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Stereocontrolled Oxidation of Six-Membered Cyclic *O*-Silyl Nitroso Acetals with *m*CPBA: Umpolung Approach to Functionalized Nitro Compounds

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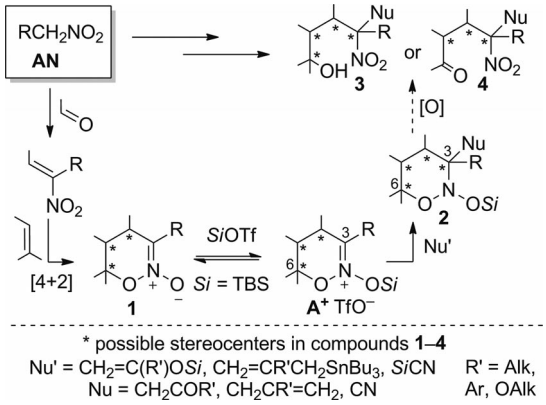
Easily available, six-membered cyclic nitroso acetals **2** are smoothly oxidized with *meta*-chloroperbenzoic acid to δ-nitro alcohols **3** or γ-nitro carbonyl compounds **4** with the retention of their relative configurations of stereocenters (diastereomeric ratio > 10:1). The reaction sequence – the generation of diastereomerically pure six-membered cyclic nitronates **1** from simple aliphatic nitro compounds (**AN**), C–C coupling of **1** with π-nucleophiles, and the oxidation of the resulting nitroso acetals **2** – is considered to be a new effective variant of the umpolung reactivity of **AN**. An original approach for the synthesis of alternative diastereomers of nitro derivatives **3** has also been suggested.

Introduction

Six-membered cyclic nitronates **1**, which are easily and stereosectively formed from aliphatic nitro compounds (**AN**), aldehydes, and olefins (Scheme 1), have been successfully applied in several total-synthesis strategies.[1,2]



Scheme 1. Electrophilic activity of nitronates **1**.

Of special note is the tandem [4+2]/[3+2] cycloaddition.[1] This process provides access to bicyclic nitroso acetals, which can be reduced to various functionalized amino derivatives. The latter have been used successfully in the syntheses of a wide range of natural compounds.

The second approach consists of the silylation of 3-alkyl-substituted **1** into 3-(α-haloalkyl)-5,6-dihydro-4*H*-1,2-oxazines with subsequent modification and reduction.[2] However, the synthetic significance of nitronates **1** is not exhausted with the strategies cited above.

Our group has recently suggested yet another possibility to use nitronates **1**.[3] It consists of the C–C coupling of **1** with π-nucleophiles (Nu′) mediated by silyl Lewis acids, which leads to nitroso acetals **2** by the reversible formation of cationic intermediates $\mathbf{A}^+$ (Scheme 1). The overall result could be considered to be a variant of the formal reversion of the traditional reactivity of **AN**, because the key stage includes the generation of an electrophilic center at C-3 in nitronate **1**, which is connected to the NO_2 group in the initial **AN**. However, the formation of nitroso acetals **2** is accompanied by the partial reduction of the nitro group of RCH_2NO_2. Therefore, the oxidation of intermediates **2** to highly functionalized nitro compounds **3** or **4** (depending on the nature of the substituent at C-6) with the cleavage of the endocyclic N–O bond is required for the completion of the **AN** reactivity umpolung. It should be noted that the nucleophilic addition to nitronate **1** usually proceeds with high diastereoselectivity[3] to give rise to nitroso acetals **2** with up to four asymmetric centers on ring carbon atoms. These centers could be retained in the resulting nitro compounds **3** or **4**. Furthermore, several approaches for the preparation of enantiomerically pure nitronates **1** have been suggested recently,[1,4] which provide the possibility for the enantioselective synthesis of **3** or **4** based on the strategy shown in Scheme 1.

At present, **3** and **4** are practically unknown. The products **3**, which have a secondary alcohol fragment, can be

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obtained by the selective reduction of the carbonyl group of respective compounds **4**. An alternative approach for the synthesis of **3** with tertiary OH groups can be hardly imagined. In turn, products **4** can be prepared by the Michael addition of either enolate anions to conjugated nitro olefines[5] or nitronate anions to α,β-unsaturated carbonyl compounds.[6] However, in spite of the significant progress recently achieved in this area (e.g. organocatalysis),[7] the formation of secondary or tertiary nitro compounds with designated configurations of the stereocenters attached to the nitro group still remains a complicated problem.[8] The development of new approaches for the diastereoselective synthesis of **3** or **4** is an urgent challenge.

Considering the above, the strategy presented in Scheme 1 could be used in the diastereo- or enantioselective synthesis of δ-functionalized nitro compounds **3** and **4** from primary **AN** and other simple precursors.

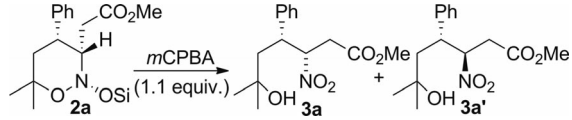
Nitroso acetals can be considered as equivalents of their respective nitroso compounds.[9] Although the oxidation of nitroso compounds is well investigated,[10] data on the oxidation of nitroso acetals is scarce. The oxidation of $MeO_2CCMe_2N(OMe)_2$ with *meta*-chloroperbenzoic acid (*m*CPBA) is the only successful example.[11,12]

Results and Discussion

The possibility of the selective oxidation of a nitroso acetal fragment was investigated with model compound **2a**. After a series of unsuccessful attempts with various oxidizers [$Pb(OAc)_4$, DDQ, $(Me_3SiO)_2/Me_3SiOTf$, $PhIF_2$] we oxidized **2a** with *m*CPBA according to a literature procedure[11] (Table 1).

The oxidation of **2a** to **3a** proceeds smoothly with rather high diastereoselectivity (Table 1). It is supposed that this process does not change the relative configuration of the stereocenters in **2a**. Therefore, the dominant isomer of nitro alcohol **3a** should be the *syn* diastereomer. A decrease in the diastereomeric ratio (*dr*) in **3a** in some experiments could be connected with the epimerization of the stereocenter at the NO_2 group by a known tautomeric process.[13] Increase of the temperature or addition of basic reagents significantly reduced the *dr* in **3a**, which is in good agreement with the foregoing interpretation. At the same time, the addition of acetic acid almost did not change the *dr* in **3a** (Table 1, Entries 1 and 3).

Table 1. Oxidation of **2a**.



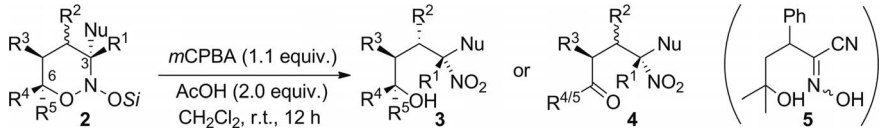
Entry	Solvent, temperature	*t* [h]	Additive	Yield of **3a** + **3a′** [%]	*dr*[a]
1	CH_2Cl_2, room temp.	12	–	76[b]	10:1
2	CH_2Cl_2, room temp.	12	K_2CO_3 (1.5 equiv.)	65[b]	6:1
3	**CH_2Cl_2, room temp.**	**12**	**AcOH (2 equiv.)**	**92**[c]	**10:1**
4	CH_2Cl_2, reflux	2.5	–	85[c]	9:1
5	$CHCl_3$, reflux	2.5	–	64[c]	9:1
6	CH_3CN, room temp.	12	–	74[b]	10:1
7	CH_3CN, reflux	2	NH_4F (1.1 equiv.)	82[b]	8:1

[a] Determined by integration of ^1H NMR spectra. [b] Determined by ^1H NMR spectroscopy with $ClCH{=}CCl_2$ as a standard. [c] Isolated yield.

Optimal reaction conditions for the reaction of **2a** (Table 1, Entry 3), were successfully applied to a series of six-membered cyclic nitroso acetals **2**. *m*CPBA oxidized most of the tested substrates **2** (Table 2).

Modification of the substituent at C-6 of **2** resulted in different classes of products: δ-nitro alcohols **3** were obtained after the oxidation of **2** if the initial compounds did not contain an alkoxy group at C-6, otherwise γ-nitro carb-

Table 2. Oxidation of **2a**–**i**.



Entry	**2**	R^2/Nu[a]	R^1	R^2	R^3	R^4	R^5	Nu	Product	Yield [%]	*dr*[b]
1	**a**	*cis*	H	Ph	H	Me	Me	CH_2CO_2Me	**3a** (*syn*)	92	10:1
2	**b**	*cis*	H	Ph	–$(CH_2)_4$–		H	CH_2CO_2Me	**3b** (*syn*)	88	12:1
3	**c**	*cis*	Me	Ph	H	Me	Me	CH_2CO_2Me	**3c** (*syn*)	86	> 20:1
4	**d**	*cis*	H	Ph	H	Me	Me	$CH_2C(O)Ph$	**3d** (*syn*)	87	10:1
5	**e**	*cis*	H	Ph	H	Me	Me	$CH_2C(CH_3){=}CH_2$	**3e**	0[c]	–[d]
6[e]	**f**	*cis*	H	Ph	H	Me	Me	CN	**3f/5**	< 15/61[f,g]	3.0:1
7	**g**	*cis*	H	Ph	H	OMe	Me	CH_2CO_2Me	**4a** (*syn*)	86	> 20:1
8[h]	**h/h′** ≈ 1.5:1	*cis*	H	An	H	OEt	H	CH_2CO_2Me	**4b/4b′** (*syn*/*anti*)	95	1.4:1
		trans	H	An	H	H	OEt	CH_2CO_2Me			
9	**i**	*trans*	H	An	H	OEt	H	CH_2CO_2Me	**4b′** (*anti*)	84	11:1

[a] Relative configuration of R^2 and Nu. [b] By integration of ^1H NMR spectra. [c] Inseparable mixture of unidentified products. [d] Not determined. [e] 3.0 equiv. of *m*CPBA, 2.0 equiv. of AcOH, and 48 h were used instead of the standard conditions. [f] By integration of the ^1H NMR spectra of the crude product. [g] γ-Hydroxyoxime **5** [(*E*)/(*Z*) ≈ 1:1] was the main product. [h] Used as a mixture of stereoisomers.

onyl compounds **4** were formed after protolysis of the acetal center at C-6 when $R^{4/5}$ was an alkoxy group.

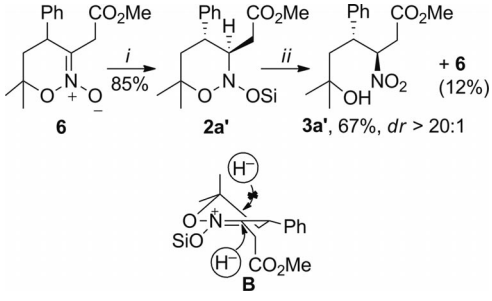
The oxidation proceeded with high diastereoselectivity with almost all substrates (the *dr*s vary from 10:1 to >20:1). However, the distillation of **3** or **4** led to a significant epimerization of the target products (e.g.: **3a**: b.p. 150–170 °C/0.08 Torr, *dr* decreased from 10:1 to 3.5:1 after distillation; **4a**: b.p. 158–162 °C/0.112 Torr, *dr* decreased from >20:1 to 3.2:1).

Several structural restrictions that prevent the oxidation of **2** were found. In particular, the oxidation failed for **2e**, which contains a C=C bond (Table 2, Entry 5). The nucleophilic C=C bond in **2** is probably oxidized more easily than the nitroso acetal fragment.

In addition, the oxidation was hindered by the influence of an electron-withdrawing group at C-3 of **2**. The conversion of **2f** (Nu = CN, Table 2, Entry 6) was less than 20% under the standard conditions. The use of 3 equiv. of oxidizer and a prolonged reaction time of 3 d led to the full conversion of **2f**, but **3f** was obtained in low yield (<15% according to NMR spectroscopy). Its isolation from the reaction mixture was complicated, because the reaction gave α-oximino cyanide **5** as the main product (yield 61%). The change of *m*CPBA to the more powerful CF_3CO_3H (generated from urea·H_2O_2 and trifluoroacetic anhydride)[14] did not increase the yield of **3f**.

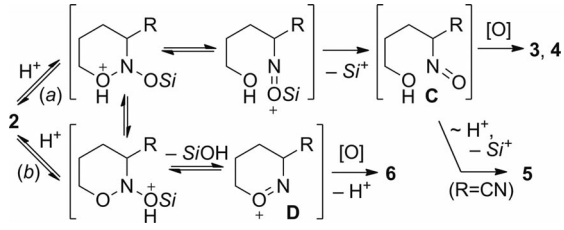
By this means, the oxidation of nitroso acetals **2** with *cis*-configured R^2 and Nu can be considered as a convenient approach for the controlled synthesis of the *syn* isomers of nitro compounds **3** and **4**. On the other hand, one cannot obtain the *anti* isomers of these nitro derivatives with this procedure. These isomers can be prepared from available nitronates **1** only as minor components of the resulting mixtures.[15] The exception is the oxidation of **2i** with *trans*-configured R^2 and Nu when the *anti* isomer **4b′** was obtained as the major product (Table 2, Entry 9).

For the directed synthesis of *anti* isomers **3′**, a modification of the method that proceeds via nitroso acetals **2′** with *trans*-configured R^2 and Nu was developed. This was accomplished through the successful synthesis of alcohol **3a′** (Scheme 2). For the preparation of **2a′**, nitronate **6**, obtained according to a standard method,[16] was reduced with Bu_3SnH by the stereoselective addition of a hydride ion to the cationic intermediate $\mathbf{B^+}$.[17] The transformation of **6** to **2a′** is the first example of the coupling of a σ-nucleophile with a cationic intermediate generated from a cyclic nitronate (cf. $\mathbf{B^+}$ in Scheme 2 and $\mathbf{A^+}$ in Scheme 1). The oxidation of **2a′** to the target *anti* isomer **3a′** proceeded smoothly with high diastereoselectivity, although it was accompanied by the formation of some nitronate **6** (Scheme 2).



Scheme 2. Synthesis of **3a′**. i: TBSOTf, Bu_3SnH, CH_2Cl_2, –78 °C, 72 h, ii: *m*CPBA, AcOH (2.0 equiv.), CH_2Cl_2, room temp., 12 h.

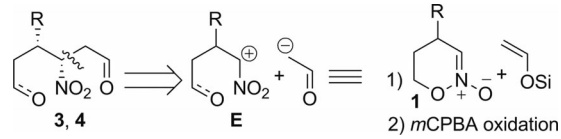
A possible mechanism for the oxidation of **2** is presented in Scheme 3. This is in good agreement with our experimental data as well as that obtained by Rudchenko at al.[11] The formation of **5** during the oxidation of **2f** and the blue color of most of the oxidation experiments indicate the intermediacy of the respective nitroso compounds **C**, which can be formally obtained by the protonation of the endocyclic oxygen atom of **2** in acidic media with subsequent N–O bond cleavage and elimination of the trialkylsilyl moiety [pathway (a)]. The oxidation of intermediates **C** leads to the target compounds **3** or **4**. Another possibility is associated with the protonation of the exocyclic oxygen atom of **2** [pathway (b)] with subsequent elimination of silanol and the formation of nitrenium cation **D**.[18] The oxidation of **2** most likely occurs through pathway (a).[19,20] The only evidence for the contribution of pathway (b) is the generation of **6** during the oxidation of **2a′**. The presence of an electron-withdrawing group (R = CN) at C-3 leads to a decrease of the rate of oxidation, and isomerization of nitroso intermediate **C** to oxime **5** occurs as a result to give **5** as the main product (Table 2, Entry 6).



Scheme 3. Possible mechanism for the oxidation of **2**.

The stereoselectivity of the oxidation of **2** is probably limited by epimerization of the stereocenter >CH(NO_2) in the targets **3** or **4**, rather than epimerization in the respective intermediates **C**. The latter epimerization would have led to irreversible isomerization to the respective oximes (similar to **5**), which would have been transformed too slowly into the corresponding **AN** under the oxidation conditions.

The results of this investigation allow one to consider easily available, six-membered cyclic nitronates **1** as the chemical equivalents **E** of functionalized **AN** with the inverted reactivity of the α-carbocation (Scheme 4). This formal umpolung was realized by a two-step procedure [coupling of **1** with silyl enolate (Nu′) and oxidation of the re-



Scheme 4. Retrosynthesis of **3** and **4**.

sulting nitroso acetal **2**] and led to functionalized nitro compounds **3** and **4** with dominantly *syn* configuration. This strategy can be considered as new approach to functionalized nitro-Michael adducts **4**. Compounds **3** and **4** are perspective precursors of amino derivatives,[21,13] and they can be subjected to other typical **AN** chemistry transformations.[21]

Conclusions

A new method for the mild oxidation of six-membered cyclic nitroso acetals **2** with *m*CPBA to functionalized nitro compounds **3** or **4** was developed. The reaction proceeds with high retention of the configuration of the stereocenter on C-3 ($dr > 10:1$). An extension of this approach to the other types of nitroso acetals is our task in the near future.

Experimental Section

General Methods: All reactions, except *m*CPBA oxidation, were performed in oven-dried (150 °C) glassware under argon. NMR spectra were recorded with a Bruker AM-300 (^{1}H: 300.13 MHz; ^{13}C: 75.47 MHz) and referenced to residual solvent peaks. Chemical shifts (δ) are reported in ppm; multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br. (broad). The ratios of stereoisomers were derived from the relative integral intensities of the characteristic signals in the ^{1}H NMR spectra. Coupling constants (J) are reported in Hertz. Key NOESY correlations are shown with arrows in Figure 1. IR spectra were recorded with a Bruker VEKTOR-22 from 400 to 4000 cm^{-1} (resolution 2 cm^{-1}) as a thin layer. Melting points were determined with a Kofler melting-point apparatus. Elemental analyses were performed at the Analytical Laboratory of the N. D. Zelinsky Institute of Organic Chemistry. HRMS data were recorded with a Bruker MicroTOFF spectrometer.

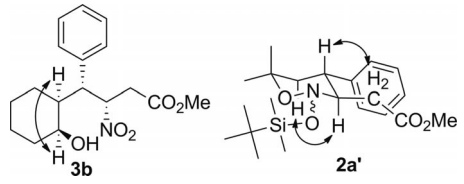


Figure 1. Key NOESY interactions in compounds **3b** and **2a′**.

Analytical TLC was performed with silica gel plates with QF-254 indicator. Visualization was accomplished with UV light and/or anisaldehyde/H_2SO_4. Preparative liquid chromatography was performed on columns with Merck silica (Kieselgel 60, 230–400 mesh). All solvents for chromatography and extractions were technical grade and distilled prior to use. The following solvents and reagents were distilled from the indicated drying agents: CH_2Cl_2, $CHCl_3$, Et_3N (CaH_2); $(CF_3CO)_2O$, Ac_2O (P_2O_5); Et_2O (Na, benzophenone ketyl). Commercial reagents: *m*CPBA (Aldrich), AcOH (Reakhim), PhCHO (Acros), 1,8-diazabicyclo[5.4.0]undec-7-ene (Acros), 4-(dimethylamino)pyridine (Aldrich), $SnCl_4$ (Acros), isobutylene (Aldrich), Bu_3SnH (Merck), 2,6-lutidine (Aldrich), *tert*-butyldimethylsilyl cyanide (TBSCN) (Aldrich).

General Procedure: AcOH (114 μL, 120 mg, 2.0 mmol) was added to a solution of **2** (1.00 mmol) and 70% *m*CPBA (271 mg, 1.1 mmol) in CH_2Cl_2 (3 mL). After 12 h at room temp., the reaction mixture was poured into a mixture of Et_2O (20 mL)/saturated aqueous $NaHCO_3$ solution (15 mL) with Na_2SO_3 (0.3 g). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 7 mL). The combined organic layers were washed successively with H_2O (15 mL) and brine (15 mL) and dried with Na_2SO_4. The solvents were evaporated in vacuo, and the residue was subjected to column chromatography on silica gel (eluent EtOAc/hexane, 1:5 → 1:2) to give pure **3** or **4** (67–95% yield) as a colorless oil.

Methyl *rel*-(3*S*,4*R*)-6-Hydroxy-6-methyl-3-nitro-4-phenylheptanoate (3a): Yield: 271 mg (92%). Colorless oil. TLC: R_f = 0.36 (silica gel; hexane/EtOAc, 1:1; anisaldehyde). IR (CCl_4 film): $\tilde{\nu}$ = 3430 (br. w, νOH), 1739 (s, νC=O), 1552 (vs, $\nu_{as}NO_2$), 1375 (s, ν_sNO_2) cm^{-1}. ^{1}H NMR (300 K, $CDCl_3$): δ = 1.05 and 1.19 [2 s, 6 H, CH_3(1) and CH_3(2)], 1.75 [br. s, 1 H, OH], 1.98 [dd, ^3J = 3.3, ^2J = 14.3 Hz, 1 H, CH_A(4)], 2.14 [dd, ^3J = 8.8, ^2J = 14.3 Hz, 1 H, CH_B(4)], 2.73 [dd, ^3J = 3.7, ^2J = 17.6 Hz, 1 H, CH_A(7)], 3.09 [dd, ^3J = 10.3, ^2J = 17.6 Hz, 1 H, CH_B(7)], 3.56 [ddd, ^3J = 3.3, ^3J = 8.8, ^3J = 10.3 Hz, 1 H, CH(5)], 3.67 [s, 3 H, CH_3(9)], 5.16 [ddd, ^3J = 3.7, ^3J = 4.8, ^3J = 10.3 Hz, 1 H, CH(6)], 7.22 [d, ^3J = 7.7 Hz, 2 H, CH(11)], 7.31–7.38 [m, 3 H, CH(12) and CH(13)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 29.3 and 30.1 (C-1 and C-2), 34.4 (C-7), 43.0 (C-4), 44.9 (C-5), 52.3 (C-9), 70.7 (C-3), 88.1 (C-6), 128.1 (C-13), 128.6 and 129.1 (C-11 and C-12), 138.9 (C-10), 170.0 (C-8) ppm. HRMS (ESI): calcd. for $C_{15}H_{21}NO_5Na$ [M + Na]$^+$ 318.1312; found 318.1308.

Methyl *rel*-(3*S*,4*R*)-4-[(1*S*,2*S*)-2-Hydroxycyclohexyl]-3-nitro-4-phenylbutanoate (3b): Yield: 281 mg (88%). White crystals, m.p. 126 °C (hexane/EtOAc, 5:1); TLC: R_f = 0.48 (hexane/EtOAc, 1:1; anisaldehyde). IR (CCl_4 film): $\tilde{\nu}$ = 3500 (br. w, νOH), 1738 (s, νC=O), 1552 (vs, $\nu_{as}NO_2$), 1373 (s, ν_sNO_2) cm^{-1}. ^{1}H NMR (300 K, $CDCl_3$): δ = 1.11–1.40 and 1.44–1.70 [2 m, 3 + 4 H CH_2(5), CH_2(4), CH_2(3) and CH_A(2)], 1.76–1.88 [m, 1 H, CH_B(2)], 1.88–2.07 [m, 2 H, CH(6), OH], 2.63 [dd, ^3J = 1.4, ^2J = 17.4 Hz, 1 H, CH_ACH_B(9)], 3.04 [dd, ^3J = 11.9, ^2J = 17.4 Hz, 1 H, CH_ACH_B(9)], 3.68 [s, 3 H, CH_3(11)], 3.70 [dd, $^3J \approx {}^3J$ = 2.6 Hz, 1 H, CH(7)], 4.07 [br. s, 1 H, CH(1)], 5.52 [ddd, ^3J = 1.4, ^3J = 5.0, ^3J = 11.9 Hz, 1 H, CH(8)], 7.06 [dd, ^4J = 1.8, ^3J = 7.1 Hz, 2 H, 2× CH(13)], 7.23–7.36 [m, 3 H, 2× CH(14) and CH(15)] ppm. ^{13}C NMR (300 K, $CDCl_3$, INEPT): δ = 19.8, 25.2, 25.6 and 34.0 (C-2, C-3, C-4 and C-5), 32.6 (C-9), 42.3 (C-7), 50.4 (C-6), 52.3 (C-11), 66.7 (C-1), 84.3 (C-8), 128.0 (C-13 or C-14), 129.0 (C-13 or C-14 and C-15), 136.2 (C-12), 170.5 (C-10) ppm. $C_{17}H_{24}NO_5$ (322.38): calcd. C 63.54, H 7.21, N 4.36; found C 63.18, H 6.92, N 4.12.

Methyl *rel*-(3*S*,4*R*)-6-Hydroxy-3,6-dimethyl-3-nitro-4-phenylheptanoate (3c): Yield: 266 mg (86%). Colorless oil. TLC: R_f = 0.35 (hexane/EtOAc, 1:1; anisaldehyde). IR (CCl_4 film): $\tilde{\nu}$ = 3445 (br. w, νOH), 1743 (s, νC=O), 1544 (vs, $\nu_{as}NO_2$), 1363 (s, ν_sNO_2) cm^{-1}. ^{1}H NMR (300 K, $CDCl_3$): δ = 0.96 and 1.11 [2 s, 6 H, CH_3(1) and CH_3(2)], 1.46 [br. s, 1 H, OH], 1.70 [s, 3 H, CH_3(10)], 1.83 [dd, $^3J \approx$ 1.0, ^2J = 14.2 Hz, 1 H, CH_A(4)], 2.10 [dd, ^3J = 10.1, ^3J = 14.2 Hz, 1 H, CH_B(4)], 2.73 [d, ^3J = 16.5 Hz, 1 H, CH_A(7)], 3.34 [d, ^3J = 16.5 Hz, 1 H, CH_B(7)], 3.48 [dd, $^3J \approx$ 1.0 Hz, ^3J = 10.1 Hz, 1 H, CH(5)], 3.68 [s, 3 H, CH_3(9)], 7.19–7.37 [m, 5 H, 2× CH(12), 2× CH(13) and CH(14)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 21.3 (C-10), 29.5 and 30.6 (C-1 and C-2), 40.3 and 42.8 (C-4 and C-7), 51.1 (C-5), 52.0 (C-9), 70.7 (C-3), 92.4 (C-6), 128.1 (C-14), 128.8 and 129.8 (C-12 and C-13), 138.7 (C-11), 169.8 (C-8) ppm. HRMS (ESI): calcd. for $C_{16}H_{24}NO_5$ [M + H]$^+$ 310.1652; found 310.1649.

***rel*-(3*S*,4*R*)-6-Hydroxy-6-methyl-3-nitro-1,4-diphenylheptan-1-one (3d):** Yield: 298 mg (87%). White crystals, m.p. 111–112 °C (pentane); TLC: R_f = 0.36 (hexane/EtOAc, 1:1; anisaldehyde). IR

($CHCl_3$ film): $\tilde{\nu}$ = 3470 (br. w, νOH), 1685 (s, νC=O), 1550 (vs, $\nu_{as}NO_2$), 1369 (s, ν_sNO_2) cm^{-1}. ^1H NMR (300 K, $CDCl_3$): δ = 1.09 and 1.22 [2 s, 6 H, CH_3(1) and CH_3(2)], 2.07 [dd, ^3J = 3.7, ^2J = 14.7 Hz, 1 H, CH_A(4)], 2.16 [br. s, 1 H, OH], 2.22 [dd, ^3J = 8.8, ^2J = 14.7 Hz, 1 H, CH_B(4)], 3.24 [dd, ^3J = 2.9, ^2J = 18.3 Hz, 1 H, CH_A(7)], 3.66 [ddd, ^3J = 3.7, ^3J = 4.8, ^3J = 8.8 Hz, 1 H, CH(5)], 3.84 [dd, ^3J = 9.5, ^2J = 18.3 Hz, CH_B(7)], 5.44 [ddd, ^3J = 2.9, ^3J = 4.8, ^3J = 9.5 Hz, CH(6)], 7.24–7.40 [m, 5 H, CH(14), CH(15) and CH(16)], 7.47 [t, ^3J = 7.3 Hz, 2 H, CH(11)], 7.60 [t, ^3J = 7.3 Hz, 1 H, CH(12)], 7.92 [d, ^3J = 7.3 Hz, 2 H, CH(10)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 29.2 and 31.0 (C-1 and C-2), 38.4 (C-7), 43.4 (C-4), 45.0 (C-5), 70.9 (C-3), 87.5 (C-6), 128.2, 128.7, 128.8, 129.1 (C-10, C-11, C-14, and C15), 128.1 (C-16), 133.9 (C-12), 136.0 (C-13), 139.2 (C-9), 195.5 (C-8) ppm. HRMS (ESI): calcd. for $C_{20}H_{22}NO_4$ $[M+H]^+$ 340.1543; found 340.1541.

Methyl *rel*-(3*S*,4*R*)-3-Nitro-6-oxo-4-phenylheptanoate (4a): Yield: 244 mg (87%). Colorless oil. TLC: R_f = 0.51 (silica gel; hexane/EtOAc, 1:1; anisaldehyde). IR (CCl_4 film): $\tilde{\nu}$ = 1739 (vs, νC=O), 1720 (vs, νC=O), 1552 (vs, $\nu_{as}NO_2$), 1375 (s, ν_sNO_2) cm^{-1}. ^1H NMR (300 K, $CDCl_3$): δ = 2.19 [s, 3 H, CH_3(1)], 2.64 [dd, ^3J = 3.3, ^2J = 17.6 Hz, 1 H CH_A(6)], 2.91 [dd, ^3J = 6.2, ^2J = 18.0 Hz, 1 H, CH_A(3)], 3.00 [dd, ^3J = 10.6, ^2J = 17.6 Hz, 1 H, CH_B(6)], 3.23 [dd, ^3J = 7.7, ^2J = 18.0 Hz, 1 H, CH_B(3)], 3.67 [s, 3 H, CH_3(8)], 3.75 [ddd, ^3J = 4.8, $^3J \approx {}^{3\,Hz}J$ = 6.5, 1 H, CH(4)], 5.21 [ddd, $^3J \approx {}^3J$ = 3.3, ^3J = 11.0 Hz, 1 H, CH(5)], 7.10 [d, ^3J = 7.1 Hz, 2 H, CH(10)], 7.28–7.36 [m, 3 H, CH(11) and CH(12)] ppm. ^{13}C NMR (300 K, $CDCl_3$, JMOD): δ = 30.4 (C-1), 34.0 (C-6), 42.8 (C-4), 44.4 (C-3), 52.0 (C-8), 84.8 (C-5), 127.9 and 128.7 (C-10 and C-11), 128.1 (C-12), 139.4 (C-9), 169.4 (C-7), 205.4 (C-2) ppm. HRMS (ESI): calcd. for $C_{14}H_{17}NO_5Na$ $[M+Na]^+$ 302.0994; found 302.0999.

Methyl *rel*-(3*S*,4*R*)-4-(4-Methoxyphenyl)-3-nitro-6-oxohexanoate (4b) and Methyl *rel*-(3*R*,4*R*)-4-(4-Methoxyphenyl)-3-nitro-6-oxohexanoate (4b′): Colorless oil. TLC: R_f = 0.37 (silica gel; hexane/EtOAc, 1:1; anisaldehyde). IR (CCl_4 film of the mixture of diastereomers): $\tilde{\nu}$ = 1734 (br. vs, νC=O), 1554 (vs, $\nu_{as}NO_2$), 1377 (s, ν_sNO_2) cm^{-1}. **4b**: ^1H NMR (300 K, $CDCl_3$): δ = 2.64 [dd, ^3J = 3.3, ^2J = 17.6 Hz, 1 H,CH_A(5)], 2.92–3.09 [m, 2 H, CH_A(2) and CH_B(5)], 3.16 [dd, ^3J = 6.6, ^2J = 18.3 Hz, 1 H, CH(2)], 3.68 [s, 3 H, CH_3(12)], 3,73–3.85 [s and m, 4 H, CH_3(7) and CH(3)], 5.17 [ddd, $^3J \approx {}^3J$ = 4.0, ^3J = 10.3 Hz, 1 H, CH(4)], 6.89 [d, ^3J = 8.4 Hz, 2 H, CH(9)], 7.04 [d, ^3J = 8.4 Hz, 2 H, CH(10)], 9.72 [s, 1 H, CH(1)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 34.9 (C-5), 41.4 (C-3), 45.0 (C-2), 52.4 (C-7), 55.4 (C-12), 85.8 (C-4), 114.6 (C-10), 128.1 (C-8), 129.3 (C-9), 159.7 (C-11), 169.7 (C-6), 199.0 (C-1) ppm. **4b′**: ^1H NMR (300 K, $CDCl_3$): δ = 2.48 [dd, ^3J = 3.3, ^2J = 17.6 Hz, 1 H, CH_A(5)], 2.82 [dd, ^3J = 4.8, ^2J = 17.6 Hz, 1 H, CH_B(5)], 2.92–3.09 [m, 1 H, CH_A(2)], 3.16 [dd, ^3J = 6.6, ^2J = 18.3 Hz, 1 H, CH_B(2)], 3.62 [s, 3 H, CH_3(12)], 3,73–3.85 [s and m, 4 H, CH_3(7) and CH(3)], 5.08 [ddd, ^3J = 2.9, $^3J \approx {}^3J$ = 10.3 Hz, 1 H, CH(4)], 6.86 [d, ^3J = 8.4 Hz, 2 H, CH(9)], 7.13 [d, ^3J = 8.4 Hz, 2 H, CH(10)], 9.57 [s, 1 H, CH(1)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 35.7 (C-5), 42.4 (C-3), 46.4 (C-2), 52.3 (C-7), 55.4 (C-12), 87.3 (C-4), 114.9 (C-10), 128.9 (C-8), 129.3 (C-9), 159.7 (C-11), 169.7 (C-6), 198.3 (C-1) ppm. HRMS (ESI): mixture of isomers; calcd. for $C_{14}H_{17}NO_6Na$ $[M+Na]^+$ 318.0948; found 318.0948.

Synthesis of *anti* Isomer 3a′: Methyl {*rel*-(3*R*,4*R*)-2-[(*tert*-butyldimethylsilyl)oxy]-6,6-dimethyl-4-phenyl-1,2-oxazinan-3-yl}acetate (2a′): TBSOTf (1.21 mmol, 278 μL) was added to a stirred solution of nitronate **6** (306 mg, 1.10 mmol) and 2,6-lutidine (33 μL, 30 mg, 0.28 mmol) in CH_2Cl_2 (10 mL) at –78 °C. The reaction mixture was stirred at –78 °C for 15 min, and Bu_3SnH (301 μL, 326 mg, 1.12 mmol) was added. After 3 d at –78 °C, the reaction mixture was poured into a mixture of hexane (15 mL) and saturated aqueous $NaHCO_3$ solution (15 mL). The organic layer was separated, and the aqueous layer was extracted with hexane (2 × 7 mL). The combined organic layers were washed successively with H_2O (15 mL) and brine (15 mL), shaken with activated charcoal, and dried with Na_2SO_4. The solvents were evaporated in vacuo. The residue was subjected to column chromatography on silica (eluent EtOAc/hexane, 1:20 → 1:10) to give pure **2a′** (370 mg, 85%, single isomer) as a colorless oil. R_f = 0.78 (hexane/EtOAc, 1:1; anisaldehyde). ^1H NMR (300 K, $CDCl_3$): δ = 0.18 and 0.23 [2 s, 6 H, CH_3(14) and CH_3(15)], 0.93 [s, 9 H, CH_3(17)], 1.34 and 1.47 [2 s, 6 H, CH_3(2) and CH_3(3)], 1.65 [dd, ^3J = 4.6, ^2J = 13.3 Hz, 1 H, CH_{2eq}(4)], 1.76 [dd, $^3J \approx {}^2J$ = 12.8 Hz, 1 H, CH_{2ax}(4)], 2.18–2.38 [m, 2 H, CH_2(7)], 3.14 [ddd, ^3J = 4.6, $^3J \approx {}^3J$ = 11.9 Hz, 1 H, CH(5)], 3.51 [s, 3 H, CH_3(9)], 3.65 [ddd, ^3J = 3.7, ^3J = 6.0, ^3J = 10.1 Hz, 1 H, CH(6)], 7.21–7.35 [m, 5 H, CH(11), CH(12) and CH(13)] ppm. ^{13}C NMR (300 K, $CDCl_3$, JMOD): δ = –4.7 and –4.0 (C-14 and C-15), 17.6 (C-16), 23.4 and 29.4 (C-2 and C-3), 26.1 (C-17), 35.3 (C-4), 44.1 (C-5), 45.2 (C-7), 51.3 (C-9), 70.7 (C-6), 76.7 (C-1), 127.0 (C-13), 128.2 and 128.8 (C-11 and C-12), 141.8 (C-10), 171.7 (C-8) ppm. $C_{21}H_{35}NO_4Si$ (393.60): calcd. C 64.08, H 8.96, N 3.56; found C 63.85, H 9.08, N 3.32.

Methyl *rel*-(3*R*,4*R*)-6-Hydroxy-6-methyl-3-nitro-4-phenylheptanoate (3a′): Compound **3a′** was obtained according to the general procedure from **2a′** in 67% yield (*dr* > 20:1, the only isomer according to ^1H NMR spectroscopy). Nitronate **6** was obtained as a byproduct in 12% yield. The IR spectrum and R_f are similar to those of **3a**. ^1H NMR (300 K, $CDCl_3$): δ = 1.08 and 1.13 [2 s, 6 H, CH_3(1) and CH_3(2)], 1.75 [br. s, 1 H, OH], 1.86 [dd, ^3J = 4.0, ^2J = 14.3 Hz, 1 H, CH_A(4)], 2.08 [dd, ^3J = 8.0, ^2J = 14.3 Hz, 1 H, CH_B(4)], 2.49 [dd, ^3J = 2.9, ^2J = 17.6 Hz, 1 H, CH_A(7)], 2.93 [dd, ^3J = 10.2, ^2J = 17.6 Hz, 1 H, CH_B(7)], 3.58 [m, 1 H, CH(5)], 3.59 [s, 3 H, CH_3(9)], 5.19 [m, 1 H, CH(6)], 7.12–7.37 [m, 5 H, CH(11), CH(12) and CH(13)] ppm. ^{13}C NMR (300 K, $CDCl_3$): δ = 28.9 and 30.7 (C-1 and C-2), 34.8 (C-7), 44.7 (C-4), 45.2 (C-5), 52.1 (C-9), 70.6 (C-3), 88.1 (C-6), 128.0 (C-13), 128.9 and 129.1 (C-11 and C-12), 138.8 (C-10), 170.1 (C-8) ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures for the synthesis of the starting compounds, selected spectroscopic data for minor isomers, atom labeling (for interpretation of spectra) and NMR spectra for new compounds.

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[17] For a discussion of stereoselectivity and mechanism, see refs.[3a,3b]

[18] For the intemediacy of nitrenium cations **D** in the reesterification of some cyclic nitroso acetals, see ref.[3c]

[19] Reversible proton migration between two oxygen atoms in **2** can give nitroso intermediate **C** anyway. Alternatively, the protonation of the acetal fragment and ring opening of **2g**–**h** during oxidation can also lead to the same products.

[20] According to X-ray data in ref.[3a] most nitroso acetals **2** exist in the solid state in a dominant conformation with an equatorial silyloxy group with endo- and exocyclic N–O bond lengths of 1.461–1.479 Å and 1.420–1.433 Å, respectively. There is one example (**2i**), where the silyloxy group is axial, and the N–O bond lengths are 1.422 Å for the endo- and 1.446 Å for the exocyclic bonds. Supposing that the dominant conformation with an equatorial silyloxy group is reactive, cleavage of the weakened endocyclic N–O bond could promote the reaction according to pathway (a).

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