Wittig olefination starting from an allylidene phosphorane and an enone. In the newest methods, a π -allyl transition-metal derivative²⁷ is used for the construction of cyclohexane rings from two C₃ components.³⁰

It is the purpose of this paper to describe, in full detail³¹ and with sufficient examples, the scope and limitations of a [3 + 3]-carbocyclization method in which enamines (A) and nitroallyl esters (B) are combined (Scheme I). The method affords monocyclic enamines (C) and mono- or bicyclic ketones (D) with diastereoselective formation of up to six adjacent stereogenic centers (if we include a subsequent reduction of the keto group). Furthermore, the reaction may be rendered enantioselective by employing chiral enamine or nitroolefin components of type E and F.

(B) Preparation of Starting Materials and Standard Reaction Conditions

The enamines **1c-1q** (Scheme II) were prepared from the corresponding ketones and secondary amines under standard conditions (TsOH, benzene, Dean-Stark trap).³² The formation of **1a** was possible under these conditions only if molecular sieves were added.³³ The preparation of **1b** followed Weingarten's TiCl₄ method³⁴ in hexane.

The configuration of these enamines was determined by NMR analysis. Enamines **1a** and **1b** have *E* configuration (>90%).³⁵

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In the enamines **1e**, *rac*-**1f**, **1k**, **1l** and **1q**, the double bond is in the conjugated position, and the enamine from 2-methylcyclohexanone and pyrrolidine has the structure *rac*-**1i** incorporating a trisubstituted double bond.

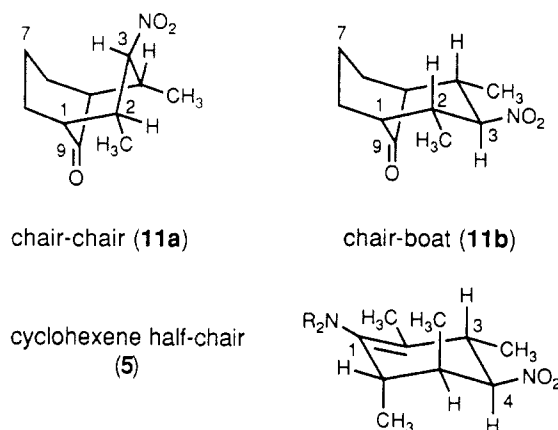
The nitroallylic esters used in this study (Scheme III) were prepared as previously described.^{7,36–38} The double bond configuration in the pivalates **2a**, **2b**, and (–)-**2d** as well as in the acetate (+)-**2c** was found to be *E*, while *rac*-**2c** was obtained as a 2:1 *E/Z* mixture^{39,40} which we were not able to separate. The optically active nitroallylic esters arise from enantioselective saponification of either *meso*-4-acetoxy-3-nitro-2-pentyl acetate or *meso*-3-acetoxy-2-nitrocyclohexyl acetate with pig liver esterase.³⁸ While we have used mainly the C₅-nitroallylic esters in this work, it was shown previously that a large variety of derivatives of this general structure is readily available.³⁶ The reactions were generally carried out in the following way: To a stirred solution of the nitroolefin in tetrahydrofuran or methylene chloride was added at dry ice temperature the enamine as a solution in the same solvent. After allowing to warm to room temperature over night, the reaction mixture was stirred, sometimes after addition of acetonitrile, for up to 4 days. In some cases, the reaction was completed by heating at reflux. The product enamines or iminium salts (see discussion in section G) were hydrolyzed by adding aqueous acid, and the 4-nitrocyclohexanones isolated and purified by flash chromatography⁴¹ and, in most cases, by subsequent crystallization. Nonaqueous workup of some reaction mixtures gave rise to the isolation of nitrocyclohexanone enamines which could then be hydrolyzed in a separate step.

(C) Products from Achiral and/or Racemic Compounds. Configurational Assignment

The isolated racemic products **3–14** and the diastereoselectivities⁴² are collected in Scheme IV. Up to five new stereogenic centers are formed in these [3 + 3]-carbocyclizations. The yields of cyclization vary from 18% to 60%, the pure diastereoisomers **3–6** and **8–14** being isolated in sometimes considerably lower yields due to separation problems. Although up to 16 diastereoisomers could theoretically have been formed, we have usually isolated only two and could detect no more than four. The major diastereoisomer prevailed by as little as 55:45 or as much as >95:5.

The assignment of configuration and conformation⁴³ of the products rests upon NMR analysis. The monocyclic derivatives **3–6** could be assigned from the ¹H NMR spectra; however, for the bicyclic examples both ¹H and ¹³C NMR measurements were necessary. For the sequence of adjacent stereogenic centers bearing methyl, nitro, and methyl groups in a cyclohexane moiety the α-NO₂ hydrogen signal is singularly characteristic; in the major diastereoisomers (**a**) of compounds **5–14** the signal appears as a doublet (10–12 Hz) of doublet (4–7 Hz) between 5.0–5.5 ppm for the bicyclo[3.3.1]nonanes and at 4.5–4.7 ppm for all the others. This leads to the unambiguous assignment of the α-NO₂ hydrogen as being in an axial position of a cyclohexane chair conformation, with an equatorial and an axial coupling partner (Scheme V). The signal of the α-NO₂ hydrogen in the minor isomers (**b**) appears

Scheme V. Some Typical Structures of Nitrocyclohexanones



at ca. 3.9 ppm as an apparent triplet ($J = 8\text{--}12$ Hz), indicating for all three neighboring hydrogens either an axial disposition in a cyclohexane chair or a pseudoaxial disposition in a cyclohexane boat conformation. The assignment of the boat conformation for the bicyclo[3.3.1]nonane system could be deduced by NOE measurements and ¹³C NMR data (see below). By analogy the bicyclo[3.2.1] systems could also be assigned the boat conformation. The large differences in the chemical shift of the α-NO₂ hydrogen signals (0.5–1.5 ppm) facilitates an easy determination of the diastereomeric ratio from the NMR spectra of the crude product mixtures. The configuration at the bridgehead positions of **8**, **11**, and **13**, derived from enamines of symmetrical ketones, follows from above. In products **9**, **10**, **12**, and **14** it was necessary to determine which bridgehead substituent is in a *cis* and which is in a *trans* position with respect to the neighboring methyl group. In compounds **9** and **12**, this can be read from the multiplicities of the α-methyl-CH proton signals; in **10** the assignment was made by analogy with the des-methyl derivative **9**; for **14**, decoupling experiments were done to arrive at the structural assignments shown in Scheme IV.

The assignment of configuration and conformation in the bicyclo[3.3.1] systems of **11**, **12**, and **14** of either the nitrocyclohexanone moieties or the second six-membered rings relies on a host of previous publications.⁴⁴ It is known that the chair-chair conformation of bicyclo[3.3.1]nonanes and -nonanones is slightly more stable^{44a} than the chair-boat conformation in the absence of an endo substituent at C(3) or C(7) (for the numbering see Scheme V). The relative conformation of the two six-membered rings can be deduced from ¹³C NMR spectra. Thus, the ¹³C resonance of C(7) in bicyclo[3.3.1]nonan-9-ones appears at δ ca. 16 ppm in the chair-boat (C(7) in the chair part) and at 21 ppm in the chair-chair conformation.^{44a,b} According to this, our products **11a** and **12** have a chair-chair and **11b** a chair-boat conformation⁴⁵ (see Scheme V). In addition, NOE measurements with compounds **11b** and **14b** demonstrated the spatial proximity of HC(2) and HC(1), HC(6), and HC(7). In the absence of the boat conformation for the substituted cyclohexane ring such interactions would not be detectable. This assignment also explains the upfield shift of the α-NO₂ hydrogen signals in the minor isomers arising from anisotropy resulting from the carbonyl group, which has only relevance to the proton at C(3) in a boat conformation. For the monocyclic⁴⁶ compounds **3–6**, NOE experiments were necessary to determine the configuration and con-

(35) The chemical shift for the hydrogen atom at the double bond is 4.4 ppm for **1a** and 4.14 ppm for **1b** (CDCl₃), which indicates *E* configuration of the double bond. See: Stradi, R.; Pocar, D. *Chim. Ind. (Milan)* **1971**, *53*, 265 and Hickmott, P. W. *Tetrahedron* **1982**, *32*, 3363.

(36) Seebach, D.; Knochel, P. *Nouv. J. Chim.* **1981**, *5*, 75. Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861.

(37) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.

(38) Eberle, M.; Egli, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 1.

(39) The order of acylation and elimination of water has no effect on the *E/Z* ratio because the dehydration of 3-nitropentane-2,4-diol gives the same 2:1 mixture of *E/Z* nitroallylic alcohol.

(40) This difference arises from the nature of the starting materials. The monoacetate leading to (+)-**2c** is derived from the *meso*-nitropentane diol and so elimination gives a single product. In the other case, a mixture of *meso*- and (±)-nitropentane diol is the starting material, this leads to the observed *E/Z* mixture of *rac*-**2c**.

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

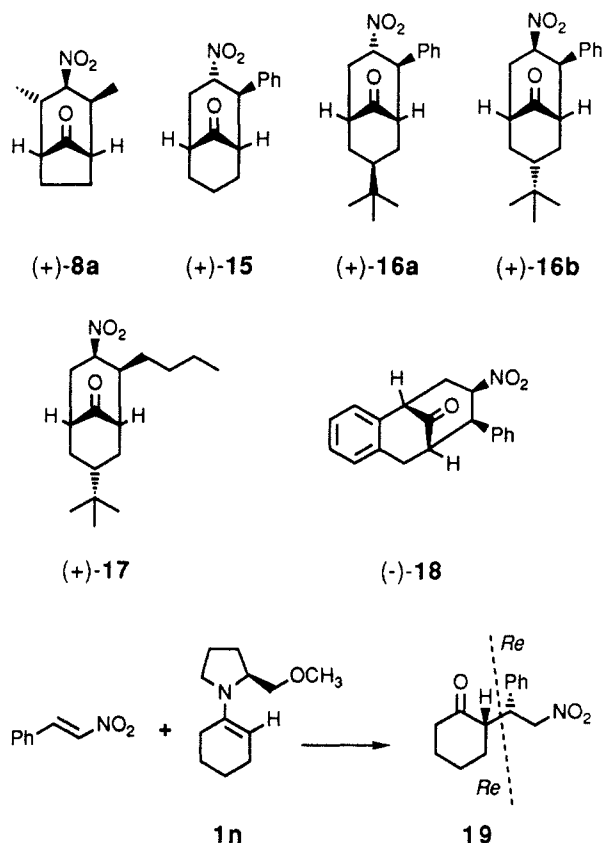
(42) In Scheme IV as well as in the text, the symbol *d* means the percentage amount of the major diastereoisomer (**a**), i.e. $d = ((\mathbf{a})/(\mathbf{a} + \mathbf{b}))100\%$.

(43) The conformation of the bicyclo[4.3.1]decane derivatives **13** was not fully assigned.

(44) (a) Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1977**, *33*, 349. Schneider, H. J.; Anson, W. *Ibid.* **1977**, *33*, 265. (b) Wiseman, J. R.; Krabbenhoft, O. *J. Org. Chem.* **1975**, *40*, 3222. (c) Peters, J. A.; van der Toorn, J. M.; van Bekkum, H. *Tetrahedron* **1974**, *30*, 633. Camps, P.; Castane, J.; Feliz, M.; Jaime, C.; Minguillon, C. *Chem. Ber.* **1989**, *122*, 1313.

(45) For details see Experimental Section.

(46) The two isomers **6** and 2-*epi*-**6** (ratio 6:1 to 8:1) could not be separated by flash chromatography or recrystallization from pentane at low temperature. The major isomer **6** has been assigned the configuration shown in Scheme IV. It was not possible to separate cleanly the four diastereoisomers of **7**, so we have been unable to determine the configuration of these cyclization products.

Scheme VI. Enantiomerically Pure Products from Enamines **1m**, **1n**, **1p**, and **1q**

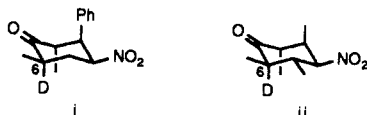
formation of all substituents at the cyclohexene (3 and 5) and cyclohexanone ring (4 and 6).⁴⁵ In the enamine,⁴⁷ the two vicinal carbon substituents (i.e. phenyl and methyl in 3 and two methyl groups in 5) are in a quasi-diaxial position, the nitro group in a quasi-equatorial position on a cyclohexene half chair. According to our NMR analysis and deuterolysis experiments,⁴⁸ the enamine hydrolysis is stereoselective (3, 4, 95% d and 5, 6 75% d), with the methyl group on the newly generated stereogenic center equatorial, consistent with preferred axial protonation of the double bond (see discussion in section H). The fact that only monodeuterio derivatives are produced⁴⁸ from the enamines and DCl indicates that neither epimerizations nor conformational changes occur during acidic aqueous workup of the reactions.

(D) Nitrocyclohexanones from (*R*)- or (*S*)-Nitroallylic Esters

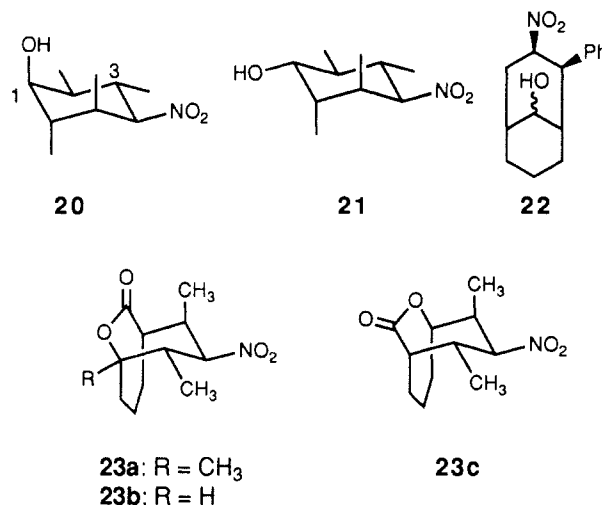
The results of the experiments aiming toward an enantioselective version of our [3 + 3]-carbocyclization, using enantiomerically pure nitroolefin components, were utterly disappointing. Thus, the enantiomerically pure^{38,49} nitroallylic acetate (+)-**2c** and the

(47) The reaction with **1a** instead of **1b** led to an intermediate cyclic enamine which could not be isolated by flash chromatography. Direct hydrolysis gave an isomeric mixture of **6** and 2-*epi*-**6** in a 2:1 ratio and a small amount of the diastereoisomer with an axial nitro group (4-*epi*-**6**); for numbering, see Scheme V.

(48) Deuterolysis with DCl (of **3** in CD₃OD and of **5** in D₂O) gave selectively the monodeuterio derivatives i (>95% D) and ii (>90% D)



(49) The value of the maximum rotation (+70.6°) reported for *S*-(+)-**2c** in our previous paper (see ref 38) has to be corrected. We noticed that the liquid product (+)-**2c** slowly racemizes upon storage even in the refrigerator (5 °C). Freshly prepared and chromatographed samples, which are of >95% ee [NMR analysis in the presence of the chiral shift reagent Eu(TFC)₃, see Experimental Section] showed a specific rotation [α]_D = +87.2° (c = 1.24, acid-free CHCl₃).

Scheme VII. Products of Reduction and Baeyer–Villiger Oxidation of Some Nitrocyclohexanones

morpholino enamine **1b** from 3-pentanone furnished the cyclic product **5** in levorotatory form, while the corresponding pivalate (–)-**2d** gave dextrorotatory samples of **5**. Also, reaction of (–)-**2d** with cyclohexanone enamine gave the bicyclic compound **11a** showing a negative optical rotation. The three reactions occurred with comparable yields and gave the same compounds as the runs using racemic starting materials. However, the products turned out to be of poor enantiomeric purity; crystallizations of (–)-**5** led to samples having a 5-fold optical activity, and from (–)-**11a**, thus obtained, large amounts of *rac*-**11a** could be crystallized.

[3 + 3]-Carbocyclization failed to occur when cyclic derivatives containing the nitroallyl ester moiety (**2e** or **2f**) and enamines were mixed: we isolated nitroketones in which just one C–C bond has been formed between the components. For a discussion, also involving the isolated intermediates of these reactions, see section G.

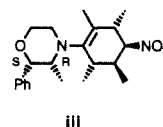
(E) Enantiomerically Pure Bicyclic 4-Nitrocyclohexanones from Enamines of (*S*)-Prolinol Methyl Ether

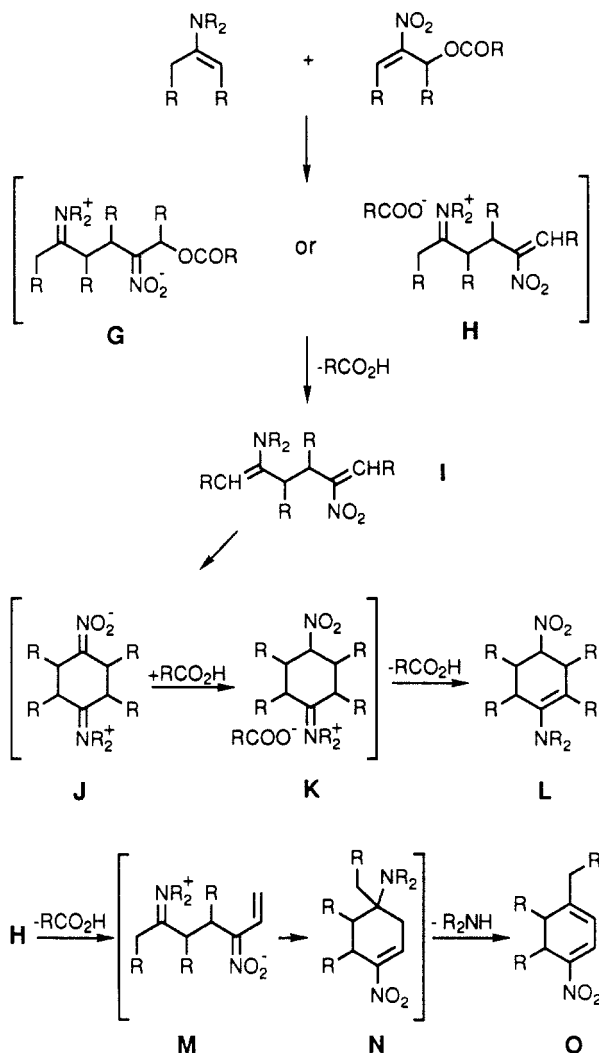
[3 + 3]-Carbocyclizations employing (*S*)-prolinol-derived enamines turned out to be much more rewarding than those with nonracemic nitroolefins. The bicyclic⁵⁰ products (**8a**, **15**–**18**) were obtained in yields of 35–45%, and with high optical activities (Scheme VI). In some cases (**15** and **16**), we confirmed by ¹H NMR measurements in the presence of a chiral shift reagent that the products had >95% ee.

The configurations and conformations of the products in Scheme VI were again determined by NMR spectroscopy. Details, including a 2D NMR analysis of **18**, are described in the Experimental Section. In contrast to the *rac*-bicyclo[3.3.1]nonanes with two methyl groups (Scheme IV), in which the nitro-substituted cyclohexane ring of the major diastereoisomers adopts a chair conformation, **15** and **16a** in the present series of phenyl- or butyl-substituted derivatives were found to have the nitrocyclohexanone ring in the boat conformation, with the nitro group in an endo rather than an exo position.

From the reaction of enamine **1g** from 4-*tert*-butylcyclohexanone and prolinol ether, of which two diastereoisomers (*R,S*

(50) When the open-chain enamines from 3-pentanone and pyrrolidine or (methoxymethyl)pyrrolidine were allowed to react with **26**, no cyclic product could be isolated. However, the enamine from pentanone and (2*S*,3*R*)-3-methyl-2-phenylmorpholine gave ca. 30% of a carbocyclization product iii which consisted of 4 diastereoisomers (ca. 6:1:1:0.5), with the one shown [or its (3'*R*,4'*R*,5'*R*,6'*S*) isomer] prevailing.



Scheme VIII. Mechanism of the [3 + 3]-Carbocyclization with Enamines and Nitroallylic Esters

and *S,S*) exist, and phenylnitropropene ester (**2b**), we isolated two diastereomeric bicyclic products (**16a** and **16b**), while we found only one (**17**) when the aliphatic nitro-heptenyl ester (**2a**) was employed.

We have not determined the absolute configuration of any of the products shown in Scheme VI, the enantiomers drawn are the ones we expect by analogy with the known⁵¹ steric course of the coupling between nitrostyrene and the enamine **1n** to give the product **19** of nitroethylation (see equation on the bottom of Scheme VI).

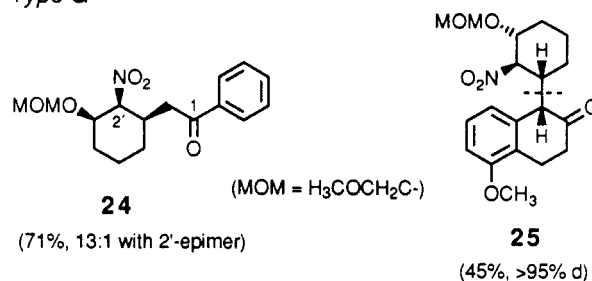
(F) Some Transformations of the 4-Nitrocyclohexanones

As stated in the introduction, it is possible to generate six stereogenic centers on a cyclohexane ring by our [3 + 3]-cyclization method, five directly, the sixth via reduction of the carbonyl group in the product. For a demonstration (Scheme VII), we have reduced compound *rac*-**6** (NaBH₄, 0 °C, EtOH), to a separable mixture of the alcohols **20** and **21** (3:1). In the major product **20**, the hydroxyl group is in an axial position on the cyclohexane ring, according to NMR analysis. Also a bicyclic product (**15**) was reduced under similar conditions to give the alcohol **22** in 62% yield and 88% d.⁴²

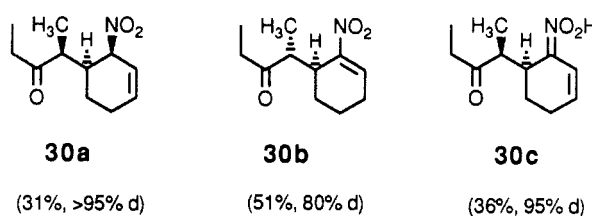
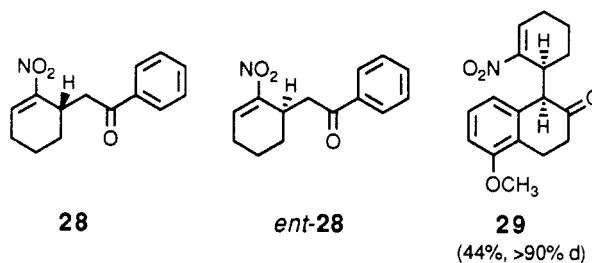
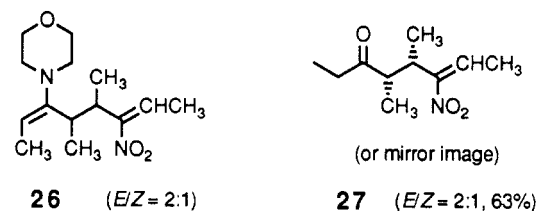
Baeyer–Villiger oxidation (MCPBA/CH₂Cl₂/+20 °C) of the bicyclononanones **11a** and **12** gave lactones **23** derived from 5-hydroxycyclooctanecarboxylic acid with five adjacent stereogenic

Scheme IX. 4-Nitroketone and Nitrocyclohexadiene Derivatives Isolated from Reactions of Nitroallylic Compounds and Enamines

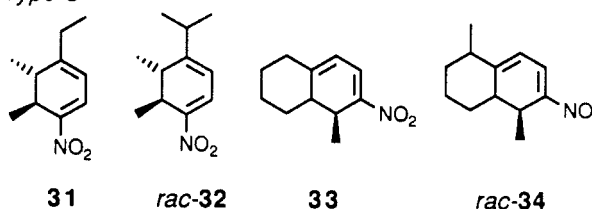
Type G



Type H / I



Type O



centers on the cyclooctane ring. The reaction is highly regioselective with **12**, but yields a 1:1 mixture of **23b** and **23c** with the more symmetrical starting material **11a**.

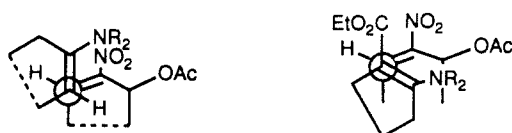
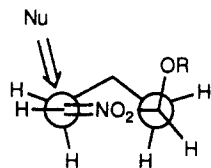
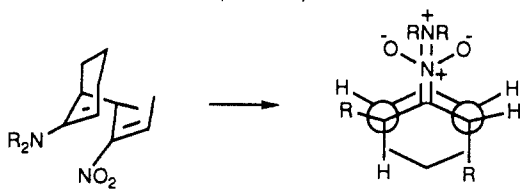
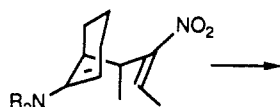
(G) Mechanism of the Reaction. Isolation of Intermediates and of Products from Side Reactions

The steps which are involved in the [3 + 3]-carbocyclization are outlined in Scheme VIII. The first carbon–carbon bond is formed in a conjugate addition (\rightarrow G)⁵² or S_N2' reaction (\rightarrow H), followed by proton transfer to give a 5-amino-2-nitrohexadiene (enamino nitro olefin I). This undergoes cyclization with formation of an iminium salt (J/K) and, if possible,⁵³ subsequently of an enamine (L). Acidic hydrolysis of K or L then leads to the 4-nitroketones isolated. There is ample precedence for each of

(51) Blarer, S. J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta* **1982**, 65, 1637. Blarer, S. J.; Seebach, D. *Chem. Ber.* **1983**, 116, 2250; 3086.

(52) With enamines, see ref 14a; with silyl enol ether, see: Seebach, D.; Brook, M. *Helv. Chim. Acta* **1985**, 68, 319 and Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, 65, 836.

(53) Before hydrolysis, bicyclic products from cyclic ketone enamines can give K but not L (Bredt's rule).

Scheme X. Selectivities in the Formation of the Carbon–Carbon Bonds**A. First C,C Bond***lk* (*syn/anti*)*ul*Nu-attack *syn* to the leaving group of **2e**–**2g****B. Second C,C Bond (I → J)****P****Q**

these steps, and, depending on the structures of the enamine and nitroolefin components employed as well as on the reaction and work up conditions chosen, intermediates can be isolated, the structures of which support this mechanism (see Schemes VIII and IX).

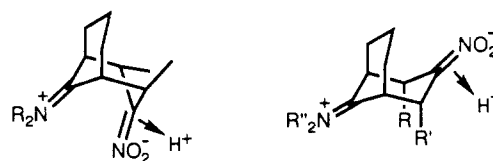
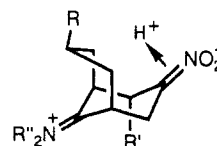
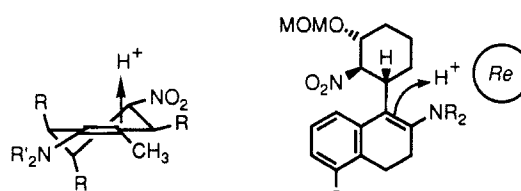
Thus, the addition of enamines to nitroolefins to form γ -nitroketones has been studied extensively.⁵⁴ Earlier we have reported S_N substitutions with nitroallylic esters ("NPP multiple coupling reagents")^{7,36} in which we could never isolate intermediates⁵⁵ still containing the RCOO group (of **G**). By choosing the poorer leaving group OMOM⁵⁶ we were able to isolate adducts such as **24** and **25** with three adjacent stereogenic centers on the cyclohexane ring. The structure of **25** was determined by X-ray diffraction⁵⁷ of both **25** itself (see Experimental Section and supplementary material) and of a precursor camphanoate,³⁸ so that the absolute configuration could be assigned as shown in Scheme IX. In some cases, we isolated nitrocyclohexadienes of type O, [4 + 2]-carbocyclization products which arise from a different type of cyclization of the primary adduct; for examples see the mono- and bicyclic derivatives **31**–**34** in Scheme IX. Their formation can be interpreted as resulting from nucleophilic attack

(54) (a) Seebach, D.; Golinski, J. *Helv. Chim. Acta* **1981**, *64*, 1413. (b) Seebach, D.; Beck, A. K.; Golinski, J.; Hay, J. N.; Laube, T. *Helv. Chim. Acta* **1985**, *68*, 162.

(55) Only when acetoxynitropropene was used instead of (pivaloyloxy)-nitropropene, a product which had not lost the acyloxy group was found. It arises from the addition of two nucleophiles, one to the acetoxo group and the other to the nitroolefin (see Knochel, P. Dissertation, ETH No. 7170, Eidgenössische Technische Hochschule, 1982).

(56) Fuji, K.; Nakano, S.; Fujita, E. *Synthesis* **1975**, 276.

(57) We would like to thank M. Egli for carrying out the X-ray analysis; the coordinates and a PLUTO plot are given in the supplementary material.

Scheme XI. Protonations**A. of Bicyclic Nitronates****R****S****T****B. of Enamines****U****V**

of the vinylnitronate unit in **M** on the iminium carbon atom with subsequent elimination of amine ($N \rightarrow O$). In one case, we have isolated an intermediate enamionitroolefin, compound **26** as a 2:1 mixture of geometrical isomers ($E/Z = 2:1$). The corresponding hydrolysis products, unsaturated nitroketones **27**–**30**, have also been obtained: they are isolated instead of 4-nitrocyclohexanones when nitrocyclohexenyl esters (**2e**–**2g**) are allowed to react with enamines.

When the products of Scheme IX are prepared with enantiomerically pure nitroallylic esters as starting material, optically active samples are isolated. Except for the acyclic derivatives **26** and **27**, those products containing more than one stereogenic center (**24**, **25**, **29**–**34**) were formed with high diastereoselectivities (see figures in Scheme IX). The recrystallizations of these products, and also of **28** (from **2e**) and *ent*-**28** (from **2f**),⁵⁸ to constant melting points and specific rotations gave samples which we assume to be enantiomerically pure. The configurations of the products **30** were not determined but assigned by analogy. The crude nitrohexadienes **31** and **33** [from (+)-**2c**] showed an optical rotation,⁵⁹ whereas **32** and **34** were prepared only from the racemic precursor *rac*-**2c**.

(H) Steric Course of the Reaction

Inspection of Scheme VIII shows that the five stereogenic centers which may be formed in situ during this carbocyclization arise from the following processes: (i) coupling of trigonal centers with formation of C–C bonds in the first and second step ($I \rightarrow J$), (ii) nitronate protonation ($J \rightarrow K$), and (iii) enamine protonation ($L \rightarrow$ nitroketone). Each of these individual steps has been studied previously by using substrates which can undergo only one of the stereoselective steps at a time.^{60–64} The multitude

(58) The enantiomeric purity and the absolute configuration were assigned by chemical correlation; we prepared *ent*-**28** from **24** of known configuration in two steps.

(59) Products **31** and **32** decomposed rather quickly so that we were not able to obtain a correct elemental analysis or a reliable $[\alpha]_D$ value.

(60) *E*-nitroolefins and *E*-enamines combine with relative topicity *lk*; see refs 51, 54.

of possibilities and the complexity of processes involved in this [3 + 3]-carbocyclization are increased by several factors. Thus, although both *E* enamines and *E*-nitroolefins are more stable than the *Z* analogues, there may be *E/Z* isomerizations^{54b} of the open-chain components under the reaction conditions. Also, the regioisomeric enamines of ketones may equilibrate in the reaction mixture, and the less stable one may be the more reactive one.⁶⁵ Furthermore, the chiral nitroallylic alcohols may react such that the enamine approaches with the allylic OCOR group in either the syn or in the anti position.⁶⁶ In spite of these ambiguities we would like to briefly discuss the steric course of the single steps (Schemes X and XI).

From the structures of the main products obtained with an unsymmetrical enamine and/or nitroallylic ester (see 3, 4, 9, 10, 12, 14, 15–18, 25, 29) we conclude that the first C–C bond is formed by combination of the trigonal centers with relative topicity⁶⁷ *lk* for simple enamines and *ul* for the enamino esters (1e and 1f; see part A in Scheme X). The nitrocyclohexenyl derivatives (2e–2g) react preferentially from the face syn to the OR group (relative topicity *ul*–1.3; products 24, 25, 29; see drawing in Scheme X, part A). In the open-chain counterparts the OR group does not seem to have a pronounced directing effect in differentiating the *re/re* from the *si/si* coupling (low optical purities of the products from the optically active 2c and 2d).⁶⁸ The conclusion is that the first C–C bond^{69,70} is formed in a highly

diastereoselective fashion and that the minor diastereoisomers (b) which were isolated stem from the not-so-selective second, ring-closing process (Scheme IV).

Since we do not know whether ring closure occurs under kinetic or thermodynamic control, it is impossible to discuss this step with any degree of certainty. If we stick to the major isomer of the bicyclic products (enamine *E* configuration enforced by the ring), we arrive at the boat P or at the chair Q (Scheme X) as possible intermediates of the cyclization step. The boat form has the attractive features of (i) involving less charge separation, (ii) having the nitronate group in the proper position for protonation with formation of the observed relative configuration of the nitro-substituted stereogenic center, and (iii) arising from an *E*-nitroolefin moiety.⁷¹

The nitronate protonations⁶³ (J → K in Scheme VIII) are highly diastereoselective in nearly all cases.⁷² Restricting the discussion to the simple bicyclo[3.3.1]nonanones⁷³ (Scheme XI), we conclude from the observed configuration of the NO₂-bearing carbon in 11a that it is formed by protonation of the chair-boat zwitterion R from the less hindered side.^{63a} The minor product 11b and compound 15 have opposite configuration of the α-NO₂-carbon which would be compatible with a protonation from the exo face of S; due to allylic [A^(1,3)] strain,⁷⁴ this chair-chair conformation might be preferred. Finally, protonation of the intermediates leading to 16b, 17, and 18 might occur from the endo face of a boat-chair form as depicted for the first two cases in T of Scheme XI, allylic strain in the chair part and a bulky 7-endo substituent R on the boat part favoring that particular conformation.

If the protonations of the enamines *rac*-3 and *rac*-5 occur axially in the usual way,^{64,75} the conformation U shown in Scheme XI part B must be the substrate. The C–C coupling to give 25 or 29 with relative topicity *ul*, rather than *lk* as in all other cases, may also be the result of a diastereoselective enamine protonation: the enamine regioisomer V with the double bond conjugated is most likely the intermediate leading to these products.

(I) Conclusion

Although we are far from fully understanding the steric course of our [3 + 3]-carbocyclization, we have established herein, that a beautiful sequence of stereoselective steps ensues—in one pot—when nitroallylic esters and enamines are allowed to react with each other. Single products with five adjacent stereogenic centers can be readily isolated from the reaction mixtures. Applications of the method to complex natural and unnatural product synthesis can be envisioned.

(J) Experimental Section

General. Melting points were determined on a Büchi 510 apparatus and are uncorrected. TLC was performed on Merck silica gel 60 F-254 analytical plates. FC (flash chromatography) was performed at 0.3–0.5 atm of pressure with use of Merck silica gel 60 (230–400 mesh).⁴¹ ¹H

(70) The selectivity in the formation of 16a and 16b in a 6:1 ratio agrees well with other reported axial/equatorial preferences⁶⁵ in the attack on *tert*-butylcyclohexanone enamines. We do not understand the reversal of this preferences with the butyl-substituted nitroallylic ester (2b); see product 17 and compare with 16a. In this connection, we should also remember that there are two diastereoisomers of 1p.

(71) The minor isomer of the bicyclic products (b) would analogously be formed involved an *E*-nitroolefinic moiety through a chair intermediate in which the two C–C bonds have been formed with relative topicity *re/re* and *si/si* (cf. Q in Scheme X). Again, this chair arrangement would be ready to be protonated to give the observed product (cf. Scheme XI).

(72) Only in the case of the monocyclic products (5/6) have we detected a few percent of an α-NO₂ epimer.

(73) The bicyclo[3.2.1]octanones (8–10), the benzobicyclo[3.3.1]nonanes (14) and the bicyclo[4.3.1]decanones (13) are also formed by highly stereoselective protonation of the intermediate nitronate units. A discussion would be more difficult than with the simple bicyclo[3.3.1]nonanones because there is less bias between endo and exo face in the first case, considerable flattening of one of the six-membered rings in the second cases and hard core conformational analysis in the third case.

(74) Johnson, F. *Chem. Rev.* 1968, 375. Hoffman, R. W. *Chem. Rev.* 1989, 1841.

(75) Beckett, C. W.; Freeman, K. N.; Pitzer, S. K. *J. Am. Chem. Soc.* 1948, 70, 4227. Barton, R. H.; Cookson, R. C.; Klyne, W.; Shoppee, C. W. *Chem. Ind. (London)* 1954, 21. Corey, E. J.; Sreen, A. R. *J. Am. Chem. Soc.* 1955, 77, 2505.



It is conceivable that the observed 2:1 selectivity of *E/Z*-nitroolefin formation in 26 and 27 reflects the *syn/anti* selectivity of the attack on *E*-2c. Another way by which partial racemization could occur would be the involvement of two different conformations with the OR group perpendicular to the plane of the double bond, so that both could undergo, for instance, *syn* elimination, leading to products of opposite chirality.

(69) With the exception of 14 and 18, the formulae in Schemes IV and VI are drawn such that the C–C bond, which we propose to have been formed first, is on the right hand side.

(61) For the reactions of silyl enol ethers with nitroolefins see ref 52.
(62) Lithium enolates and nitroolefins can be forced to react with *lk* or *ul* relative topicity, depending upon the configuration of the components: Häner, R.; Laube, T.; Seebach, D. *Chimia* 1984, 38, 255.

(63) Diastereoselective protonation of nitronate anion derivatives: (a) Zimmerman, H. E. *Molecular Rearrangements*; De Mayo, P., Ed.; J. Wiley: New York, 1963; p 345. Zimmerman, H. E. *Acc. Chem. Res.* 1987, 20, 263. (b) Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* 1985, 107, 3601, and ref 5.

(64) (a) Protonation of enamines is usually not highly diastereoselective; see: Hickmott, P. W. *Tetrahedron* 1982, 38, 1975, 1998–2006 and references cited therein. (b) Examples of diastereoselective protonation of cyclohexanone enamines are as follows: Colonna, F. P.; Forchiassin, M.; Pitacco, G.; Risalti, A.; Valentin, E. *Tetrahedron* 1970, 26, 5289. Hickmott, P. W.; Finell, N. F. *J. Chem. Soc., Perkin Trans. 1* 1978, 340. Laskovics, F. M.; Schulman, E. M. *J. Am. Chem. Soc.* 1977, 99, 6672. Ficini, J.; Touzin, A. M. *Tetrahedron Lett.* 1972, 2093; 2097.

(65) For the discussion of the reactivity of enamines from 2- and 2,4-substituted cyclohexanones see ref 64a, p 2011 ff and also Pfau, M.; Revial, G.; Guignant, A.; d'Angelo, J. *J. Am. Chem. Soc.* 1985, 107, 273. The reactivity of tetralone enamines is discussed in Pitacco, G.; Colonna, F. P.; Valentin, E.; Risalti, A. *J. Chem. Soc., Perkin Trans. 1* 1974, 1625. For the *tert*-butyl-substituted enamines see also refs 22, 44.

(66) For a general extensive discussion of the stereochemical course of S_N' and S_E' type reaction, see: Houk, R. N.; Paddon-Row, H. N.; Rondan, N. G. *J. Mol. Structure* 1983, 103, 197. Vogel, E.; Caravatti, G.; Franck, P.; Aristoff, P.; Moody, C.; Becker, A.-M.; Felix, D.; Eschenmoser, A. *Chem. Lett.* 1987, 219. Matassa, V. G.; Jenkins, P. R.; Kümin, A.; Damm, L.; Schreiber, J.; Felix, D.; Zass, E.; Eschenmoser, A. *Isr. J. Chem.* 1989, 29, 321.

(67) Prelog, V.; Helmchen, G. *Angew. Chem.* 1982, 94, 614; *Angew. Chem., Int. Ed. Engl.* 1982, 21, 567. Seebach, D.; Prelog, V. *Angew. Chem.* 1982, 94, 696; *Angew. Chem., Int. Ed. Engl.* 1982, 21, 654.

(68) We assume that the reason for formation of partially racemized products from *E*-2c and *E*-2d is poor *syn/anti* preference (*re/re* and *si/si* coupling become competitive) and not *E/Z* isomerization of the nitroallylic esters under reaction conditions. This assumption is supported by the fact that the lithium enolate of methyl acetate and 2-(benzyloxy)-3-nitro-3-pentane react (certainly irreversibly! See ref 62) with formation of four diastereoisomers in the ratio of 5:5:1:1, with the two major diastereoisomers being epimeric at C(3). This was proven by conversion of the two major diastereoisomers to the lactones (iv) and (v) and NMR analysis.

and ^{13}C NMR spectra were measured in CDCl_3 at 300 MHz and 75 MHz, respectively, on a Bruker WM-300 instrument. Infrared spectra were measured on a Perkin-Elmer 782 spectrophotometer. Optical rotations were recorded by using a 10-cm, 1-mL cell on a Perkin-Elmer 241 polarimeter. Elemental analyses were correct to within $\pm 0.3\%$.

Materials. Tetrahydrofuran (THF) was freshly distilled from potassium under argon. Acetonitrile was purchased from Fluka (puriss) and was stored over molecular sieves (4 Å). Methylene chloride (CH_2Cl_2) was distilled from P_2O_5 and stored over Al_2O_3 . Absolute ether was purchased from Fluka (puriss), otherwise ether was distilled from sodium hydroxide.

Starting Materials. The enamines **1a–1p** and the allylic esters **2a, 2b**, (+)-**2c**, and **2e–2g** were prepared as described in the text. The enantiomeric excess (ee) of the nitroolefin (+)-**2c** with an $[\alpha]_D$ value of $+87.2^\circ$ ($c = 1.24$, CHCl_3)⁴⁹ was $>95\%$ according to ^1H NMR analysis (300 MHz) in hexadeuterobenzene in the presence of the chiral shift reagent $\text{Eu}(\text{TFC})_3$ (tris[3-(2,2,2-trifluoro-1-hydroxy-ethylidene)-*d*-camphorato]europium, Uvasol from Merck). *rac*-(3-*E/Z*)-3-Nitro-3-penten-2-yl acetate (**2c**) was prepared as follows. Acetyl chloride (46.9 g, 0.6 mol) was added to an ice-cooled emulsion of 3-nitro-2,4-pentandiol (71.4 g, 0.47 mol, prepared from nitromethane and acetaldehyde³⁸) in CH_2Cl_2 (200 mL) to afford a clear, red solution. After warming to room temperature the solution was heated under reflux for 1.5 h; the HCl gas produced during the reaction was neutralized with aqueous sodium hydroxide solution. After cooling to room temperature the reaction mixture was washed with ice/water (3×250 mL). The combined aqueous layers were extracted with ether (2×200 mL) and the combined ethereal phases dried (MgSO_4) and evaporated. The crude mixture (containing di-, monoacetate, and diol) was dissolved in absolute ether (200 mL) and added to a suspension of dicyclohexylcarbodiimide (100 g, 0.48 mol) in ether (100 mL). After the addition of copper(I) chloride³⁷ (5 g) the mixture was stirred in the dark for 4 days at room temperature. The thick suspension was diluted with ether (150 mL), and oxalic acid was added in portions until the gas evolution (CO_2) had ceased. The mixture was filtered through Celite, and the remaining solid was washed with cold ether (2×50 mL). The liquid was evaporated and the residual dark brown oil filtered through silica gel (10 cm, 250 g) and washed with ether under TLC control. The product-containing fractions were combined and evaporated, and the residue was distilled under high vacuum yielding 40 g of a slightly impure 2:1 mixture (by 90 MHz NMR) of *E/Z*-*rac*-**2c**, which was stored in the freezer. For the cyclization reactions, the crude *rac*-**2c** was distilled once again in the Kugelrohr apparatus, to afford a green-yellow oil: bp $75\text{--}85^\circ\text{C}$ (0.2 Torr); ^1H NMR (90 MHz) δ 7.23 (q, $J = 8$ Hz, $\text{HC}(4)\text{-E}$), 6.20–5.80 (m, 3 H, $\text{HC}(2)\text{-(E/Z)}$, $\text{HC}(4)\text{-Z}$), 2.07 (s, 3 H, CH_3CO), 2.04 (d, $J = 7$ Hz, 6 H, $\text{H}_3\text{C}(1)\text{-E/Z}$), 1.60 (d, $J = 6$ Hz, 3 H, $\text{HC}(5)\text{-E}$), 1.47 (d, $J = 6$ Hz, 3 H, $\text{HC}(5)\text{-Z}$).

(-)-(**2R,3E**)-3-Nitro-3-penten-2-yl Pivalate (**2d**). The allylic pivalate **2d** was prepared in two steps from the same optically active precursor (2*S,3S,4R*)-4-hydroxy-3-nitro-2-pentyl acetate as (+)-**2c**.

(a) (**2R,3R,4S**)-4-Acetoxy-3-nitro-2-pentyl Pivalate. Concentrated sulfuric acid (3 drops) was added to a suspension of (2*S,3S,4R*)-4-hydroxy-3-nitro-2-pentyl acetate³⁸ (2.04 g, 10.7 mmol) in freshly distilled pivalic acid anhydride (2.98 g, 16 mmol). The mixture became warm and clear, and after a few minutes the product began to precipitate. After 15 min, ice/water (20 mL) was added and the mixture extracted with ether (3×20 mL). The organic phases were washed successively with water, a saturated NaHCO_3 solution, and brine and dried (MgSO_4). Evaporation of the solvent gave a pale yellow solid, which after recrystallization (pentane/ether, 1:2) yielded 2.9 g (95%) as colorless needles: mp 115°C ; $[\alpha]_D = -3.2^\circ$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz) δ 5.37 (m, 2 H, $\text{HC}(2)$, $\text{HC}(4)$), 4.61 (dd, $J = 6.7$, 8.5 Hz, 1 H, $\text{HC}(3)$), 2.05 (s, COCH_3), 1.33 (2 d, $J = 6.5$, 6.8 Hz, 6 H, $\text{H}_3\text{C}(1)$, $\text{H}_3\text{C}(5)$), 1.18 (s, 9 H, $\text{C}(\text{CH}_3)_3$); MS m/e (rel intensity) 224 (12, M^+), 174 (2), 149 (3), 143 (18), 99 (40), 98 (17), 70 (12), 61 (30), 57 (27), 56 (100), 43 (9). Anal. ($\text{C}_{12}\text{H}_{21}\text{NO}_6$) C, H, N.

(b) (**2R,3R,4S**)-4-Hydroxy-3-nitro-2-pentyl Pivalate. Concentrated sulfuric acid (0.55 mL) was added to a solution of the diester (2.9 g, 10.7 mmol) prepared as above in methanol (40 mL) at 0°C . After stirring for 45 min at room temperature, the mixture was poured onto ice and extracted with ether ($\times 4$). The combined organic phases were washed with brine and dried (MgSO_4), and the solvent was evaporated. The resulting slowly crystallizing oil was pure by ^1H NMR and was used directly. For spectroscopic analysis, an analytical sample was recrystallized from ether at -50°C : mp 83°C ; $[\alpha]_D = +0.4^\circ$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz) δ 5.48 (dq, $J_d = 7.8$, $J_q = 6.3$ Hz, 1 H, $\text{HC}(2)$), 4.50 (dd, $J = 7.8$, 4.9 Hz, 1 H, $\text{HC}(3)$), 4.20 (br m, 1 H, $\text{HC}(4)$), 2.36 (s, 3 H, OH), 1.37 (d, $J = 6.3$ Hz, 3 H, $\text{H}_3\text{C}(1)$), 1.32 (d, $J = 7.5$ Hz, 3 H, $\text{H}_3\text{C}(5)$), 1.16 (s, 9 H, $\text{C}(\text{CH}_3)_3$); MS m/e (rel intensity) 233 (<1 , M^+), 169 (1), 142 (1), 103 (3), 85 (28), 57 (100), 43 (11), 41 (11). Anal. ($\text{C}_{10}\text{H}_{19}\text{NO}_5$) C, H, N.

(-)-(**2R,3E**)-3-Nitro-3-penten-2-yl Pivalate (**2d**). Dicyclohexylcarbodiimide (2.5 g, 12 mmol) and copper(I) chloride³⁷ (0.5 g) were added to a solution of hydroxy pivalate (1.61 g, 6.9 mmol) in absolute ether (30 mL), and the mixture was heated under reflux for 4 days under argon in the dark. After the mixture was cooled to room temperature, oxalic acid was added in portions until gas evolution (CO_2) had ceased. The mixture was filtered through Celite and the remaining solid washed with cold ether (2×20 mL). The liquid was evaporated and FC (pentane/ether 6:1) of the residue gave (-)-**2d** (1.5 g, 95%) as a pale green-yellow oil, which solidified in the freezer: $[\alpha]_D = -27.0^\circ$ ($c = 1$, CHCl_3); ^1H NMR (300 MHz) δ 7.20 (q, $J = 7.7$ Hz, 1 H, $\text{HC}(4)$), 5.95 (q, $J = 6.8$ Hz, 1 H, $\text{HC}(2)$), 2.05 (d, $J = 7.7$ Hz, 3 H, $\text{HC}(5)$), 1.60 (d, $J = 6.8$ Hz, 3 H, $\text{HC}(1)$), 1.19 (s, 9 H, $\text{C}(\text{CH}_3)_3$); MS m/e (rel intensity) no M^+ , 169 (16), 149 (3), 105 (6), 103 (7), 85 (7), 67 (12), 57 (100), 41 (27). Anal. ($\text{C}_{10}\text{H}_{17}\text{NO}_4$) C, H, N.

[3 + 3]-Carbocyclizations. **General Procedure I (GP I).** The enamine (1.1 equiv) either neat or as a THF solution was added slowly with stirring to a solution of the nitroallylic ester (1 equiv) in THF (20 mL for 5 mmol) at -78°C under argon and the solution allowed to warm up to room temperature over 15 h. If the nitroallylic ester had been consumed completely (TLC), the orange solution was diluted with acetonitrile (1.5 times of the volume of THF) and stirred in the dark at room temperature for 40–60 h. The reaction was completed by heating the mixture under reflux for 3–8 h. After the reaction was cooled to room temperature, 10% aqueous racemic tartaric acid solution (50 mL) was added to the deep red mixture, and it was again stirred for 1.5 h (for monocyclic enamines 5 h). After the addition of solid NaCl (2 g), the mixture was extracted with ether (3×30 mL). The combined organic layers were washed successively with a 10% HCl solution (30 mL), a saturated NaHCO_3 solution (30 mL), and brine (30 mL), and each aqueous phase was reextracted with ether (30 mL). The ethereal layers were dried (MgSO_4) and evaporated to give a viscous brown oil, which, after FC, afforded the desired cyclization products.

General Procedure II (GP II). A solution of the enamine (1.05 equiv) in THF (1 mL) was added slowly with stirring to a solution of the nitroallylic ester (1 equiv) in THF (10 mL for 3 mmol) at -78°C under argon. The stirred solution was allowed to warm up to room temperature over 15 h. After cooling to 0°C , the orange solution was diluted with acetonitrile (twice the volume of THF) and stirred in the dark at room temperature for 40–60 h. The mixture was evaporated and the resulting brown oil chromatographed (FC) to yield the cyclic nitroenamine as an air-sensitive, slightly orange oil.

General Procedure III (GP III) for Reaction with Enantiomerically Pure Prolinol Methyl Ether Enamines. A solution of the enamine (10 mmol) in CH_2Cl_2 (5–10 mL) was added dropwise to a solution of the nitroallylic ester (10 mmol) in CH_2Cl_2 (30 mL) at -78°C under argon. After warming to room temperature over 14 h, the mixture was hydrolyzed by the addition of 1 N HCl (10 mL) and water (5 mL) and then heated under reflux for 1 h. The mixture was cooled to room temperature, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3×40 mL) and the combined organic fractions washed with 1 N HCl (2×20 mL), water (20 mL), and brine (20 mL), dried (MgSO_4), and evaporated. FC of the residue followed by recrystallization from boiling ether or ether/ CH_2Cl_2 afforded the required product.

General Procedure IV (GP IV) for the Reaction of Cyclic Nitroallylic Esters with Enamines. The enamine (1.0–1.2 equiv) in THF (1 mL) was added slowly with stirring to a solution of the nitroallylic ester (1 equiv) in THF (10 mL for 3 mmol) at -10 to -20°C under argon and the solution stirred for 1–3 days at 4°C . The yellow to red mixture was hydrolyzed with 10% aqueous tartaric acid solution for 1–3 h at room temperature. Isolation of the products was then as for GP I.

rac-2,6-Dimethyl-1-morpholino-4-nitro-5-phenyl-1-cyclohexene (**3**). The nitroolefin **2b** (4.0 g, 15 mmol) was allowed to react with **1b** (2.3 g, 15 mmol) according to GP III and, after warming up to room temperature, the mixture was washed with a cold, saturated NaHCO_3 solution ($\times 2$) and brine ($\times 1$), dried, and evaporated. The orange-red oil was chromatographed (FC, CH_2Cl_2) and the crude product recrystallized from warm ether to give **3** (2.37 g, 50%, $d > 95\%$): mp $119\text{--}121^\circ\text{C}$; ^1H NMR (300 MHz) δ 7.26–7.22 (m, 3 H, CH_{arom}), 7.12–7.08 (m, 2 H, CH_{arom}), 4.90–4.83 (ddd, $J = 11.2$, 5.6, and 4.5 Hz, 1 H, $\text{HC}(4)$), 3.78–3.69 (m, 4 H, H_2COCH_2), 3.53 (d, $J = 4.5$ Hz, 1 H, $\text{HC}(5)$), 2.95–2.81 (m, 5 H, H_2CNCH_2 , $\text{HC}(6)$), 2.62–2.53 (dd, $J = 18$, 11.2 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(3)$), 2.44–2.37 (dd, $J = 18$, 5.6 Hz, 1 H, $\text{H}_{\text{eq}}\text{C}(3)$), 1.80 (s, 3 H, $\text{H}_3\text{CC}(2)$), 1.34 (d, $J = 7$ Hz, 3 H, $\text{H}_3\text{CC}(6)$); MS m/e (rel intensity) 316 (M^+), 209 (2), 299 (7), 270 (26), 178 (13), 131 (14), 117 (100), 91 (32), 41 (16). Anal. ($\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_3$) C, H, N.

rac-2,6-Dimethyl-4-nitro-3-phenylcyclohexan-1-one (**4**). The nitroolefin **2b** (4.82 g, 18.2 mmol) was allowed to react with **1b** (2.86 g, 18.5 mmol) according to GP III, and after warming up to room temperature, the solvent was evaporated. The oily residue was dissolved in methanol

(60 mL) and cooled to -15°C , and a 10% HCl solution (60 mL) was added in portions. After warming up to 0°C over 3 h, the mixture was extracted with CH_2Cl_2 ($\times 3$), and the organic fractions were washed successively with a saturated NaHCO_3 solution, water, and brine, dried (MgSO_4), and evaporated. The crude product was recrystallized from boiling ether (after first adding a little pentane) to afford **4** (2.65 g, 59%, $d > 95\%$): mp $93\text{--}94^{\circ}\text{C}$; ^1H NMR (300 MHz) δ 7.31–7.25 (m, 3 H, CH_{arom}), 6.99–6.96 (m, 2 H, CH_{arom}), 5.24 (td (ddd), $J_1 = 5$ Hz, $J_d = 10$ Hz, 1 H, HC(4)), 3.72 (td (ddd), $J_1 = 5$ Hz, $J_d = 1.5$ Hz, 1 H, HC(3)), 3.08–2.99 (qd, $J_q = 7.5$ Hz, $J_d = 5$ Hz, 1 H, HC(2)), 2.77–2.68 (qdd, $J_q = 6.5$ Hz, $J_d = 13$, 6.5 Hz, 1 H, HC(6)), 2.44–2.35 (dddd, $J = 13.5$, 6.5, 5, and 1.5 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(5)$), 2.25–2.13 (td (ddd), $J_1 = 13.5$ Hz, $J_d = 10$ Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(5)$), 1.35 (d, $J = 7.5$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.22 (d, $J = 6.5$ Hz, 3 H, $\text{H}_3\text{CC}(6)$); MS m/e (rel intensity) 247 (M^+ , 3.4), 201 (5), 161 (52), 131 (57), 131 (57), 118 (94), 105 (54), 91 (100), 43 (24), 27 (12). Anal. ($\text{C}_{14}\text{H}_{17}\text{NO}_3$) C, H, N.

rac-2,3,5,6-Tetramethyl-4-deuterio-4-nitro-3-phenylcyclohexan-1-one (d^6 -4). A solution of 20% DCl in D_2O (5 mL) was added to a solution of **3** (500 mg, 1.58 mmol) in CH_3OD (10 mL) at -10°C and the mixture stirred at 0°C for 15 h. The mixture was extracted with CH_2Cl_2 (2×20 mL), and the organic layers were washed with a saturated NaHCO_3 solution (20 mL) and brine (20 mL), dried (MgSO_4), and evaporated to give the crude monodeuterated product. Recrystallization from boiling ether yielded d^6 -**4** (313 mg, 80%, $d > 95\%$): mp $92\text{--}93^{\circ}\text{C}$; ^1H NMR (300 MHz) δ 7.31–7.25 (m, 3 H, CH_{arom}), 7.00–6.97 (m, 2 H, CH_{arom}), 5.24 (td (ddd), $J_1 = 5$ Hz, $J_d = 10$ Hz, 1 H, HC(4)), 3.71 (td (ddd), $J_1 = 5$ Hz, $J_d = 1.5$ Hz, 1 H, HC(3)), 3.06–3.01 (qd, $J_q = 7.5$ Hz, $J_d = 5$ Hz, 1 H, HC(2)), 2.43–2.36 (dd, $J = 13.9$, 5 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(5)$), 2.23–2.14 (dd, $J = 13.5$, 10 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(5)$), 1.34 (d, $J = 7.5$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.22 (d, $J = 6.5$ Hz, 3 H, $\text{H}_3\text{CC}(6)$); MS m/e (rel intensity) M^+ region 250 (3.2), 249 (22), 248 (100), 247 (4.5).

rac-2,3,5,6-Tetramethyl-1-morpholino-4-nitro-1-cyclohexene (5). The enamine **1b** (2.3 g, 11 mmol) was allowed to react with **rac-2c** (1.73 g, 10 mmol) according to GP II (60 h room temperature) to give after FC (pentane/ether 8:1) 1.2 g (45%) of a slightly yellow oil which was by 90-MHz NMR $>90\%$ diastereomerically pure **5**. Recrystallization from pentane at -20°C gave analytically pure samples. Spectral data (^1H and ^{13}C NMR, IR, MS) were identical with (–)-**5**.

(–)-**2,3,5,6-Tetramethyl-1-morpholino-4-nitro-1-cyclohexene [(–)-5]**. The enamine **1b** (0.95 g, 6.1 mmol) was allowed to react with **E-(+)-2c** (1 g, 5.8 mmol) according to GP II (60 h room temperature) to give after FC (pentane/ether 8:1) 805 mg (52%) of a slightly yellow oil which was diastereomerically pure (–)-**5** (by 90-MHz NMR). This was recrystallized from pentane at -20°C . The first crystalline material (440 mg) had mp $55\text{--}57^{\circ}\text{C}$ and $[\alpha]_D = -25.0^{\circ}$ ($c = 1$, CHCl_3). After three further recrystallizations, the remaining 126 mg had $[\alpha]_D = -107.0^{\circ}$ ($c = 1$, CHCl_3) and mp 80°C (not sharp). After a further recrystallization, the $[\alpha]_D$ value was constant, so that an $[\alpha]_D$ of -107.0° can be used for determining an approximate ee of 20% for this reaction. (–)-**5**: ^1H NMR (300 MHz) δ 4.43 (dd, $J = 10.0$, 4.0 Hz, 1 H, CHNO_2), 3.77–3.65 (m, 4 H, $(\text{CH}_2)_2\text{O}$), 2.88 (qdm, $J_q = 6.7$ Hz, $J_d = 10.0$ Hz, 1 H, HC(3)), 2.85–2.70 (m, 4 H, $\text{N}(\text{CH}_2)_2$), 2.38 (qm, $J_q = 7.0$ Hz, 1 H, HC(6)), 2.28 (qdd, $J_q = 6.9$ Hz, $J_d = 4.0$, 2.1 Hz, 1 H, HC(5)), 1.72 (d, $J = 1.1$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.18 (d, $J = 7.0$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 1.06 (d, $J = 6.7$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), 0.92 (d, $J = 6.9$ Hz, 3 H, $\text{H}_3\text{CC}(5)$); MS m/e (rel intensity) 268 (M^+ , 67), 238 (11), 223 (16), 222 (100), 207 (60), 206 (23), 193 (16), 192 (28), 170 (26), 166 (30), 95 (11), 86 (15), 69 (55). Anal. ($\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3$) C, H, N.

NOE Experiment. Irradiation on the methyl group at C(3) gave a positive NOE at HC(4), HC(3), and $\text{CH}_3\text{C}(2)$ and no 1,3-diaxial NOE, which indicates an equatorial position of CH_3 at C(3). Irradiation on the methyl group at C(5) gave a positive NOE at HC(5), HC(6), and HC(2). The 1,3-diaxial NOE to HC(2) indicates an axial position of CH_3 at C(5). Irradiation on the methyl group at C(6) gave a positive NOE at HC(6), HC(5), HC(4), and CH_2N on the morpholine residue. The 1,3-diaxial NOE to HC(4) indicates an axial position of CH_3 at C(6) and an equatorial position of the nitro group at C(4).

(+)-**2,3,5,6-Tetramethyl-1-morpholino-4-nitro-1-cyclohexene [(+)-5]**. **E-(+)-2d** (600 mg, 2.8 mmol) was allowed to react with **1b** (460 mg, 2.95 mmol) according to GP II (60 h room temperature) and subsequent FC afforded (+)-**5** (387 mg, 50%). Crystallization from pentane gave cubic crystals with mp 57°C and an $[\alpha]_D$ value of $+21.2^{\circ}$ ($c = 1$, CHCl_3), indicating an approximate ee of 20% [determination see (–)-**5**]. The first recrystallization from pentane yielded a product with $[\alpha]_D = +30.2^{\circ}$ ($c = 1$, CHCl_3). Spectral data (^1H and ^{13}C NMR, IR, MS) were identical with (–)-**5**. Anal. ($\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_3$) C, H, N.

rac-2,3,5,6-Tetramethyl-4-nitro-cyclohexan-1-one (6) and 2-epi-6. Hydrolysis of enamine **5** (250 mg, 0.93 mmol) in a biphasic system (15 mL CHCl_3 /10 mL 10% HCl) at $+4^{\circ}\text{C}$ for at least 40 h (NMR control) gave the crude nitroketone (163 mg, 6:1 to 8:1 mixture of **6** and 2-*epi*-**6**;

if the starting enamine **5** was from the oily mother liquid and not from pure crystals, a third diastereoisomer with an axial nitrosubstituent 4-*epi*-**6** was also detected in $<10\%$). FC (pentane/ether 5:1) gave 70% of an unseparated mixture of **6** and 2-*epi*-**6**, which also could not be separated by crystallization. (When the third diastereoisomer 4-*epi*-**6** was present, mixed fractions were also obtained.) **6** (with 10% 2-*epi*-**6**): mp $34\text{--}35^{\circ}\text{C}$; ^1H NMR (300 MHz) δ 4.77 (dd, $J = 9.0$, 4.7 Hz, 1 H, HC(4)), 2.51 (qd, $J_q = 7.2$ Hz, $J_d = 5.8$ Hz, 1 H, HC(6)), 2.42 (qdd, $J_q = 6.9$ Hz, $J_d = 5.8$, 4.8 Hz, 1 H, HC(5)), 2.33 (qdd, $J_q = 6.2$ Hz, $J_d = 11.4$, 9.0 Hz, 1 H, HC(3)), 2.27 (qd, $J_q = 6.3$ Hz, $J_d = 11.4$ Hz, 1 H, HC(2)), 1.26 (d, $J = 7.2$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 1.16 (d, $J = 6.2$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), 1.14 (d, $J = 6.3$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.01 (d, $J = 6.9$ Hz, 3 H, $\text{H}_3\text{CC}(5)$); MS m/e (rel intensity) 199 (M^+ , 2), 153 (6), 144 (8), 125 (10), 113 (17), 97 (26), 96 (11), 83 (30), 81 (11), 69 (100), 57 (14), 56 (24), 55 (47), 43 (39), 41 (45). Anal. ($\text{C}_{10}\text{H}_{17}\text{NO}_3$) C, H, N. 4-*epi*-**6**: ^1H NMR (300 MHz) δ 4.62 (dd, $J = 4.3$, 2.1 Hz, 1 H, HC(4)), 3.22 (qd, $J_q = 6.7$ Hz, $J_d = 5.4$ Hz, 1 H, HC(6)), 2.97 (qd, $J_q = 6.5$ Hz, $J_d = 12.1$ Hz, 1 H, HC(2)), 2.74 (qdd, $J_q = 7.4$ Hz, $J_d = 5.4$, 2.1 Hz, 1 H, HC(5)), 2.01 (qdd, $J_q = 6.8$ Hz, $J_d = 12.1$, 4.5 Hz, 1 H, HC(3)), 1.19 (d, $J = 6.8$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), 1.07 (d, $J = 6.5$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.01 (d, $J = 6.7$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 0.93 (d, $J = 7.2$ Hz, 3 H, $\text{H}_3\text{CC}(5)$).

(+)-**2-Deuterio-2,3,5,6-tetramethyl-4-nitro-1-cyclohexanone (d^2 -6).** Hydrolysis of (+)-**5** (80 mg, 0.23 mmol) in 10% DCl (2 mL) and D_2O (6 mL) at $+4^{\circ}\text{C}$ for 24 h gave after FC d^2 -**6** (55 mg, 89%, $d > 90\%$): ^1H NMR (300 MHz) δ 4.78 (dd, $J = 9.4$, 4.7 Hz, 1 H, HC(4)), 2.51 (qd, $J_q = 7.2$ Hz, $J_d = 5.7$ Hz, 1 H, HC(6)), 2.42 (qdd, $J_q = 6.9$ Hz, $J_d = 5.7$, 4.7 Hz, 1 H, HC(5)), 2.33 (qd, $J_q = 6.4$ Hz, $J_d = 9.4$ Hz, 1 H, HC(3)), 1.26 (d, $J = 6.8$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 1.17 (d, $J = 6.4$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), 1.13 (s, 3 H, $\text{H}_3\text{CC}(2)$), 1.01 (d, $J = 6.9$ Hz, 3 H, $\text{H}_3\text{CC}(5)$); MS m/e (rel intensity) 200 (M^+ , 3), 154 (8), 144 (9), 126 (13), 114 (16), 98 (22), 97 (24), 84 (19), 83 (29), 82 (14), 70 (84), 69 (100), 68 (10), 67 (11), 57 (28), 56 (54), 55 (56), 43 (64), 41 (77). Anal. $\text{C}_{10}\text{H}_{16}\text{NO}_3$ (D counted as 2 H) C, H, N.

rac-2-Propyl-3,5,6-trimethyl-4-nitro-1-cyclohexanone (7). **rac-2c** (870 mg, 5 mmol) in THF was allowed to react with **1c** (920 mg, 5.5 mmol) in THF (1 mL) following GP I (30 h room temperature, 15 h heating under reflux) to give after FC (pentane/ether 8:1) an unseparated mixture of four diastereoisomers (720 mg, 64%, ratio not determined). The two main diastereoisomers showed the same signal pattern (^1H NMR) for the C(4) proton as **rac-6**. For analytical purposes, the main fraction was rechromatographed. Anal. ($\text{C}_{12}\text{H}_{21}\text{NO}_3$) C, H, N.

rac-2,4-Dimethyl-3-nitrobicyclo[3.2.1]octan-8-one (8a and 8b). **rac-2c** (870 mg, 5 mmol) in THF was allowed to react with **1d** (755 mg, 5.5 mmol) in THF (1 mL) when GP I was followed (50 h room temperature, 1.5 h of heating under reflux) to give a diastereomeric mixture of **8a** and **8b**, from which both diastereoisomers were isolated ($d > 90\%$) pure by FC in a ratio of 4:1 and a combined yield of 57%. **8a**: 426 mg (45%); mp $75\text{--}76^{\circ}\text{C}$; ^1H NMR (300 MHz) δ 4.65 (dd, $J = 11.6$, 6.3 Hz, 1 H, HC(3)), 2.91 (qdd, $J_q = 6.5$ Hz, $J_d = 11.6$, 2.5 Hz, 1 H, HC(2)), 2.77 (qdd, $J_q = 7.2$ Hz, $J_d = 6.3$ Hz, 4.0, 1 H, H(C4)), 2.26–2.21 (m, 1 H), 2.16–2.06 (m, 2 H), 1.91–1.76 (m, 3 H, HC(6), HC(7)), 1.05 (d, $J = 6.5$ Hz, 3 H, CH_3), 0.94 (d, $J = 7.2$ Hz, 3 H, CH_3); MS m/e (rel intensity) 197 (<1 , M^+), 123 (40), 121 (5), 95 (39), 93 (16), 81 (100), 69 (18), 67 (32), 55 (82), 43 (25), 41 (48), 39 (25). Anal. ($\text{C}_{10}\text{H}_{15}\text{NO}_3$) C, H, N. **8b**: 139 mg (12%); mp 40°C ; ^1H NMR (300 MHz) δ 3.84 (t (dd), $J = 8.1$ Hz, 1 H, HC(3)), 2.84 (m, 2 H, HC(2), HC(4)), 2.13–1.90 (m, 6 H, HC(1), HC(5), $2 \times \text{CH}_2$), 1.16 (d, $J = 7.1$ Hz, 6 H, $2 \times \text{CH}_3$); MS m/e (rel intensity) 197 (1, M^+), 150 (34), 135 (10), 123 (53), 122 (64), 107 (48), 95 (67), 94 (45), 93 (42), 83 (91), 81 (92), 79 (39), 77 (25), 67 (51), 55 (100), 53 (40), 41 (86), 39 (70), 27 (60). Anal. ($\text{C}_{10}\text{H}_{15}\text{NO}_3$) C, H, N.

(+)-**2,4-Dimethyl-3-nitrobicyclo[3.2.1]octan-8-one (8a).** **rac-2c** (520 mg, 3 mmol) in THF was allowed to react with **1m** (600 mg, 3.3 mmol) in THF (1 mL) by following GP I (100 h room temperature). The crude product ($d > 80\%$) was chromatographed (pentane/ether 3:1) to yield pure (+)-**8a** (236 mg, 40%, $d > 95\%$, ee = 90%⁷⁶) as a crystalline solid ($[\alpha]_D = +81.4^{\circ}$ ($c = 1$, CHCl_3)) and a mixed fraction (50 mg, 90% (+)-**8a**, 10% **8b**). Double recrystallization (ether/pentane) gave colorless crystals with a constant $[\alpha]_D$ value of $+90.6^{\circ}$ ($c = 1$, CHCl_3). Spectral data (^1H and ^{13}C NMR, IR, MS) were identical with those of **rac-8a**.

Ethyl rac-2,4-Dimethyl-3-nitro-8-oxobicyclo[3.2.1]octanecarboxylate (9). **rac-2c** (870 mg, 5 mmol) was allowed to react with **1e** (1.26 g, 5.5 mmol) according to GP I (72 h room temperature, 8 h heating under reflux) to give two diastereoisomers in a ratio of 2:1 (^1H NMR), which could not be completely separated by FC (pentane/ether 4:1). In ad-

(76) The enantiomeric excess was determined by comparison of the observed $[\alpha]_D$ value of the crude product and the $[\alpha]_D$ value of the product recrystallized to constant melting point and constant optical rotation.

dition to diastereomerically pure **9** (372 mg, 28%), a mixture of **9** and the other diastereoisomer⁷⁷ (290 mg, 22%) was also obtained: mp 85–86 °C; ¹H NMR (300 MHz) δ 4.68 (dd, $J = 11.7, 6.3$ Hz, 1 H, HC(3)), 4.27 (m, 2 H, H₂CO), 3.36 (qd, $J_q = 6.2$ Hz, $J_d = 11.7$ Hz, 1 H, HC(2)), 2.81 (qdd, $J_q = 7.1$ Hz, $J_d = 6.3, 4.1$ Hz, 1 H, HC(4)), 2.58 (m, 1 H), 2.42 (m, 1 H, HC(5)), 2.20 (m, 1 H), 2.03 (m, 1 H), 1.82 (m, 1 H), 1.32 (t, $J = 7.1$ Hz, 3 H, CH₂CH₃), 1.01 (d, $J = 6.2$ Hz, 3 H, H₃CC(4)), 0.97 (d, $J = 7.1$ Hz, 3 H, H₃CC(2)); MS m/e (rel intensity) (no M⁺), 224 (14), 177 (14), 167 (11), 165 (12), 149 (18), 137 (17), 121 (100), 119 (15), 109 (20), 107 (19), 105 (15), 93 (65), 91 (21), 81 (24), 79 (29), 67 (25), 55 (29), 43 (20), 41 (38), 29 (52). Anal. (C₁₃H₁₉NO₃) C, H, N.

Ethyl *rac*-2,4,5-Trimethyl-3-nitro-8-oxobicyclo[3.2.1]octane-carboxylate (10). *rac*-**2c** (870 mg, 5 mmol) was allowed to react with *rac*-**1f** (1.34 g, 6 mmol) in 1 mL THF according to GP I (70 h room temperature, 5 h heating under reflux) to give a diastereoisomeric mixture, from which pure **10** (164 mg, 12%, $d > 90\%$) was isolated by FC (pentane/ether 2:1) together with a mixture of diastereoisomers (91 mg, 6%). For analytical purposes the pure fraction was recrystallized from pentane at -20 °C: mp 112–113 °C; ¹H NMR (300 MHz) δ 4.72 (dd, $J = 11.8, 6.0$ Hz, 1 H, HC(3)), 4.28 (q, $J = 7.1$ Hz, 2 H, OCH₂), 3.30 (qdd, $J_q = 6.2, J_d = 11.8, 0.8$ Hz, 1 H, HC(2)), 2.57–2.49 (m, 2 H), 2.08–1.87 (m, 2 H), 1.32 (t, $J = 7.1$ Hz, 3 H, CH₂CH₃), 1.02 (d, $J = 6.2$ Hz, 3 H, CH₃C(2)); 0.81 (d, $J = 7.1$ Hz, 3 H, CH₃C(4)); MS m/e (rel intensity) 283 (M⁺, 0.3), 238 (17), 209 (10), 179 (25), 163 (18), 151 (35), 139 (11), 135 (100), 123 (19), 121 (24), 109 (48), 107 (79), 93 (44), 69 (53). Anal. (C₁₄H₂₁NO₅) C, H, N.

***rac*-2,4-Dimethyl-3-nitrobicyclo[3.3.1]nonan-9-one (11a and 11b).** *rac*-**2c** (400 mg, 2.3 mmol) was allowed to react with *rac*-**1g** (384 mg, 2.5 mmol) in THF (1 mL) according to GP I (70 h room temperature, 5 h heating under reflux) to give two diastereoisomers which were separated by FC (pentane/ether 4:1) to give **11a** (204 mg, 42%) in the form of a crystallizing oil and **11b** (80 mg, 16%) as an oil. For analysis, **11a** was recrystallized from pentane/ether (5:1). **11a**: mp 119–120 °C; ¹H NMR (300 MHz) δ 5.27 (dd, $J = 12.1, 6.5$ Hz, 1 H, HC(3)), 2.96 (qdd, $J_q = 6.6$ Hz, $J_d = 12.1$, ca. 6 Hz, 1 H, HC(2)), 2.87 (qdd, $J_q = 7.2$ Hz, $J_d = 6.5, 2.2$ Hz, 1 H, HC(4)), 2.38 (br s, 2 H, HC(1), HC(5)), 2.30–2.14 (m, 3 H), 1.92–1.65 (m, 3 H), 1.11 (d, $J = 6.6$ Hz, 3 H, CH₃), 0.89 (d, $J = 7.2$ Hz, 3 H, CH₃); ¹³C NMR δ 215.69 (C(9)), 89.77 (C(3)), 52.99 (CH), 50.50 (CH), 41.82 (CH), 34.22 (CH), 33.37 (CH₂), 28.94 (CH₂), 20.52 (C(7)), indicating a chair-chair conformation,^{44a} in agreement with the low field HC(3) signal in the ¹H NMR at 5.27 ppm and the coupling pattern described in the text), 15.72 (2 \times CH₃); MS m/e (rel intensity) 211 (M⁺, 26), 165 (24), 137 (71), 135 (17), 109 (35), 107 (24), 96 (16), 95 (100), 93 (31), 81 (98), 79 (18), 69 (93), 67 (69), 55 (86), 43 (44), 41 (30). Anal. (C₁₁H₁₇NO₃) C, H, N. **11b**: ¹H NMR (300 MHz) δ 3.81 (tdd, $J = 11.8$ Hz, 1 H, HC(3)), 2.66 (qdd, $J_q = 6.8$ Hz, $J_d = 11.8, 3.2$ Hz, 2 H, HC(2), HC(4)), 2.18 (m, 2 H, HC(1), HC(5)), 2.13–1.87 (m, 5 H), 1.68 (m, 1 H, HC(7)-exo), 1.05 (d, $J = 6.75$ Hz, 6 H, 2 \times CH₃); ¹³C NMR δ 216.03 (CO), 93.93 (C(3)), 52.40 (C(1), C(5)), 39.44 (C(2), C(4)), 34.93 (C(6), C(8)), 19.94 (2 \times CH₃), 16.61 (C(7)), indicating a chair-boat conformation,^{44a} (C(7) in the chair part) in agreement with the C(3) signal in the ¹H NMR at 3.81 ppm and the NOE experiment; MS m/e (rel intensity) 211 (M⁺, 10), 165 (19), 164 (44), 149 (30), 137 (38), 121 (24), 107 (24), 95 (73), 81 (98), 69 (45), 55 (57), 41 (100). Anal. (C₁₁H₁₇NO₃) C, H, N.

NOE Experiment (11b). Irradiation on the hydrogen at C(2) (respectively C(4)) gave a positive NOE at the bridge head hydrogens (HC(1) respectively HC(5)), at the multiplet corresponding to H_{endo}C(7) and H_{exo}C(6) (respectively H_{exo}C(8)) at the methyl group attached to C(2) (respectively C(4)) and surprisingly also at HC(3). (A NOE between two vicinal and trans diaxial hydrogens.) Irradiation on the hydrogen at C(3) gave a positive NOE at the bridge head hydrogens (HC(1) respectively HC(5)), at the methyl group attached to C(2) (respectively C(4)) and again at HC(2) (respectively HC(4)). These NOE experiments were only compatible with the expected chair-boat conformation with the substituents in the boat part.

(+)-2,4-Dimethyl-3-nitrobicyclo[3.3.1]nonan-9-one (11a). *E*-(+)-**2c** (568 mg, 3.4 mmol, 80% ee) was allowed to react with **1g** (568 mg, 3.5 mmol) in THF (1–2 mL) according to GP I to give after FC and recrystallization (see *rac*-**11a**) 266 mg (40%) of a crystalline compound which was recrystallized into two fractions, first *rac*-**11a** (138 mg, mp 120 °C) and second (+)-**11a** (82 mg, $[\alpha]_D = +40.8^\circ$, mp 104–106 °C). (In a preliminary experiment, the recrystallized mixture had an $[\alpha]_D$ value of +11.4°). Spectral data (¹H and ¹³C NMR, IR, MS) were identical with those of *rac*-**11a**.

***rac*-1,2,4-Trimethyl-3-nitrobicyclo[3.3.1]nonan-9-one (12).** *rac*-**2c** (870 mg, 5 mmol) was allowed to react with *rac*-**1i** (908 mg, 5.5 mmol) in THF (1 mL) according to GP I (70 h room temperature, 10 h heating under reflux) to give two diastereoisomers in a ratio of 6:1 (¹H NMR analysis). FC (pentane/ether 5:1) failed to separate the diastereoisomers but provided them as a mixture (379 mg, 34%) in the form of a crystallizing oil. Recrystallization from pentane/ether (5:1) gave diastereomerically pure **12** (261 mg, 23%): mp 81–84 °C; ¹H NMR (300 MHz) δ 5.34 (dd, $J = 11.9, 6.5$ Hz, 1 H, HC(3)), 2.85 (qdd, $J_q = 7.2, J_d = 6.5, 2.4$ Hz, 1 H, HC(4)), 2.61 (qdd, $J_q = 6.5$ Hz, $J_d = 12$ Hz, 1 H, HC(2)), 2.48 (br s, 1 H, HC(5)), 2.21–2.09 (m, 3 H), 1.87–1.45 (m, 3 H), 1.10 (d, $J = 6.5$ Hz, 3 H, CH₃C(2)), 1.07 (s, 3 H, CH₃C(1)), 0.86 (d, $J = 7.2$ Hz, 3 H, CH₃C(4)); ¹³C NMR δ 215.19 (CO), 90.67 (CH-3), 53.12 (CH), 41.77 (CH), 40.11 (CH), 36.94 (CH₂), 33.26 (CH₂), 21.62 (CH₃), 21.06 (C(7)), indicating a chair-chair conformation,^{44a} see **11a**), 15.74 (CH₃), 12.73 (CH₃); MS m/e (rel intensity) 179 (9), 151 (16), 109 (40), 107 (15), 95 (100), 83 (15), 81 (54), 69 (71), 67 (30), 55 (41), 43 (29), 41 (56). Anal. (C₁₂H₁₉NO₃) C, H, N.

***rac*-7,9-Dimethyl-8-nitrobicyclo[4.3.1]decan-10-one (13a and 13b).** *rac*-**2c** (870 mg, 5 mmol) was allowed to react with **1j** (755 mg, 5.5 mmol) according to GP I (36 h room temperature, 15 h heating under reflux) to give, after FC (pentane/ether 5:1), the two diastereomerically pure [4.3.1]octanone derivatives **13a** [444 mg (35%)] and **13b** [293 mg (25%)]. **13a**: mp 65 °C; ¹H NMR (300 MHz) δ 5.00 (dd, $J = 11.1, 4.6$ Hz, 1 H, HC(8)), 2.90–2.54 (m, 4 H), 2.17–2.06 (m, 1 H), 1.90–1.38 (m, 7 H), 1.08 (d, $J = 6.6$ Hz, 3 H, CH₃), 0.98 (d, $J = 7.1$ Hz, 3 H, CH₃); MS m/e (rel intensity) 225 (14, M⁺), 179 (8), 161 (9), 151 (17), 121 (9), 109 (45), 107 (13), 95 (96), 81 (67), 55 (90), 41 (100). Anal. (C₁₂H₁₉NO₃) C, H, N.

13b: mp 81–82 °C; ¹H NMR (300 MHz) δ 3.97 (t (dd), $J = 11.0$ Hz, 1 H, HC(8)), 2.74–2.66 (qdd, $J_q = 6.6$ Hz, $J_d = 11.0$ Hz, 2 H, HC(7), HC(9)), 2.32–2.25 (m, 2 H, HC(1), HC(6)), 2.03–1.93 (m, 2 H), 1.85–1.67 (m, 4 H), 1.57–1.47 (m, 2 H), 1.02 (d, $J = 6.6$ Hz, 6 H, 2 \times CH₃); MS m/e (rel intensity) 225 (14, M⁺), 179 (9), 178 (18), 163 (29), 151 (10), 135 (18), 124 (40), 121 (14), 109 (44), 95 (100), 81 (60), 69 (60), 67 (45), 55 (88), 41 (85). Anal. (C₁₂H₁₉NO₃) C, H, N.

***rac*-6,8-Dimethyl-7-nitro-3'-methoxy-2,3-benzobicyclo[3.3.1]nonan-9-one (14a and 14b).** *rac*-**2c** (870 mg, 5 mmol) was allowed to react with **1l** (6-methoxy, 1.26 g, 5.5 mmol) by following GPI (100 h room temperature) to give two diastereoisomers in a ratio of 5:4 (¹H NMR analysis), which could not be separated by FC (pentane/ether 6:1). The yield was 755 mg (52%) of the pure diastereomeric mixture. Three recrystallizations from pentane/ethyl acetate (2:1) gave **14a** (200 mg, 14%, $d > 90\%$). From the mother liquid of the first crystallization, after three additional recrystallizations **14b** (150 mg, 10%, $d > 90\%$) was isolated. **14a**: mp 176–178 °C; ¹H NMR (300 MHz) δ 6.97 (d, $J = 8.5$ Hz, 1 H, CH_{arom}), 6.83 (dd, $J = 8.5, 2.7$ Hz, 1 H, CH_{arom}), 6.68 (d, $J = 2.5$ Hz, 1 H, CH_{arom}), 4.51 (dd, $J = 12.1, 5.2$ Hz, 1 H, HC(7)), 3.81 (s, 3 H, OCH₃), 3.36 (d, $J = 18.2$ Hz, 1 H, HC(4)), 3.33 (br s, 1 H, HC(1)), 3.19 (dd, $J_{gem} = 18.2$ Hz, $J_{vic} = 6.4$ Hz, 1 H, HC(4)), 3.00 (qdd, $J_q = 6.4$ Hz, $J_d = 11.8, 6.4$ Hz, 1 H, HC(6)), 2.79 (m, 1 H, HC(8)), 2.68 (m, 1 H, HC(5)), 1.14 (d, $J = 6.5$ Hz, 3 H, CH₃), 1.04 (d, $J = 7.2, 3$ H, CH₃). (By analogy to **11a**, **14a** was assigned to have a chair conformation in the nitro-substituted ring, where the HC(7), due to the presence of the benzo system, appears at 4.5 ppm and not at >5 ppm as for the corresponding HC(3) in **11a**); MS m/e (rel intensity) 289 (75, M⁺), 215 (91), 187 (29), 173 (73), 161 (28), 160 (34), 159 (38), 158 (21), 115 (28), 69 (100), 41 (72). Anal. (C₁₆H₁₉NO₄) C, H, N.

14b: mp 152 °C; ¹H NMR (300 MHz) δ 6.97 (d, $J = 8.5$ Hz, 1 H, CH_{arom}), 6.84 (dd, $J = 8.5, 2.6$ Hz, 1 H, CH_{arom}), 6.65 (d, $J = 2.5$ Hz, 1 H, CH_{arom}), 3.95 (dd, $J = 11.8, 10.1$ Hz, 1 H, HC(7)), 3.80 (s, 3 H, OCH₃), 3.32 (dd, $J = 16.8, 4.3$ Hz, 1 H, H_{exo}C(4)), 3.19 (dd, $J = 16.8$ Hz, 2.5, 1 H, H_{endo}C(4)), 3.13 (br s, 1 H, HC(1)), 2.84 (qdd, $J_q = 7.0$ Hz, $J_d = 10.1, 1.0$ Hz, 1 H, HC(8)), 2.70 (qdd, $J_q = 6.7$ Hz, $J_d = 11.8, 6.5$ Hz, 1 H, HC(6)), 2.36 (m, 1 H, HC(5)), 1.25 (d, $J = 7.0$ Hz, 3 H, CH₃), 1.08 (d, $J = 6.7, 3$ H, CH₃). (By analogy to **11b** the nitro-substituted ring of compound **14b** was assigned to have a boat conformation, in agreement with the NOE experiment); MS m/e (rel intensity) 289 (66, M⁺), 215 (64), 187 (13), 173 (45), 161 (21), 160 (28), 159 (30), 158 (15), 145 (15), 115 (24), 77 (15), 69 (100), 55 (22), 41 (57). Anal. (C₁₆H₁₉NO₄) C, H, N.

NOE Experiment (14b). Irradiation on the hydrogen at C(6) gave a positive NOE at the bridge-head hydrogen HC(5), at the HC(4) signal at 3.19 ppm (indicating that this signal corresponds to H_{endo}C(4)), at the methyl group attached to C(6), and still surprisingly also at HC(7). This is a NOE between two vicinal and trans diaxial hydrogens! Irradiation on the hydrogen at C(7) gave a positive NOE at the bridge head hydrogens HC(1) and HC(5), at the two methyl groups attached to C(6) and C(8), and again at HC(6) and HC(8). These NOE experiments were only compatible with a chair-boat conformation with the methyl and

(77) The major one has the same signal pattern (dd) for C(3) as **9**. This is the only example where two diastereoisomers have the opposite configuration to each other at both methyl-bearing C atoms.

the nitro substituents in the boat part.

(+)-(2R,3S)-3-Nitro-2-phenylbicyclo[3.3.1]nonan-9-one (15). Reaction of **2b** (5.35 g, 20.3 mmol) with **1n** (3.87 g, 20 mmol) according to GP III gave after FC (CH_2Cl_2 /petroleum ether 2:1) and recrystallization (ether) **15** (1.73 g, 34%) as colorless crystals ($d > 95\%$, $ee^{78} > 95\%$): mp 101–102 °C; $[\alpha]_D^{25} = +58.8$ ($c = 1$, CH_2Cl_2); ^1H NMR (300 MHz) δ 7.43–7.01 (m, 5 H), 4.60 (td (ddd), $J_1 = 12$ Hz, $J_d = 5$ Hz, 1 H, HC(3)), 3.75 (dd, $J = 12$, 3 Hz, 1 H, HC(2)), 2.80–1.60 (m, 10 H); ^{13}C NMR δ 215.25 (s), 140.86 (CH), 128.84 (CH), 127.69 (CH), 127.37 (CH), 126.39 (CH), 85.93 (CH), 52.88 (CH), 51.07 (CH₂), 42.84 (CH), 35.28 (CH₂), 34.89 (CH₂), 32.39 (CH₂), 15.38 (C(7), indicating together with the coupling pattern of the ^1H NMR a chair-boat conformation^{44a} similar to **11b**); MS m/e (rel intensity) 259 (M^+ , 0.7), 212 (100), 184 (16), 144 (33), 117 (35), 91 (72), 59 (12), 43 (20), 29 (11). Anal. ($\text{C}_{15}\text{H}_{17}\text{NO}_3$) C, H, N.

(+)-(2R,3S,7S)-7-tert-Butyl-3-nitro-2-phenylbicyclo[3.3.1]nonan-9-one (16a) and (+)-(2R,3R,7R)-7-tert-Butyl-3-nitro-2-phenylbicyclo[3.3.1]nonan-9-one (16b). From **2b** (2.51 g, 9.5 mmol) and **1p** (2.37 g, 9.4 mmol) were obtained by following GP III, two crystalline diastereoisomers in a 5:1 ratio. **16a** (1.14 g, 39%) and **16b** (0.21 g, 7%) were isolated in diastereomerically pure form by fractional crystallization (ee of **16a** $> 95\%$, ee of **16b** was not determined). **16a**: mp 206–207 °C; $[\alpha]_D^{25} = +30.7^\circ$ ($c = 1.32$, CH_2Cl_2); ^1H NMR (300 MHz) δ 7.36–7.12 (m, 5 H, phenyl), 4.60 (td (ddd), $J_1 = 12$ Hz, $J_d = 4$ Hz, 1 H, HC(3)), 3.79 (dd, $J = 12$, 4 Hz, 1 H, HC(2)), 2.90–2.52 (m, 4 H, 2 \times HC(4), HC(1), HC(5)), 2.28–2.08 (m, 3 H, HC(7), $\text{H}_{ax}\text{C}(8)$, $\text{H}_{eq}\text{C}(6)$), 1.77 (td (ddd), $J_1 = 14$ Hz, $J_d = 2.5$ Hz, 1 H), 1.73 (td (ddd), $J_1 = 14$ Hz, $J_d = 3$ Hz, 1 H), 0.98 (s, 9 H, ^tbu); ^{13}C NMR δ 216.07 (s), 140.85 (s), 129.02 (CH), 127.85 (CH), 127.24 (CH), 86.10 (CH), 52.17 (CH), 51.75 (CH), 42.16 (CH), 36.67 (HC(7)), 36.55, 36.18, 33.07, 31.97, 27.76 (CH₃) (the signal for C(7) appears at 36.7 ppm, which clearly indicates a chair-boat conformation,^{44a} in agreement with the same signal pattern in the ^1H NMR as **15**); MS m/e (rel intensity) 315 (M^+ , 1.9), 269 (21), 268 (81), 212 (20), 211 (21), 185 (10), 183 (12), 171 (16), 155 (10), 144 (21), 143 (19), 129 (23), 117 (67), 115 (33), 105 (18), 91 (96), 83 (17), 69 (16), 57 (100), 55 (31), 41 (56), 29 (27). Anal. ($\text{C}_{19}\text{H}_{25}\text{NO}_3$) C, H, N. **16b**: mp 206 °C; $[\alpha]_D^{25} = +66.3^\circ$ ($c = 1.32$, CH_2Cl_2); ^1H NMR (300 MHz) δ 7.36–7.04 (m, 5 H, phenyl), 5.50 (ddd, $J = 13$, 6, 4 Hz, 1 H, HC(3)), 3.99 (td (ddd), $J_1 = 2$ Hz, $J_d = 6$ Hz, 1 H, HC(2)), 2.88–2.70 (m, 3 H, HC(1), $\text{H}_{eq}\text{C}(4)$, HC(5)), 2.64–2.55 (dddd, $J = 14$, 11.5, 5, 2.5 Hz, 1 H, $\text{H}_{eq}\text{C}(6)$ or $\text{H}_{eq}\text{C}(8)$), 2.49–2.40 (dddd, $J = 14$, 11.5, 5, 2.5 Hz, 1 H, $\text{H}_{eq}\text{C}(6)$ or $\text{H}_{eq}\text{C}(8)$), 2.32 (dddd, $J = 13$, 4, 2, 2 Hz, 1 H, $\text{H}_{ax}\text{C}(4)$), 1.93 (td (ddd), $J_1 = 14$ Hz, $J_d = 3$ Hz, 1 H, $\text{H}_{ax}\text{C}(6)$ or $\text{H}_{ax}\text{C}(8)$), 1.80 (td (ddd), $J_1 = 14$ Hz, $J_d = 3$ Hz, 1 H, $\text{H}_{ax}\text{C}(6)$ or $\text{H}_{ax}\text{C}(8)$), 1.42–1.26 (t (ddd), $J = 14$, 5 Hz, 1 H, HC(7)) 0.93 (s, 9 H, ^tbu) (Besides the lack of any methine ^{13}C NMR signal below 40 ppm,^{44a} the upfield shift of the resonance of HC(7) in the ^1H NMR of about 1 ppm relative to **16a**, together with the large coupling constant^{44c} of 11.5 Hz between HC(6) or (8) and HC(5) or (1)), indicates a boat-chair conformation with the boat in the *tert*-butyl-substituted ring); ^{13}C NMR δ 217.33 (s), 136.42 (s), 129.22 (CH), 128.85 (CH), 128.25 (CH), 79.41 (CH), 54.82 (CH), 47.79 (CH), 41.88 (CH), 40.23 (CH), 34.19 (CH₂), 32.29 (CH₂), 32.05 (CH₂), 27.9 (CH), 27.35 (CH₃); MS m/e (rel intensity) 315 (M^+ , 1.7), 269 (15), 268 (57), 212 (12), 211 (13), 174 (20), 143 (12), 117 (33), 115 (17), 105 (11), 91 (42), 84 (19), 83 (16), 69 (20), 57 (100), 55 (26), 43 (24), 41 (32), 29 (15). Anal. ($\text{C}_{19}\text{H}_{25}\text{NO}_3$) C, H, N.

(+)-(2S,3R,7R)-2-*n*-Butyl-7-*tert*-butyl-3-nitrobicyclo[3.3.1]nonan-9-one (17). Reaction of **2a** (0.63 g, 2.9 mmol) and **1p** (9.73 g, 2.9 mmol) according to GP III provided after recrystallization (pentane/ether) **17** (0.32 g, 37%, $d > 90\%$, $ee = 90\%$) as colorless crystals: mp 124 °C; $[\alpha]_D^{25} = +46.5^\circ$ ($c = 0.8$, CH_2Cl_2); ^1H NMR (300 MHz) δ 5.20 (td (ddd), $J_1 = 4$ Hz, $J_d = 12.5$ Hz, 1 H, HC(3)), 2.78–2.26 (m, 7 H), 1.76 (td (ddd), $J_1 = 14$ Hz, $J_d = 3$ Hz, 1 H, $\text{H}_{ax}\text{C}(6)$ or $\text{H}_{ax}\text{C}(8)$), 1.62 (td (ddd), $J_1 = 14$ Hz, $J_d = 3$ Hz, 1 H, $\text{H}_{ax}\text{C}(6)$ or $\text{H}_{ax}\text{C}(8)$), 1.58–1.35 (m, 1 H, HC(7)), 0.90 (s, 9 H, ^tbu), 1.29–1.04 (m, 6 H), 0.86 (t, $J = 7$ Hz, 3 H, $\text{H}_3\text{C}(4'')$) (boat-chair conformation,^{44a} assignment by analogy to **16b**); ^{13}C NMR δ 216.23, 78.8, 48.1, 45.6, 41.8, 41.3, 33.1, 32.8, 31.9, 31.6, 29.4, 27.5, 26.3, 22.5, 14.4; MS m/e (rel intensity) 296 (M^+ , 0.3), 173 (11), 163 (11), 149 (10), 123 (14), 111 (20), 109 (21), 107 (17), 97 (15), 95 (39), 93 (17), 85 (23), 83 (39), 81 (39), 79 (21), 69 (41), 67 (35), 57 (100), 55 (56), 43 (28), 41 (62), 29 (29). Anal. ($\text{C}_{17}\text{H}_{29}\text{NO}_3$) C, H, N.

(-)-(6R,7R)-7-Nitro-6-phenyl-2,3-benzobicyclo[3.3.1]nonan-9-one (18). The reaction of **2b** (3.01 g, 11.7 mmol) and **1q** (2.85 g, 11.7 mmol) according to GP III yielded after recrystallization (ether) **18** (1.58 g,

44%, $d > 90\%$). The configuration was established by 2D ^1H NMR spectroscopy:⁷⁹ mp 188–189 °C; $[\alpha]_D^{25} = -99.7^\circ$ ($c = 1.68$, CH_2Cl_2); ^1H NMR (300 MHz) δ 7.36–7.05 (m, 9 H, CH_{arom}), 5.10–5.00 (ddd, $J = 13$, 7, 4.5 Hz, 1 H, HC(7)), 4.14 ppm (ddd, $J = 7$, 2, 2 Hz, 1 H, HC(6)), 3.75 (ddd, $J = 3.5$, 3.5, 2 Hz, 1 H, HC(5)), 3.75–3.65 (dd, $J = 18$, 7 Hz, 1 H, $\text{H}_{eq}\text{C}(8)$), 3.53 (dd, $J = 18$, 2 Hz, 1 H, $\text{H}_{ax}\text{C}(8)$), 3.10 (dddd, $J = 7$, 2, 2, 2 Hz, 1 H, HC(1)), 2.93 (ddd, $J = 13$, 13, 3.5 Hz, 1 H, $\text{H}_{ax}\text{C}(4)$), 2.42–2.34 (dddd, $J = 13$, 4.5, 3.5, 2 Hz, 1 H, $\text{H}_{eq}\text{C}(4)$) (The chemical shift for HC(3) of 5.1 ppm and the coupling constants in the ^1H NMR^{44c} indicates a chair conformation for the nitrosubstituted ring); MS m/e (rel intensity) 307 (M^+ , 1.1), 231 (21), 205 (20), 155 (12), 130 (12), 129 (90), 128 (18), 118 (12), 117 (96), 116 (18), 115 (52), 105 (36), 103 (11), 91 (100), 77 (13). Anal. ($\text{C}_{19}\text{H}_{17}\text{NO}_3$) C, H, N.

rac-4-Nitro-2,3,5,6-tetramethylcyclohexanol (20 and 21). *rac*-5 (C(6) epimeric mixture (8:1)) (300 mg, 1.5 mmol) in ethanol (10 mL) was treated with NaBH_4 (60 mg, 1.5 mmol) at 0 °C for 3 h. After careful addition of 10% HCl (2 mL) the solvent was evaporated and FC (pentane/ether 3:1) gave pure alcohol **20** (134 mg, 44%), a fraction contaminated with starting material (56 mg, 19%), and **21** (80 mg, 25%). The ratio of axial to equatorial alcohols was about 3:1. For analysis, samples were crystallized at -50 °C from pentane/ether (5:1). **20**: mp 68–70 °C; ^1H NMR (300 MHz) δ 4.47 (dd, $J = 11.2$, 5.4 Hz, 1 H, HC(4)), 3.53 (br s, 1 H, HC(1)), 2.38 (qdd, $J_q = 6.2$ Hz, $J_d = 11.2$, 11.2 Hz, 1 H, HC(3)), 2.26 (qdd, $J_q = 7.4$ Hz, $J_d = 5.4$, 2.1 Hz, 1 H, HC(5)), 2.13 (qdd, $J_q = 7.5$ Hz, $J_d = 2.4$, 2.1 Hz, 1 H, HC(6)), 1.55 (br s, 1 H, OH), 1.50 (qdd, $J_q = 6.9$ Hz, $J_d = 11.2$, 4.2 Hz, 1 H, HC(2)), 1.15 (d, $J = 7.4$ Hz, 3 H, $\text{H}_3\text{CC}(5)$), 1.08 (d, $J = 6.8$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.07 (d, $J = 7.5$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 0.97 (d, $J = 6.3$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), (+ D_2O , the signal at 1.55 disappears); MS m/e (rel intensity) no M^+ , 173 (1), 155 (5), 138 (11), 137 (100), 121 (4), 111 (13), 109 (11), 97 (39), 96 (8), 95 (38), 85 (19), 83 (15), 81 (26), 69 (75), 67 (15), 57 (27), 55 (65), 43 (38), 41 (53). Anal. ($\text{C}_{10}\text{H}_{19}\text{NO}_3$) C, H, N.

NOE Experiment. Irradiation at the signal of the axial methyl group at C(5) gave a positive NOE of the signals due to HC(6), HC(5), and HC(3). No NOE was observed at HC(1), indicating that the OH-group is in axial position.

21: mp 115–116 °C; ^1H NMR (300 MHz) δ 4.51 (dd, $J = 11.7$, 5.1 Hz, 1 H, HC(4)), 3.61 (dd, $J = 10.5$, 4.9 Hz, 1 H, HC(1)), 2.42 (qdd, $J_q = 7.3$ Hz, $J_d = 5.1$, 2.4 Hz, 1 H, HC(5)), 2.11 (qdd, $J_q = 7.2$ Hz, $J_d = 4.9$, 2.2 Hz, 1 H, HC(6)), 2.01 (qdd, $J_q = 6.2$ Hz, $J_d = 11.5$, 11.5 Hz, 1 H, HC(3)), 1.52 (br s, 1 H, OH), 1.35 (qdd, $J_q = 6.4$ Hz, $J_d = 11.1$, 10.5 Hz, 1 H, HC(2)), 1.11 (d, $J = 6.4$ Hz, 3 H, $\text{H}_3\text{CC}(2)$), 1.08 (d, $J = 7.2$ Hz, 3 H, $\text{H}_3\text{CC}(6)$), 1.03 (d, $J = 7.3$ Hz, 3 H, $\text{H}_3\text{CC}(5)$), 0.99 (d, $J = 6.2$ Hz, 3 H, $\text{H}_3\text{CC}(3)$), (+ D_2O , the signal at 1.52 disappears); MS m/e (rel intensity) no M^+ , 155 (11), 138 (11), 137 (100), 121 (7), 109 (8), 97 (68), 96 (14), 95 (30), 85 (26), 83 (20), 81 (21), 69 (65), 57 (25), 55 (62), 45 (20), 43 (39), 41 (40). Anal. ($\text{C}_{10}\text{H}_{19}\text{NO}_3$) C, H, N.

rac-9-Hydroxy-3-nitro-2-phenylbicyclo[3.3.1]nonane (22). Sodium borohydride (33.8 mg, 0.8 mmol) was added in portions to a solution of **15** (0.46 g, 1.8 mmol) in ethanol (50 mL) at 0 °C under argon. The mixture was allowed to warm up to room temperature, and after careful addition of 1 N HCl (10 mL), the mixture was extracted with CH_2Cl_2 ($\times 3$). Removal of the solvent and recrystallization ($\times 2$) from boiling ether gave **22** (0.29 g, 62%) as colorless crystals: mp 192–94 °C; ^1H NMR (300 MHz) δ 7.2–7.12 (m, 5 H, CH_{arom}), 4.22 (m, 1 H), 3.54–3.46 (m, 1 H), 2.54 (br s, 1 H), 2.42–2.26 (m, 1 H), 1.94 (dd, $J = 12$, 5 Hz, 1 H), 1.80–1.24 (m, 7 H); MS m/e (rel intensity) 243 (M^+ , 5), 213 (40), 133 (11), 129 (17), 128 (11), 117 (33), 115 (25), 105 (17), 91 (100), 81 (44), 79 (17), 77 (12), 67 (14), 41 (14).

rac-2,4-Dimethyl-5-hydroxy-3-nitrocyclooctanecarboxylic Acid Lactones (23a and 23c). *m*-Chloroperbenzoic acid (1 g, 55% purity, 3.2 mmol) was added to a solution of **11a** (100 g, 0.5 mmol) in CH_2Cl_2 (10 mL) and the mixture stirred at room temperature for 1 week. Another portion of peracid (0.5 g, 55% purity, 1.6 mmol) was added and the reaction stirred for a further week. Sodium thiosulfate solution (10%, 10 mL) was added and the mixture extracted with CH_2Cl_2 (3×20 mL), washed with a saturated NaHCO_3 solution (10 mL), and brine (10 mL) and evaporated to give the crude product. FC (pentane/ether 1:1) yielded an unseparated 1:1 mixture of the two diastereoisomeric lactones **23a** and **23c** (72 mg, 67%): mp 120–123 °C; ^1H NMR (300 MHz) δ 5.1–5.0 (m, 1 H (**23a**) + 1 H (**23c**), HC(5)), 4.6–4.4 (2m, 1 H (**23a**) + 1 H (**23c**), HC(3)), 3.3–1.7 (m), 1.12–1.04 (m, 12 H, 2 CH_3 (**23a**) + 2 CH_3 (**23c**)). Anal. ($\text{C}_{11}\text{H}_{17}\text{NO}_4$) C, H, N.

rac-5-Hydroxy-2,4,5-trimethyl-3-nitrocyclooctanecarboxylic Acid Lactone (23b). *m*-Chloroperbenzoic acid (1 g, 55% purity, 3.2 mmol) was added to a solution of **12** (100 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) and the mixture stirred at room temperature for 1 week. Another portion of peracid (0.5 g, 55% purity, 1.6 mmol) was added and stirred for a further week. Sodium thiosulfate solution (10%; 10 mL) was added and

(78) The enantiomeric excess was determined by NMR in the presence of the chiral shift reagent $\text{Eu}(\text{dcm})_3$.

the mixture extracted with CH_2Cl_2 (3 \times 20 mL), washed with a saturated NaHCO_3 solution (10 mL), and brine (10 mL), and evaporated to give the crude product. FC (pentane/ether 2:1) yielded crystalline **23b** (57 mg, 53%, $d > 90\%$): mp 142–43 °C; ^1H NMR (300 MHz) δ 5.15 (dd, $J = 11.9, 5.4$ Hz, 1 H, HC(3')), 3.16 (br m, 1 H, HC(1')), 2.86 (qd, $J_a = 6.6$ Hz, $J_d = 12$ Hz, 1 H, HC(4')), 2.61 (qm, $J_a = 6.5$ Hz, 1 H, HC(2')), 2.2–1.7 (m, 6 H), 1.51 (s, 3 H, $\text{H}_3\text{C}(5')$), 1.06 (d, $J = 6.5$ Hz, 3 H, H_3C), 1.04 (d, $J = 6.5$ Hz, 3 H, H_3C); MS m/e (rel intensity) no M^+ , 195 (7), 177 (9), 149 (13), 121 (10), 109 (32), 107 (14), 95 (25), 81 (25), 69 (100), 67 (22), 55 (27), 43 (79), 41 (56). Anal. ($\text{C}_{12}\text{H}_{19}\text{NO}_4$) C, H, N.

(1*R*,2'*S*,3'*R*)-2-[3'-(Methoxymethoxy)-2'-nitrocyclohexenyl]-1-phenylethan-1-one (**24**). *N*-(1-Phenylethenyl)morpholine (1.2 g, 6.4 mmol) was allowed to react with (*S*)-**2g** (1.0 g, 5.4 mmol) in THF (5 mL) according to GP IV (72 h, 4 °C). FC (pentane/ether 3:1) gave **24** (1.45 g, 89%) as a colorless oil (diastereomeric ratio 3*R*:3*S* = 13:1): ^1H NMR (300 MHz) δ 7.92–7.42 (m, 5 H, CH_{arom}), 5.17 (t (dd), $J = 4.5$ Hz, 1 H, HC(2')), 4.71 (d, $J = 7.0$ Hz, 1 H, OCH_2O), 4.68 (d, $J = 7.0$, 1 H, OCH_2O), 3.9 (ddd, $J = 12.0, 4.5$ and 4.5 Hz, 1 H, HC(3')), 3.37 (s, 3 H, OCH_3), 3.03 (dd, $J = 18.1, 7.2$ Hz, 1 H, HC(2')), 2.91 (dd, $J = 18.1, 7.2$ Hz, 1 H, HC(2')), 2.63 (m, 1 H, HC(1')), 2.20–1.18 (m, 6 H, $(\text{CH}_2)_3$). The analysis was carried out with the deprotected, crystalline alcohol. Anal. ($\text{C}_{14}\text{H}_{17}\text{NO}_4$) C, H, N.

(1*S*,1'*R*,2'*S*,3'*R*)-5-Methoxy-1-[3'-(methoxymethoxy)-2'-nitrocyclohexenyl]-2-tetralone (**25**). **11** (5-methoxy, 1.5 g, 6.1 mmol) was allowed to react with (*S*)-**2g** (1.0 g, 5.4 mmol) in THF (20 mL) according to GP IV (72 h, 4 °C) to give **25** (0.87 g, 45%) as rhombic, colorless crystals: mp 134–136 °C; $[\alpha]_D = -82.7^\circ$ ($c = 1.0$, CHCl_3); ^1H NMR (300 MHz) δ 7.27 (dd, $J = 8.0, 7.5$ Hz, 1 H, CH_{arom}), 7.04 (d, $J = 7.5$ Hz, 1 H, CH_{arom}), 6.84 (d, $J = 8.0$ Hz, 1 H, CH_{arom}), 4.65 (d, $J = 7.0$ Hz, 1 H, OCH_2O), 4.55 (dd, $J = 10.0, 9.5$ Hz, 1 H, HC(2')), 4.53 (d, $J = 7.0$ Hz, 1 H, OCH_2O), 4.04 (ddd, $J = 11.5, 10.0$ and 4.5 Hz, 1 H, HC(1')), 3.86 (s, 3 H, ArOCH_3), 3.42–3.35 (m, 1 H), 3.29 (s, 3 H, CH_2OCH_3), 3.25 (d, $J = 2.5$ Hz, 1 H, C(2)), 3.08 (tt (dddd), $J = 12.5, 2.5$ Hz, 1 H), 2.73–2.08 (m, 4 H), 1.65–1.40 (m, 2 H), 1.30 (tt (dddd), $J = 13.0, 3.5$ Hz, 1 H), 1.18–0.68 (m, 2 H); MS m/e (rel intensity) 364 ($\text{M}^+ + 1$), 363 (M^+ , 7), 301 (6), 284 (11), 271 (25), 254 (19), 253 (39), 211 (17), 191 (14), 176 (32), 175 (25), 147 (27), 111 (17), 45 (100). Anal. ($\text{C}_{19}\text{H}_{25}\text{NO}_6$) C, H, N. Crystal structure analysis⁷⁹ of **25**: Formula, $\text{C}_{19}\text{H}_{25}\text{NO}_6$; monoclinic; $P2_1$; $a = 10.162$ (2) Å; $b = 7.717$ (1) Å; $c = 12.471$ (7) Å; $\beta = 107.98$ (3)°; $V = 930.3$ Å³; $d_x = 1.30$ g cm⁻³; $(\sin \theta/\lambda)_{\text{max}} = 0.70$; reflections recorded, 2888; reflections $[I > 3\sigma(I)]$, 2037; $R = 0.079$.

(*E/Z*)-4,5-Dimethyl-6-nitro-6-octen-3-one (**27**). *E*-(+)-**2c** (480 mg, 2.8 mmol) and **1b** (450 mg, 2.9 mmol) were mixed as described in GP I. After the mixture was warmed to 10 °C overnight, 10% tartaric acid (10 mL) was added, and after the solution was stirred for 1.5 h, isolation of the product according to GP I gave *E/Z*-**27** (63% of a 2:1 mixture (*E/Z*)). FC (pentane/ether 10:1) yielded pure *E*-**27** (150 mg, 27%, $d > 95\%$) and the diastereomeric mixture of *E/Z*-**27** (145 mg, 26%). *E*-**27**: $[\alpha]_D = -17.0^\circ$ ($c = 1.06$, CHCl_3); ^1H NMR (300 MHz) δ 7.00 (q, $J = 7.4$ Hz, 1 H, HC(7)), 3.26 (qd, $J_a = 7.0$ Hz, $J_d = 10.3$ Hz, 1 H, CHCH_3), 3.06 (qd, $J_a = 6.9$ Hz, $J_d = 10.3$ Hz, 1 H, CHCH_3), 2.49 (qd, $J_a = 7.3$ Hz, $J_d = 18.1$ Hz, 1 H, HC(2)), 2.28 (qd, $J_a = 7.3$ Hz, $J_d = 18.1$ Hz, 1 H, HC(2)), 1.89 (d, $J = 7.4$ Hz, 3 H, HC(8)), 1.23 (d, $J = 7.0$ Hz, 3 H, CH_3), 1.14 (d, $J = 6.9$ Hz, 3 H, CH_3), 0.95 (t, $J = 7.3$ Hz, 3 H, $\text{H}_3\text{C}(1)$); MS m/e (rel intensity) no M^+ , 153 (54), 126 (5), 95 (24), 81 (6), 67 (19), 57 (100), 55 (13), 53 (9), 43 (17), 41 (17), 29 (40). Anal. ($\text{C}_{10}\text{H}_{17}\text{NO}_3$) C, H, N. A sample of **26** from the reaction mixture taken before the addition of acid showed (NMR analysis) the same 2:1 ratio for the *E/Z* moiety, and parts of the signal for the enamine proton (integration < 1 H) are indicative of an *E* configuration of the enamine double bond.

(*S*)-2-(2'-Nitrocyclohexenyl)-1-phenylethan-1-one (**28**). *N*-(1-Phenylethenyl)morpholine (2.0 g, 10.6 mmol) was allowed to react with (*S*)-**2e** (2.0 g, 10.8 mmol) in THF (50 mL) according to GP IV (72 h, 3 °C). FC (pentane/ether 3:1) gave **28** (2.10 g, 80%) as colorless needles: mp crude 78–92 °C, recrystallized (pentane/ether) 82–83 °C; $[\alpha]_D$ (crude) = +28.2°, $[\alpha]_D$ (recrystallized) = +34.2° ($c = 1.0$, CHCl_3), ee of crude product = 80%;⁸⁰ ^1H NMR (90 MHz) δ 8.0–7.8 (m, 2 H, CH_{arom}), 7.6–7.3 (m, 4 H, CH_{vinyl} and CH_{arom}), 3.8–3.5 (m, 1 H, C(1')), 3.3 (dd, $J = 16, 10$ Hz, 1 H, HC(2)), 2.9 (dd, $J = 16, 10$ Hz, 1 H, HC(2)), 2.5–1.5 (m, 6 H, $(\text{CH}_2)_3$); MS m/e (rel intensity) 245 (M^+ , < 1), 200 (6), 199 (40), 198 (6), 197 (6), 120 (9), 106 (8), 105 (100), 79 (7), 77 (48), 51 (11). Anal. ($\text{C}_{14}\text{H}_{15}\text{NO}_3$) C, H, N.

(*S*)-2-(2'-Nitrocyclohexenyl)-1-phenylethan-1-one (*ent*-**28**). Concen-

trated HCl (5 drops) was added to a solution of **24** (0.8 g, 3 mmol) in methanol (20 mL), and the mixture was heated under reflux for 0.5 h. The solvent was evaporated and the residue diluted with ether (40 mL) and dried (MgSO_4), and the solvent again removed. The crude product was mixed at –20 °C with mesyl chloride (0.35 g, 3.1 mmol) in CH_2Cl_2 (10 mL) and (*N,N*-dimethylamino)pyridine (0.38 g, 3.1 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at 0 °C for 1 h and cooled to –40 °C and tetramethylguanidine (0.38 g, 3.3 mmol) in CH_2Cl_2 (5 mL) added. After 1 h at 0 °C, 1 N HCl (20 mL) was added and the mixture extracted with CH_2Cl_2 . Removal of the solvent and FC (pentane/ether 3:1) yielded *ent*-**28** (0.52 g, 71%): mp 83 °C; $[\alpha]_D = -33.8^\circ$ ($c = 1.2$, CHCl_3).

(2*R*,3*S*)-5-Methoxy-1-(2'-nitrocyclohexenyl)-2-tetralone (**29**). The enamine **11** (5-methoxy, 2.7 g, 11 mmol) in THF (10 mL) was allowed to react with (*R*)-**2g** (2.0 g, 10.8 mmol) in THF (25 mL) according to GP IV (48 h, 4 °C). After the addition of 10% tartaric acid solution (20 mL) stirring was continued for 3 h and work up followed GP I. FC (pentane/ether 3:1) gave pure **29** (1.2 g, 44%) as pale yellow crystals: mp 74–76 °C; $[\alpha]_D$ (crude) = +158.2° ($c = 1.4$, CHCl_3); $[\alpha]_D$ (recrystallized) = +173.5° ($c = 1.1$, CHCl_3), (ee not determined); ^1H NMR (300 MHz) δ 7.46 (t (dd), $J = 4.0$ Hz, 1 H, CH_{vinyl}), 7.17 (dd, $J = 7.5, 6.0$ Hz, 1 H, CH_{arom}), 6.81 (d, $J = 6.0$ Hz, 1 H, CH_{arom}), 6.56 (d, $J = 7.5$ Hz, 1 H, CH_{arom}), 3.86 (s, 3 H, OCH_3), 3.64–3.54 (m, 1 H, C(1')), 3.48 (d, $J = 8.0$ Hz, 1 H, HC(1')), 3.46 (ddd, $J = 16.5, 6.5$ and 1.5 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(3)$), 3.03 (ddd, $J = 16.5, 12.5$ and 5.0 Hz, 1 H, $\text{H}_{\text{ax}}\text{C}(3)$), 2.76 (ddd, $J = 18.0, 5.0$ and 1.5 Hz, 1 H, $\text{H}_{\text{eq}}\text{C}(4)$), 2.45–2.20 (m, 3 H, $\text{H}_{\text{ax}}\text{C}(4)$, $\text{H}_2\text{C}(4')$), 1.78–1.35 (m, 4 H, $(\text{CH}_2)_2$); MS m/e (rel intensity) 302 ($\text{M}^+ + 1$), 301 (M^+ , 11), 255 (29), 191 (27), 177 (13), 176 (83), 175 (41), 163 (11), 148 (12), 147 (100), 131 (11), 115 (34), 111 (27), 103 (14), 91 (29), 77 (23). Anal. ($\text{C}_{17}\text{H}_{19}\text{NO}_4$) C, H, N.

(2*S*,1'*S*,2'*S*)-2-(2'-Nitro-3-cyclohexenyl)pentane-3-one (**30a**). (*S*)-**2e** (2.0 g, 10.8 mmol) was allowed to react with **1b** (2.0 g, 13 mmol) according to GP IV (48 h, 4 °C). Work up was as for GP I, and FC (pentane/ether 4:1) gave 2-*epi*-**30b** (0.41 g, 18%, $d = 85\%$) and, after recrystallization, **30a** (0.71 g, 31%, $d > 95\%$). The product **30a** was found to decompose at room temperature within a few days. **30a**: mp 43–44 °C; $[\alpha]_D = +13.2^\circ$ ($c = 1.1$, CHCl_3); ^1H NMR (300 MHz) δ 6.27–6.21 (m, 1 H, CH_{vinyl}), 5.78–5.71 (m, 1 H, CH_{vinyl}), 5.10 (t (dd), $J = 4.5$ Hz, 1 H, HC(2')), 2.63 (qd, $J_a = 7.2$ Hz, $J_d = 18.2$ Hz, 1 H, $\text{H}_2\text{C}(4)$), 2.46 (qd, $J_a = 7.2$ Hz, $J_d = 18.2$ Hz, 1 H, $\text{H}_2\text{C}(4)$), 2.55–1.59 (m, 6 H), 1.12 (t, $J = 7.2$ Hz, 3 H, $\text{H}_3\text{C}(5)$), 1.09 (d, $J = 7.0$ Hz, 3 H, $\text{H}_3\text{C}(1)$); MS m/e (rel intensity) 211 (M^+ , > 1), 181 (3), 165 (15), 151 (7), 107 (22), 87 (19), 80 (12), 79 (50), 77 (13), 69 (11), 57 (100). Anal. ($\text{C}_{11}\text{H}_{17}\text{NO}_3$) C, H, N.

(2*R*,1'*S*)-2-(2'-Nitro-2-cyclohexenyl)pentane-3-one (**30b**). (*S*)-**2e** (1.0 g, 5.4 mmol) was allowed to react with **1b** (1.0 g, 6.5 mmol) according to GP IV (48 h, 4 °C), and after the addition of 1 N HCl (10 mL) the mixture was heated under reflux for 0.5 h. The solvent was evaporated, the residue extracted with ether, and the etheral solution then treated as for GP I. FC (pentane/ether 3:1) yielded **30b** (0.58 g, 51%, $d = 80\%$): bp 190 °C (1 Torr) (Kugelrohr); $[\alpha]_D = -83^\circ$ ($c = 1.3$, CHCl_3); ^1H NMR (300 MHz) δ 7.34 (td, $J_a = 1.0$ Hz, $J_d = 4.5$ Hz, 1 H, CH_{vinyl}), 3.51–3.46 (m, 1 H, C(1')), 2.98 (qd, $J_a = 4.5$ Hz, $J_d = 7.1$ Hz, 1 H, HC(2')), 2.66–2.40 (m, 2 H, $\text{H}_2\text{C}(4)$), 2.40–2.30 (m, 2 H, $\text{H}_2\text{C}(4')$), 1.78–1.51 (m, 4 H, $(\text{CH}_2)_2$), 1.07 (t, $J = 7.2$ Hz, 2 H, $\text{H}_3\text{C}(5)$), 0.99 (d, $J = 7.1$ Hz, 3 H, $\text{H}_3\text{C}(1)$); MS m/e (rel intensity) 211 (M^+ , < 1), 182 (2), 165 (9), 154 (10), 107 (18), 96 (7), 95 (8), 94 (8), 91 (17), 79 (39), 77 (15), 67 (12), 57 (100). Anal. ($\text{C}_{11}\text{H}_{17}\text{NO}_3$) C, H, N.

(2*S*,1'*S*)-2-(2'-*aci*-Nitro-3'-cyclohexenyl)pentane-3-one (**30c**). (*S*)-**2e** (1.0 g, 5.4 mmol) was allowed to react with **1b** (1.0 g, 6.5 mmol) according to GP IV (60 h, 4 °C). Ice (20 g) was added and after 0.5 h of stirring 10% tartaric acid solution (10 mL) was added and the mixture stirred for a further 1.5 h at room temperature. The mixture was extracted with ether (3 \times) and the organic layer washed with brine and dried (MgSO_4). Concentration of the mixture to a volume of 20 mL, addition of pentane, and crystallization at –18 °C gave **30c** (0.41 g, 36%, $d > 90\%$) as colorless crystals, which were found to decompose within a few days: mp 94–95 °C dec; ^1H NMR (90 MHz) δ 6.6 (dt, $J_a = 10$ Hz, $J_i = 1$ Hz, 1 H, CH_{vinyl}), 6.4 (br s, 1 H, NOOH), 6.2 (dt, $J_a = 10$ Hz, $J_i = 3$ Hz, 1 H, CH_{vinyl}), 2.8–1.3 (m, 8 H), 1.1 (d, $J = 6$ Hz, 3 H, $\text{H}_3\text{C}(1)$), 1.0 (t, $J = 7$ Hz, 3 H, $\text{H}_3\text{C}(5)$); MS m/e (rel intensity) 211 (M^+ , < 1), 181 (3), 165 (7), 107 (18), 93 (6), 87 (13), 80 (9), 79 (38), 69 (10), 57 (100). Anal. ($\text{C}_{11}\text{H}_{17}\text{NO}_3$) C, H, N.

From the reactions leading to **6**, **11**, and **12**, the apolar byproducts **31**, **33**, and **34** were isolated by chromatography in 10–20% yield. They were purified by a second FC and found to be light and temperature sensitive. When **31** and **33** were produced from (+)-**2c**, they both showed an optical rotation.

5,6-Dimethyl-4-ethyl-1-nitro-1,3-cyclohexadiene (**31**): ^1H NMR (300 MHz) δ 7.32 (d, $J = 6.2$ Hz, 1 H, HC(2)), 5.78 (ddd, $J = 6.2, 2 \times 1-2$

(79) For details, see the supplementary material.

(80) The enantiomeric excess was determined by comparison with the $[\alpha]_D$ value of the enantiomerically pure *ent*-**28**.

Hz, 1 H, HC(3)), 2.95 (br q, $J = 7.0$ Hz, 1 H, HC(6)), 2.25–2.15 (qd, $J_q = 7.2$ Hz, $J_d = 1$ –2 Hz, 1 H, HC(5)), 2.34–2.11 (2 qd, $J_q = 7.4$ Hz, $J_d = 16$ Hz, 2 H, CH₂), 1.11 (t, $J = 7.4$ Hz, 3 H, CH₂CH₃), 1.06 (d, $J = 7.0$ Hz, 3 H, H₃CC(6)), 1.00 (d, $J = 7.2$ Hz, 3 H, H₃CC(5)); decoupling experiment, irradiation on H₃CC(5) gave a br s at 2.2 ppm, irradiation on CH₂CH₃ gave two d with $J = 16$ Hz at 2.34–2.11 ppm; MS m/e (rel intensity) 181 (M⁺, 39), 152 (23), 149 (21), 135 (12), 134 (24), 120 (46), 119 (26), 107 (47), 106 (100), 105 (64), 91 (55), 79 (20), 28 (69).

2-Methyl-3-nitrobicyclo[4.4.0]^{1,6}deca-3,5-diene (33): ¹H NMR (300 MHz) δ 7.26 (d, $J = 6.4$ Hz, 1 H, HC(3)), 5.74 (br d, $J = 6.4$ Hz, 1 H, HC(4)), 2.87 (qd, $J_q = 7.0$ Hz, 1.4 Hz, 1 H, HC(1)), 1.4–2.4 (m, 10 H), 1.14 (d, $J = 7.0$, 3 H, CH₃).

rac-2,7-Dimethyl-3-nitrobicyclo[4.4.0]^{1,6}deca-3,5-diene (34): ¹H NMR (300 MHz) δ 7.26 (d, $J = 6.4$ Hz, 1 H, HC(4)), 5.78 (d, $J = 6.4$ Hz, 1 H, HC(5)), 2.87 (qd, $J_q = 7.0$ Hz, $J_d = 1.3$ Hz, 1 H, HC(2)), 2.70 (m, 1 H, HC(7)), 2.48 (dm, $J_d = 12.5$ Hz, 1 H, HC(1)), 1.85–1.40 (m, 6 H), 1.20 Hq, $J = 7.1$ Hz, 3 H, CH₃), 1.11 (q, $J = 7.0$, 3 H, CH₃); MS m/e (rel intensity) 207 (M⁺ + 1, 30), 190 (54), 161 (11), 151 (17), 146 (21), 145 (20), 136 (22), 131 (29), 119 (21), 117 (32), 115 (24), 105 (100), 91 (62), 77 (39), 65 (22), 55 (22), 41 (46). Anal. (C₁₂H₁₆NO₂) C, H, N.

rac-4-Isopropyl-2,3-dimethyl-1-nitro-1,3-cyclohexadiene (32): *rac*-2c (870 mg, 5 mmol) was allowed to react with 3-pyrrolidino-2-methylpentene (isomeric mixture of 2- and 3-pentene, 842 mg, 5.5 mmol) according to GP I (50 h room temperature, 8 h heating under reflux) to

give **32** (364 mg, 37%, $d > 90\%$), which could be recrystallized from pentane at -20 °C to give yellow crystals. Bicyclic products could be detected in trace amounts by NMR: mp 37–38 °C; ¹H NMR (300 MHz) δ 7.34 (dd, $J = 6.3$, 1.0 Hz, 1 H, HC(6)), 5.80 (dd, $J = 6.3$, 1.2 Hz, 1 H, HC(5)), 2.96 (qd, $J_q = 7.0$ Hz, $J_d = 1.0$ Hz, 1 H, HC(2)), 2.38 (dd, $J = 6.9$, 6.8 Hz, 1 H), 2.26 (qd, $J_q = 7.1$ Hz, $J_d = 1.2$ Hz, HC(3)), 1.15 (d, $J = 6.8$ Hz, 3 H, CH₃), 1.09 (d, $J = 6.9$ Hz, 3 H, CH₃), 1.04 (d, $J = 7.0$ Hz, 3 H, CH₃), 1.00 (d, $J = 7.1$ Hz, 3 H, CH₃); MS m/e (rel intensity) 195 (M⁺, 38), 152 (12), 149 (12), 138 (44), 136 (34), 134 (25), 119 (34), 107 (53), 106 (100), 105 (36), 91 (63), 79 (42), 77 (57), 65 (32), 53 (21), 51 (20), 43 (93), 41 (58), 39 (36), 27 (25). Anal. (C₁₁H₁₇NO₂) C, H, N.

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Supplementary Material Available: Listing of in depth IR and/or ¹³C NMR spectral data for compounds cited in the work, a 2D ¹H NMR of **18**, the measurement and interpretation of NOE obtained with **5**, **11b**, and **14b**, and elemental analyses and the coordinates of the X-ray crystal structure of **25** (12 pages). Ordering information is given on any current masthead page.

Preparation of Polymers with Controlled Molecular Architecture. A New Convergent Approach to Dendritic Macromolecules

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Abstract: The novel convergent growth approach to topological macromolecules based on dendritic fragments is described. The polyether dendritic fragments are prepared by starting from what will become the periphery of the molecule and progressing inward. In the first step, 2 mol of a benzylic bromide is condensed with the two phenolic groups of the monomer, 3,5-dihydroxybenzyl alcohol, under phase-transfer conditions. After transformation of the benzylic alcohol functionality of the growing molecule into the corresponding bromide, the procedure is repeated with stepwise addition of the monomer followed again by activation of the benzylic site. After several generations of growth, the resulting dendritic wedges, in their benzylic bromide form, can be coupled to a polyfunctional core such as 1,1,1-tris(4'-hydroxyphenyl)ethane to form the final hyperbranched macromolecule. Unique features of the convergent approach include the control over the nature and placement of the groups that are placed at the periphery of the molecule and the fact that each growth step only involves reaction at a single site of the growing macromolecule. The dendrimers can be purified by normal flash chromatography and are fully characterized by use of a combination of spectroscopic and chromatographic techniques. They double their molecular weight at each generation growth step, become progressively denser and more compact, and have a very low polydispersity. The scope and versatility of the "convergent" approach is compared to the more established "divergent" approach to dendritic macromolecules.

Introduction

The synthesis of polymers with highly controlled molecular architectures has gained increased importance due to the rising demand for specialty polymers that possess novel properties.¹ In particular, a family of hyperbranched polymers prepared by multiplicative growth from a central core has attracted much attention, as the polymers appear to adopt a spherical shape free of the sort of chain entanglement that is so characteristic of other more conventional high polymer systems. While early work on hyperbranched molecules was carried out more than a dozen years ago,² it was not until the mid 1980's that Tomalia³ and Newkome⁴

reported their independently conceived approaches to highly branched "starburst" and "arborol" structures. A very extensive review⁵ of this and related synthetic^{6,7} or theoretical^{8,9} work has

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