A Novel NO_2/OH Exchange in α-Nitro Ketones: a Mechanistic Investigation

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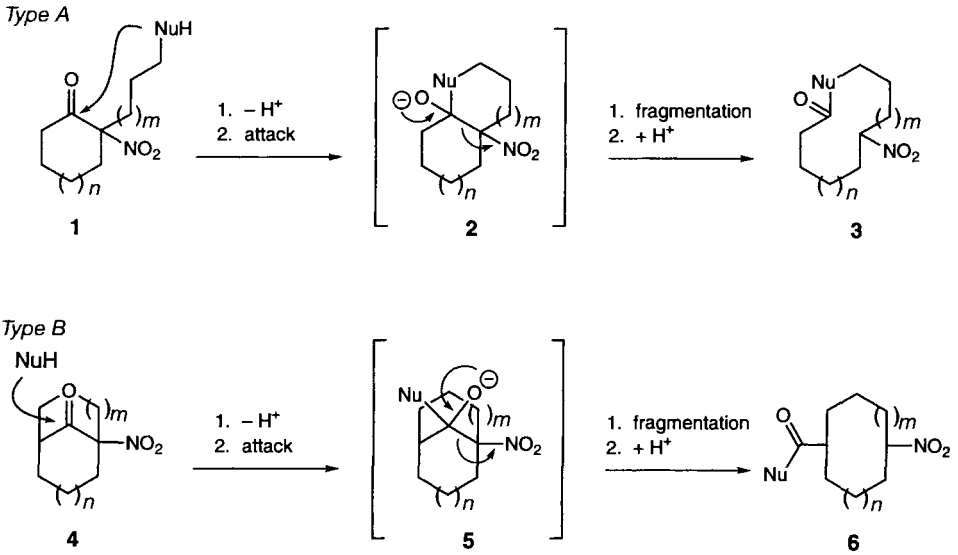
The reaction of α-nitro ketones to the corresponding α-hydroxy ketones under basic aqueous conditions, a novel transformation, was studied. The investigation revealed that the reaction is only possible with α-nitro ketones that are CH-acidic in the α'-position and readily deprotonated under the reaction conditions. The NO_2/OH exchange was established to proceed with retention of configuration at the stereogenic center, and labeling experiments have shown that the OH O-atom originates, to a great extent, from the solvent. In particular, the stereochemical course of the reaction and the incorporation of external nucleophiles led us to propose a mechanism that involves neighboring-group participation. The product formation is explained by a double S_N2 reaction, which proceeds *via* a *Favorskii*-like cyclopropanone intermediate.

1. Introduction. – We have been engaged for several years in the investigation of α-activated cyclic ketones as starting materials for the construction of macrocyclic compounds (for reviews, see [1][2]). In particular, α-nitro cycloalkanones have been thoroughly studied as substrates for the preparation of ring-enlarged carbocycles, lactones, and lactams. They have been used for the synthesis of the ketone fragrances (±)-muscone and *Exaltone*® [3][4], the lactones phoracantholide I (racemic [5] and enantiomerically enriched [6]), (±)-dihydrorecifeiolide and (±)-15-hexadecanolide [5], the lactone antibiotic A 26771 B [7], the macrocyclic spermidine alkaloids (±)-inandenin-10-ol, inandenin-10-one, and (±)-oncinotine [8], and analogs thereof [9], and for the preparation of other macrocyclic frameworks such as cyclophanes [10–12] or benzolactones [13]. Two different ring-enlargement types have been applied in these investigations: the ZIP reaction that incorporates the side chains of α-substituted α-nitro ketones **1** into the ring (*Type A*, *Scheme 1*) and the ring-enlargement reaction that cleaves the one-atom bridge of bicyclic α-nitro ketones **4** (*Type B*, *Scheme 1*). Both types of transformations involve the attack of a nucleophile at the carbonyl C-atom of the starting ketones **1** or **4**. The subsequent fragmentations of the thus obtained β-nitro alcoholates **2** and **5**, respectively, lead to stabilized nitronate anions that are protonated during workup and provide ring-enlarged compounds of the type **3** and **6**, or of subsequent products.

Whereas *Type A* seems to have a general character, *Type B* shows an interesting restriction. We accidentally found that bicyclic α-nitro ketone **7a**, the enol form of a 4-nitro 1,3-dione, did not lead to the corresponding ring-enlarged product when treated

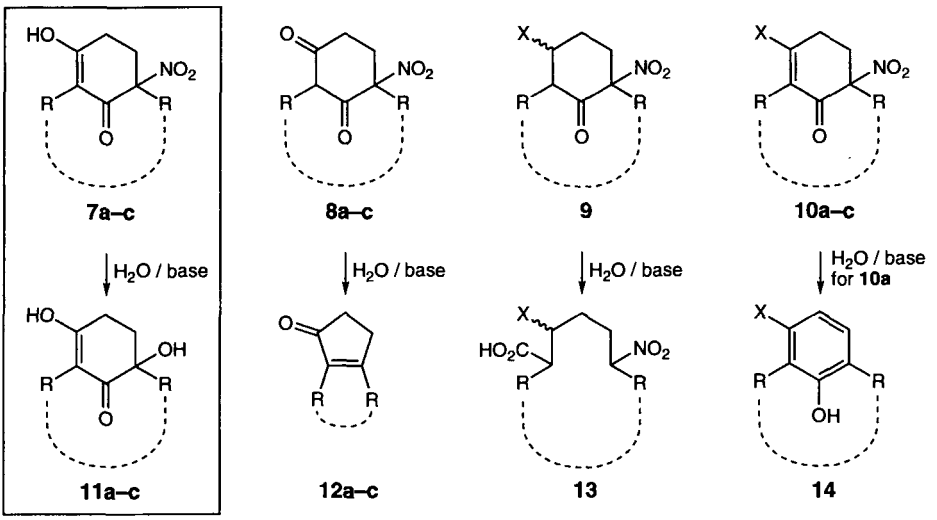
[1]) Part of the diploma theses of *C.G.* and *E.-S. J.*, and of the planned Ph.D. thesis of *A. Y.*, University of Zurich.

Scheme 1



with K_2CO_3 in H_2O. Instead, dihydroxy ketone **11a** was formed (*Scheme 2*) – obviously by NO_2/OH exchange. This reaction seems interesting from a mechanistic and preparative point of view. A radical mechanism, as proposed for the nitroalkane → alkyl-nitrite rearrangement [14], was regarded as unlikely due to the mild and ionic reaction condi-

Scheme 2[a])



[a]) For R, X, base, and yields, see *Table 1*.

tions. Even though direct nucleophilic replacements of NO_2 groups of nitroalkanes are known [15], we considered an S_N1 or S_N2 reaction as rather improbable for the formation of the dihydroxy compound **11a** from the precursor **7a**. Under basic conditions, NO_2 groups are usually displaced by nucleophiles only if they are located in activated positions (*e.g.*, benzylic [16], allylic [17], or β to a C=O function [18]). The NO_2 group of **7a**, however, is not in an activated position. A direct substitution of the S_N2-type appears to be additionally disfavored, because the site of attack for a nucleophile would be in a hidden groove of the bicyclic starting material, underneath the one-atom bridge, a region that is almost inaccessible for an external reagent. We thus reasoned that not a simple S_N reaction but a reaction with a more complex mechanism must be responsible for the formation of **11a** from **7a**. We found evidence that this is in fact correct, and here we report the corresponding investigation and data.

2. Results. – *Scope and Limitation of the Reaction.* The above-mentioned reaction, which transforms a NO_2 compound to the corresponding OH derivative (*e.g.*, reaction **7a** → **11a**), was investigated in more detail. The results of a series of relevant experiments are summarized in *Scheme 2* and *Table 1*. The experiments were performed under standardized conditions using four types of compounds: with **7a**, the enol form of an α-nitro 1,3-dione and some homologs (compounds **7b,c**), some analogs (**8a–c**; α-nitro 1,3-diones

Table 1. *Experiments Related to the Investigation of the Scope of the NO_2/OH Exchange Reaction* (for structures, see *Scheme 2*)

	Starting Material				Product	
Entry	No.	R,R	X	Base	No.	Yield [%]
1	**7a**	$-(CH_2)_9-$	–	KOH	**11a**	72
2	**7a**	$-(CH_2)_9-$	–	K_2CO_3	**11a**	85
3	**7a**	$-(CH_2)_9-$	–	KCN	**11a**	78
4	**7a**	$-(CH_2)_9-$	–	DBU	**11a**	90
5	**7a**	$-(CH_2)_9-$	–	Et_3N	**11a**	84
6	**7a**	$-(CH_2)_9-$	–	$(i\text{-}Pr)_2NH$	**11a**	56
7	**7a**	$-(CH_2)_9-$	–	pyridine	**11a**	8[a])
8	**7a**	$-(CH_2)_9-$	–	none	–	–[b])
9	**7b**[c])	$-(CH_2)_7-$	–	K_2CO_3	**11b**	68
10	**7c**	Et,Et	–	K_2CO_3	**11c**	44[a])
11	**8a**	$-(CH_2)_6-$	–	K_2CO_3	**12a**	73
12	**8b**	$-(CH_2)_5-$	–	K_2CO_3	**12b**	75
13	**8c**	$-(CH_2)_3-$	–	K_2CO_3	**12c**	65
14	**9**	$-(CH_2)_9-$	HO	K_2CO_3	**13**	24
15	**10a**	$-(CH_2)_9-$	MeO	K_2CO_3	**14**	46
16	**10b**	$-(CH_2)_9-$	AcO	K_2CO_3	**11a**[d])	67
17	**10c**	$-(CH_2)_9-$	H	K_2CO_3	–	–[b])

[a]) Starting material was recovered (*Entry 7*: 90%, *Entry 10*: 50%). [b]) The starting material was recovered almost quantitatively. [c]) Compound **7c** exists as the enol in the crystal (X-ray analysis) and as the dione in $CDCl_3$ solution (NMR evidence). [d]) Exchange product **11a** was presumably formed *via* **7a** by prior hydrolysis of the acetate **10a**.

in their keto forms), and some more distant relatives (β-hydroxy α-nitro ketone **9** and non-acidic 2,3-unsaturated α-nitro ketones **10a–c**)[2]).

The general reaction conditions applied for the experiments presented in *Table 1* were elaborated by optimization of the transformation of **7a** to **11a** in H_2O/K_2CO_3. The use of a good excess (5–10 equiv.) of base proved to be optimal for a fast and high-yielding reaction, and the conversion was most conveniently performed in refluxing solvent. The reaction started to proceed fairly quickly only at temperatures above 60° (NMR control). Finally, reflux conditions were chosen to ensure a constant and reproducible reaction temperature.

As can be immediately seen from *Scheme 2*, the four types of starting materials – compounds **7**, **8**, **9**, and **10** – show quite different behavior upon treatment with base in H_2O. Only the acidic 3-hydroxylated 2,3-unsaturated 2′-nitro ketones of the type **7** ($pK_a \approx 9$), which are in fact enols of CH-acidic 1,3-diones of the type **8**, undergo the NO_2/OH exchange reaction by formation of alcohols of the type **11**. 1,3-Diones of the type **8**, which are less acidic (as normal ketones) due to their specific bicyclic structures (they would violate *Bredt*'s rule upon deprotonation), and the β-functionalized and/or 2,3-unsaturated nitro ketones of the type **9** and **10** did not show this reaction. Compounds of the type **8** and compound **9** gave rise to ring-enlargement reactions according to *Type B* in *Scheme 1*, whereby the ring-enlargement products arising from **8a–c** led subsequently, under the basic aqueous reaction conditions, to the cyclopentenones **12a–c** by a cascade of decarboxylation of the intermediary β-oxo acids and intramolecular aldol condensations. This transformation has already been described in detail for **8a** [19]. Rather astonishing in the set of experiments is the observation that the 2,3-unsaturated ketones **10a–c** are almost inert under the reaction conditions. As a matter of fact, MeO derivative **10a** only gave rise to the formation of the MeO-substituted hydroxy cyclophane **14**, apparently by elimination of HNO_2, when heated for a prolonged period of time with base. The *O*-Ac compound **10b** yielded the deacylated 'exchange product' **11a**, but probably *via* the intermediate **7a** and not by direct NO_2/OH exchange. In fact, none of the compounds of the type **10** showed the NO_2/OH exchange reaction without alteration of the group X. Interestingly, a ring enlargement according to *Type B* (*Scheme 1*) was also not observed.

The data in *Table 1* additionally reveal that the NO_2/OH exchange reaction is sensitive to the strength of the base used. The prerequisite seems to be that the base should be strong enough to deprotonate the enols ($pK_b < \sim 5$, *Entries 1–6*); the nature of the base, whether it is inorganic or organic, is not important (*Entries 1–3 vs. Entries 4–6*). If no or too weak a base is used, no or negligible exchange reaction is observed (*Entries 7* and *8*, resp.; pK_b(pyridine) = 8.75).

Stereochemical Course of the Reaction. The reactions leading from NO_2 compounds of the type **7** to the corresponding OH derivatives of the type **11** proceed with virtually complete retention of configuration at the stereogenic center. This was established *pars pro toto* with optically active (+)-(*R*)-**7a** (*Scheme 3*). A sample of this compound was obtained by resolution of *rac*-**7a**. The reaction of *rac*-**7a** with (1*S*)-camphanoyl chloride afforded a mixture of the diastereoisomeric compounds of the type **15**, from which the ester (1*S*,1′*R*)-**15** was obtained by repetitive HPLC. Hydrolysis provided the desired

[2]) The syntheses of the starting materials of the types **7–10** are described in *Chapt. 4*.

Scheme 3

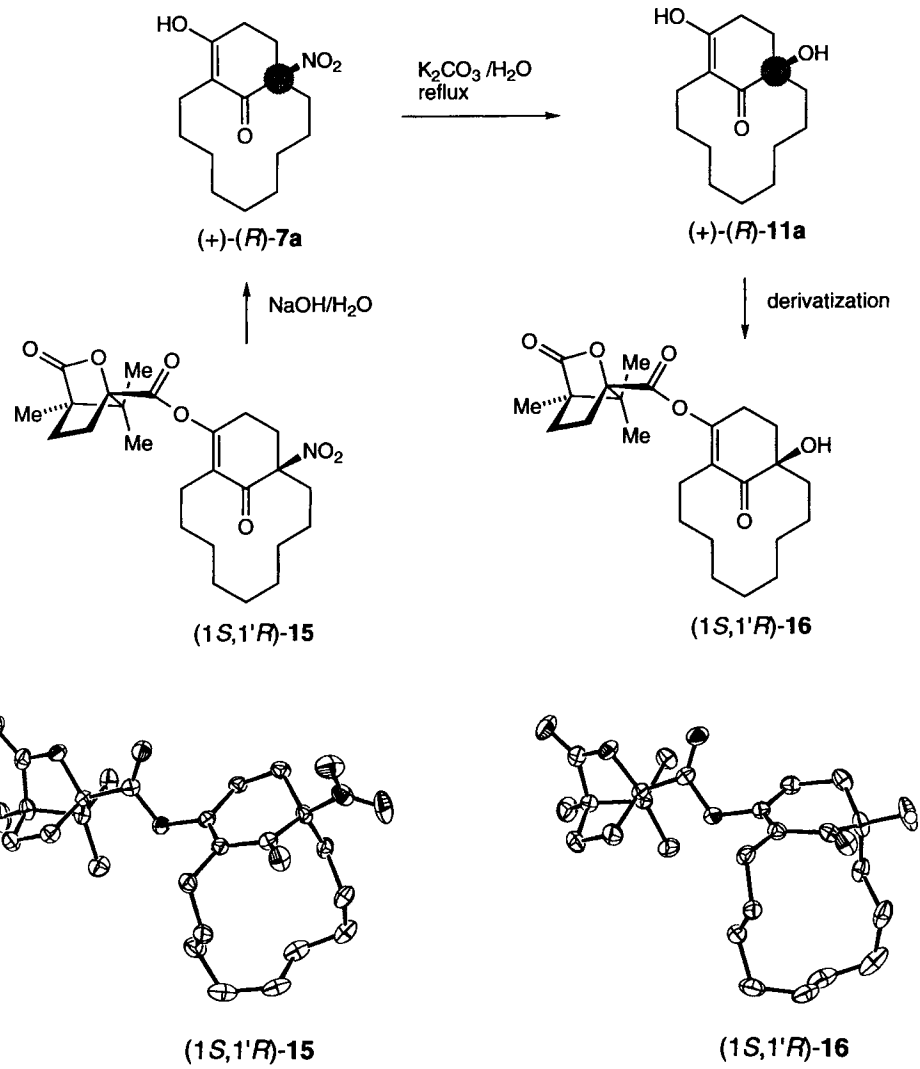


Fig. 1. *ORTEP Plots* [32] *of the molecular structures of (1S,1'R)-***15** *and (1S,1'R)-***16** (ellipsoids with 50% probability; H-atoms omitted for clarity)

optically enriched NO_2 compound (+)-(*R*)-**7a** (98% ee) that led to the OH derivative (+)-(*R*)-**11a** (95% ee) upon the usual treatment with base in H_2O. The absolute configurations of (+)-(*R*)-**7a** and (+)-(*R*)-**11a** were unambiguously established by single-crystal X-ray analysis of their (1*S*)-camphanoyl derivatives (1*S*,1'*R*)-**15** and (1*S*,1'*R*)-**16**, respectively (*Fig. 1*).

The Source of the OH Group. Since the source of the incorporated OH group was not clear – it might have come either from the solvent or from the NO_2 group – α-nitro ketone **7a** was treated with base in $H_2{}^{18}O$. A partially labeled form of the hydroxy ketone **11a**

was obtained and analyzed by EI-MS. The isotopic pattern of the molecular ion (*Fig. 2*) revealed that *ca.* 72% of the OH O-atom was incorporated from the solvent. About 5% of the doubly labeled product was found, too, indicating that the 3-hydroxy 2,3-unsaturated ketone moieties of **7a** or **11a** exchanged, to a small extent, their O-atoms with the O-atoms of the solvent[3]). To unambiguously establish the position where the O-atom of

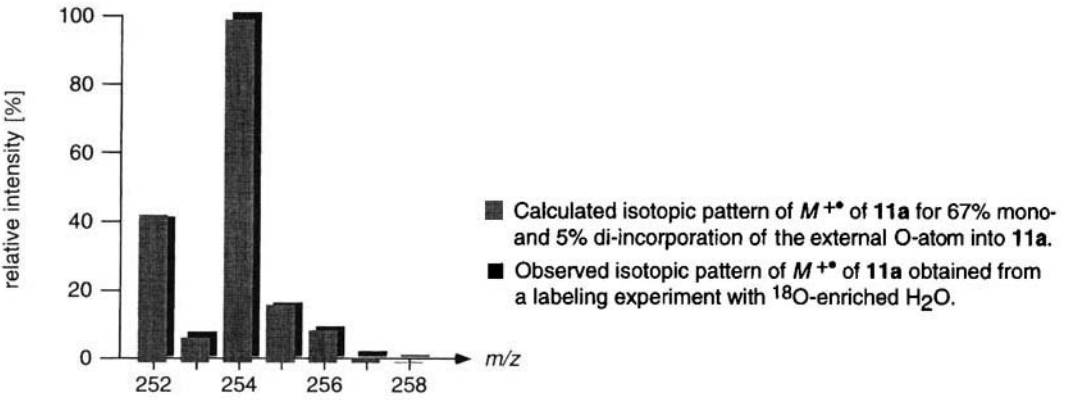


Fig. 2. *Comparison of the experimental and calculated isotopic patterns of the* $M^{+\cdot}$ *ion of* **11a** *obtained from a labeling experiment with* ^{18}O*-enriched* H_2O

the solvent was incorporated, a NO_2/OH-exchange experiment was performed with **7a** in $H_2{}^{17}O$-enriched H_2O as the reaction medium. As indicated by comparison of the ^{17}O-NMR spectra of the unlabeled sample of **7a** (*Fig. 3,a*) and of the sample of **7a** obtained from the labeling experiment (*Fig. 3,b*), the O-atom from the solvent is found with high preference in the OH group in α-position to the C=O group. The two other O-atoms, which were already present in the starting material, exchanged to less than 10% (estimated limit of detection).

Since it must be assumed that the OH group from the solvent is incorporated into the compounds of the type **11** by a nucleophilic attack of HO^- at the corresponding C-atom somewhere on the path from compounds **7** to the products, other nucleophiles were expected to replace NO_2 similarly. As already shown in *Table 1*, however, the reaction of **7a** with KCN in H_2O led to the OH compound **11a** and not to the nitrile **17**: thus, CN^- was evidently acting as a base and not as a nucleophile (*Scheme 4*). This might be due to successful competition of the nucleophile HO^- that is also present in the reaction mixture. The HO^- species, as part of the solvent, is located in close proximity to the substrate on the surface of the surrounding solvent cage and might react faster than an 'external' nucleophile. In fact, if H_2O is omitted as the solvent, and the conjugate acid

[3]) In two control experiments (performed in ^{18}O- and ^{17}O-enriched H_2O, resp.; see *Exper. Part*), it was shown that the incorporation of the O-atom from the solvent does not substantially occur prior to or after the 'exchange reaction' – neither in the C=O and the enol positions nor at the NO_2 group. Thus, the possibility of incorporation of the O-atom from the solvent *via* the NO_2 group can be excluded.

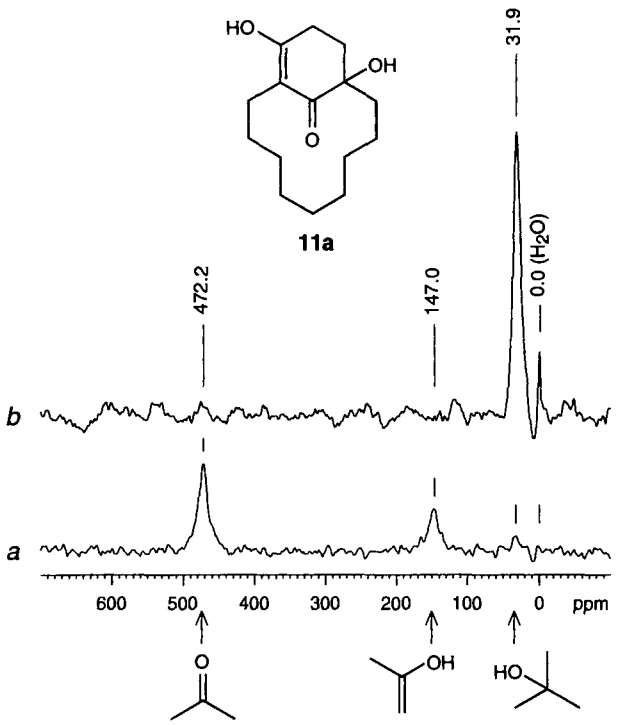
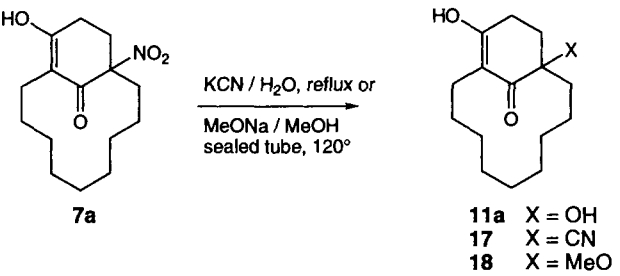


Fig. 3. *Comparison of the ^{17}O-NMR spectra of* **11a** *obtained from a reaction performed in H_2O of natural isotopic composition* (a) *and from a reaction performed in ^{17}O-enriched H_2O* (b)

Scheme 4



of the nucleophile (NuH) is used instead, the incorporation of other nucleophiles can be observed. For instance, when **7a** was treated with MeONa in MeOH at 120° in a sealed tube, MeO derivative **18** was obtained in *ca.* 60% yield, however, still along with the OH compound **11a** (*ca.* 40%). As in the case of the labeling experiment with $H_2{}^{18}O$ described above, the incorporation of the external nucleophile was not complete. The amount of 30–40% of 'alternative O' that is incorporated into **11a** is too significant to be ignored as an experimental error. The additional O has to be obtained from the NO_2 groups, which are the sole alternative source, and its incorporation has to be accounted for by the mechanism to be proposed for the transformation.

3. Discussion. – The data outlined above lead to a collection of facts connected to the successful exchange of an NO_2 with an OH group in α-nitro ketones. *1*) The reaction occurs only with readily enolized CH-acidic α-nitro 1,3-diones, apparently from their deprotonated forms; *2*) the transformation proceeds with virtually complete retention of configuration at the stereogenic center; *3*) the O-atom of the introduced OH group originates, to the greater part, from the solvent and to a lesser extent from the NO_2 group of the starting material, and *4*) the OH group (or the MeO group) is introduced by a nucleophilic attack at the originally NO_2-bearing C-atom at a certain stage of the transformation. It can further be concluded from the data that the transformation is most probably not a radical reaction involving a homolytic cleavage of the C–NO_2 bond in the initial step and not a simple S_N1 or S_N2 displacement. All these reactions should not be restricted to starting compounds of the type **7** and should also be observed with compounds of the type **8**, **9**, and **10**[4]). A radical as well as an S_N1 reaction would be expected to lead, at least partially, to racemization, whereas an S_N2 reaction should cause inversion of configuration at the stereogenic center. Complete retention of configuration at the center of chirality is observed, however, as we have already disclosed above. In particular, this stereochemical feature together with the (most probable) necessity of a deprotonated starting material[5]) led us to propose a mechanism that involves neighboring-group participation. The mechanism explains the stereoselectivity of the product formation by a double S_N2 reaction and is consistent with all experimental data. It is depicted in *Scheme 5*, with compound **7a** as the starting material.

We assume that, analogously to the *Favorskii* reaction, an intermediate of the type **19** is formed by intramolecular nucleophilic displacement of the NO_2 group of **7**. Unlike the *Favorskii* reaction, however, the external nucleophile does not add to the C=O group of **19** to initiate ring contraction. Instead, the nucleophile attacks the formerly NO_2-bearing C-atom (C(3)[6])) leading to the opening of the three-membered ring and reconstruction of the original C framework. The attack of the deprotonated solvent explains the observed incorporation of external nucleophiles into the molecules; the attack of NO_2^-, which remains sufficiently long in the solvent cage for the transformation, accounts for the *ca.* 30% of 'alternative O'-derived products. The double-inversion of configuration at the stereogenic center results in the net retention of configuration that is observed.

The proposed mechanism for the NO_2/OH exchange is not as peculiar as it might seem at first glance. Although there is no direct precedence, the displacement of the NO_2 group by an intramolecular reaction with a carbanion is quite plausible. It is conceivable

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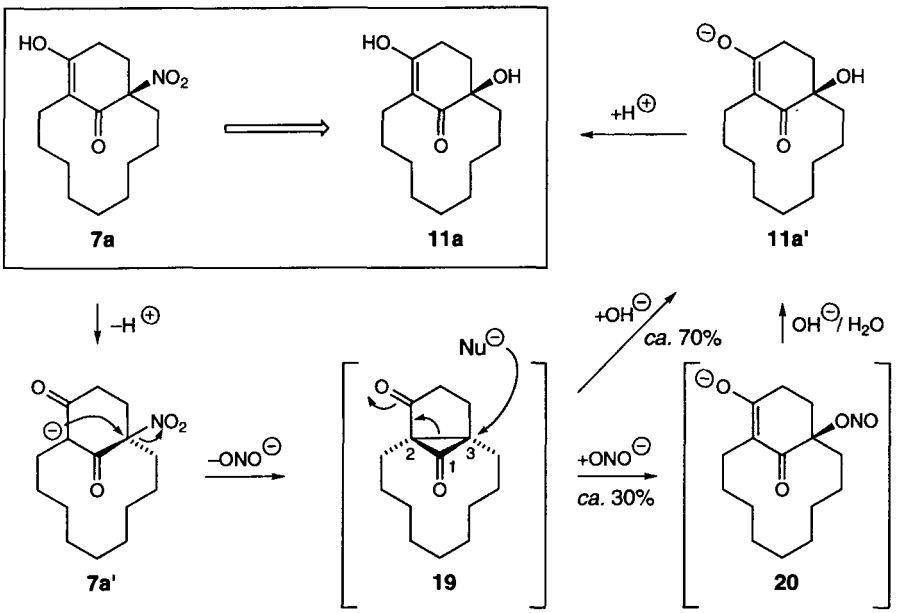
[4]) If a homolytic cleavage of the C–NO_2 bond or an S_N-type reaction would be responsible for the NO_2/OH exchange for compounds **7**, the analogous transformation should also be conceivable for all compounds of the types **8**, **9**, and **10**. Compounds **8** and **9**, however, follow an alternative reaction path that might simply be energetically favored. Since no alternative reaction paths are followed by compounds of the type **10**, the inertness of these materials can be considered as an argument against a radical or a direct S_N reaction.

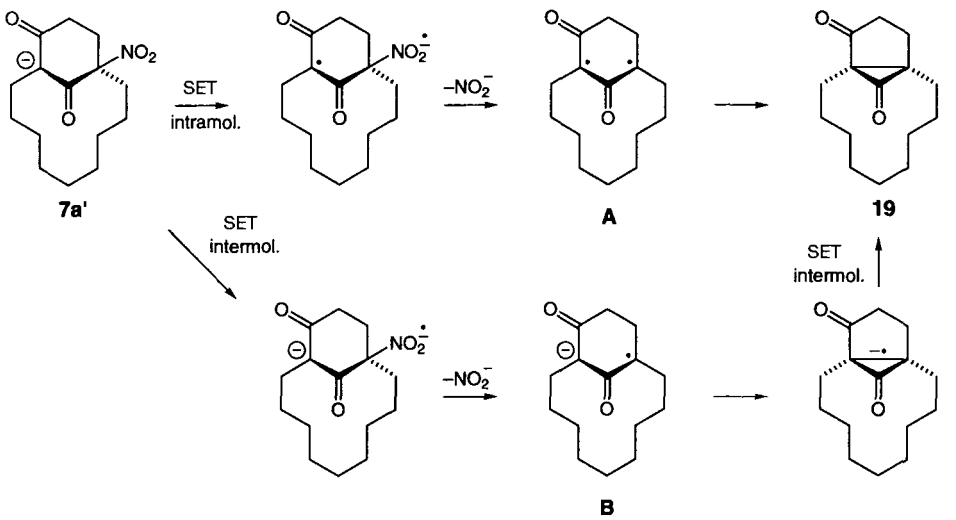
[5]) The deprotonation of the starting material might also be important to prevent a ring-enlargement reaction: the anionic deprotonation products of compounds **7** should be protected against nucleophilic attack at the C=O position. By prevention or retardation of the ring enlargement, however, alternative and rather slow processes might become dominant.

[6]) An arbitrary numbering is chosen for the discussion.

Scheme 5



Scheme 6

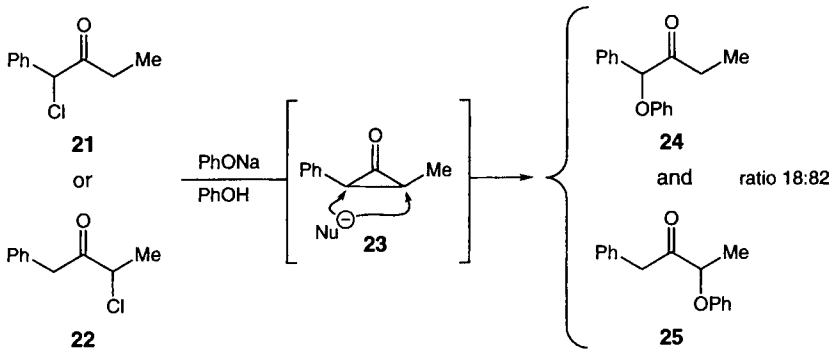


that substitutive cyclopropanation can occur even with leaving groups of lesser quality, due to the proximity of the nucleophile. However, an alternative radical process, as proposed by a reviewer, involving an intra- or intermolecular single-electron transfer (SET) from the enolate of the 1,3-dione moiety to the tertiary NO_2 group according to *Scheme 6* cannot be excluded with certainty (for a review on radical-anion reactions of

NO_2 compounds, see [20]). There is an indication from literature, though, that such a process might not be operative in our case: α-nitro esters, which are close relatives to our α-nitro ketones, undergo no replacement of the NO_2 group when treated with sodiomalonic esters, which are close analogs of the deprotonated 1,3-dione moiety in our case [21]. The radical reactions comprise also the difficulty to explain the stereochemical course of our transformation. One would have to assume that either the formations of the intermediary three-membered-ring structures are concerted with cleavage of the C–NO_2 bonds (which is without precedence in the literature), or that the lifetimes of the radical intermediates of the type **A** or **B** are extremely short as to prevent conformational equilibration prior to the ring closure. Addition of radical scavengers such as $CuCl_2$ or 1,3-dinitrobenzene as well as conducting the transformations in the dark or at daylight did not alter the course of the reactions.

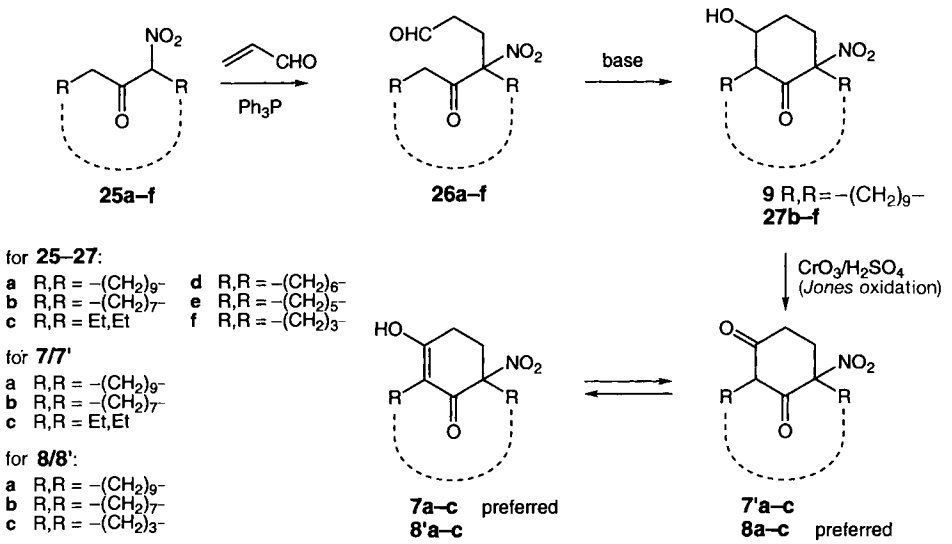
The 'anomalous', non-*Favorskii*-type ring opening of the three-membered ring intermediate **19** is also conceivable. The ring-opening reaction leads to a well-stabilized anion, which indeed should represent a fairly good leaving group. Because of the two C=O groups of **19**, the C(2)–C(3) bond is strongly polarized, and, thus, C(3) is predestined to be attacked by a nucleophile. Similar unexpected products in attempted *Favorskii* reactions are known in the literature [22–24]: *e.g.*, the reaction of each of the isomeric α-chloro ketones **21** or **22** with PhONa afforded the same mixture of isomeric 'substitution products' **24**/**25** in a ratio of 18:82 (*Scheme 7*). The product formation can be explained by the opening of the intermediary cyclopropanone **23** by attack of the nucleophile at either of the two α-positions of the ketone, leading preferentially to the more stable enolate intermediate.

Scheme 7



4. Synthesis of the Starting Compounds. – The syntheses of the compounds of the type **7**–**10** used as the starting materials for our mechanistic investigations are straightforward [3][7][10][19][25]. *Michael* addition of the CH-acidic α-nitro ketones **25a**–**f** [26] to acrylaldehyde provided the aldehydes **26a**–**f**, which were cyclized by base-catalyzed intramolecular aldol reactions to the β-hydroxy ketones **9** and **27b**–**f** (*Scheme 8*). Their oxidation with *Jones* reagent led to the desired 1,3-diones **7'a**–**c** and **8a**–**c**, the former isomerizing immediately to the more stable enol forms **7a**–**c**. Methylation of **7a** with MeI in presence of K_2CO_3 provided enol ether **10a** along with the *C*-alkylated isomer **10a'**,

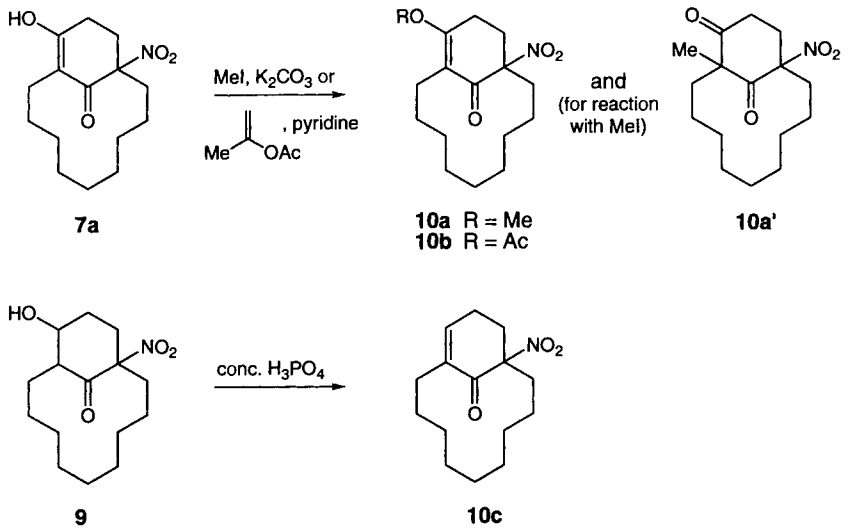
Scheme 8



and enol acetate **10b** was formed by reaction of **7a** with isopropenyl acetate under basic conditions (*Scheme 9*). Finally, the model compound **10c** was obtained from aldol **9** by treatment with conc. H_3PO_4.

The yields of the above transformations are all reasonably high (43–96%) and could possibly be improved by optimization of the corresponding reaction conditions. Except for the intramolecular aldol reactions leading to the cyclic β-hydroxy ketones **9** and

Scheme 9



29b–c, where the most effective base for the cyclization had to be found, no optimizations were performed.

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Experimental Part

General. Unless otherwise stated: all org. solvents were distilled prior to use. For the reactions, THF and Et_2O were dried over Na-ketyl. All reactions were carried out under Ar. Soln. of salts and acids for workup procedures were prepared in deionized H_2O. Extracts were dried (Na_2SO_4) and evaporated *in vacuo*. Chromatography: silica gel *Merck 60* (40–63 μm). M.p.: *Mettler FP-5/FP-52*. UV Spectra (MeOH): *Perkin-Elmer 555* spectrophotometer, λ in nm (lg ε). CD Spectra (EtOH): *JASCO J-500*; λ in nm ($\Delta\varepsilon_{max}$, $\Delta\varepsilon_{min}$, $\Delta\varepsilon = 0$). IR Spectra ($CHCl_3$): *Perkin-Elmer 781* or *Perkin-Elmer 297*; in cm^{-1}. ^{1}H-NMR: at 300 MHz in $CDCl_3$; *Bruker AC-300* or *Bruker ARX-300*; δ in ppm rel. to $CHCl_3$ (= 7.26 ppm), J in Hz. ^{13}C-NMR: at 75.6 MHz in $CDCl_3$; *Bruker ARX-300*; δ in ppm rel. to $CDCl_3$ (= 77.0 ppm); multiplicities from DEPT experiments. ^{17}O-NMR: at 81.4 MHz in (D_5)pyridine; *Bruker AMX-600*; δ in ppm rel. to H_2O (= 0.0 ppm). CI-MS: with NH_3 as the reactant gas; EI-MS: *Finnigan MAT 90* or *Finnigan SSQ 700* at 70 eV; ESI-MS: *Finnigan TSQ 700*; data in *m/z*. (rel.%, where appropriate).

1. Reactions Summarized in *Table 1.* – 1.1. *General Procedure and Results.* A soln. of a compound of the type **7**–**10** and of a base (5–10 mol-equiv.) in H_2O, and, when necessary to dissolve the starting material, acetone was heated to reflux for 4 h. The mixture was cooled to 23°, acidified with 10% aq. HCl soln., and extracted with AcOEt. The solvent was evaporated and the residue purified by recrystallization and/or chromatography.

Entry 1. The reaction of **7a** (200.0 mg, 0.71 mmol) with KOH (450 mg, 8.0 mmol) in H_2O (2 ml) afforded, after recrystallization of the residue (CH_2Cl_2/hexane) and chromatography of the mother liquid (CH_2Cl_2/acetone 9:1), **11a** (130 mg, 0.52 mmol, 72%) as slightly brownish crystals.

Entry 2. The reaction of **7a** (50.0 mg, 0.18 mmol) with K_2CO_3 (98 mg, 0.71 mmol) in H_2O (2 ml) afforded, after workup as described above, **11a** (38 mg, 0.15 mmol, 85%).

Entry 3. The reaction of **7a** (40.0 mg, 0.14 mmol) with KCN (40 mg, 0.61 mmol) in H_2O (2 ml) afforded, after workup as described above, **11a** (28 mg, 0.11 mmol, 78%).

Entry 4. The reaction of **7a** (31.0 mg, 0.11 mmol) with DBU (1,8-diazabicyclo[5.4.0]undec-7-ene; 70 mg, 0.46 mmol) in H_2O (2 ml) afforded, after workup as described above, **11a** (25 mg, 0.10 mmol, 90%).

Entry 5. The reaction of **7a** (80.0 mg, 0.28 mmol) with Et_3N (230 mg, 2.27 mmol) in H_2O (1 ml) afforded, after workup as described above, **11a** (60 mg, 0.24 mmol, 84%).

Entry 6. The reaction of **7a** (100.0 mg, 0.36 mmol) with $(i\text{-}Pr)_2NH$ (350 mg, 3.5 mmol) in H_2O (4 ml) afforded, after workup as described above, **11a** (50 mg, 0.20 mmol, 56%).

Entry 7. The reaction of **7a** (25.0 mg, 0.089 mmol) with pyridine (60 mg, 0.74 mmol) in H_2O (1 ml) afforded, after workup as described above, **11a** (1.8 mg, 0.007 mmol, 8%) and recovered **7a** (22.5 mg, 0.080 mmol, 90%).

Entry 8. The reaction of **7a** (25.0 mg, 0.089 mmol) in H_2O (1.5 ml) without base afforded no new product; **7a** was recovered almost quantitatively, even when heating was prolonged for 3 d.

Entry 9. The reaction of **7b** (50.0 mg, 0.20 mmol) with K_2CO_3 (109 mg, 0.79 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 98:2), **11b** (30 mg, 0.13 mmol, 68%) as a colorless oil.

Entry 10. The reaction of **7c** (53 mg, 0.25 mmol) with K_2CO_3 (138 mg, 1.00 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 98:2), **11c** (20 mg, 0.11 mmol, 44%) as a slightly yellow oil, and recovered **7c** (27 mg, 0.15 mmol, 59%).

Entry 11. The reaction of **8a** (50 mg, 0.21 mmol) with K_2CO_3 (116 mg, 0.84 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 98:2), **12a** (25 mg, 0.15 mmol, 73%) as a colorless oil.

Entry 12. The reaction of **8b** (50 mg, 0.22 mmol) with K_2CO_3 (123 mg, 0.89 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 98:2), **12b** (25 mg, 0.17 mmol, 75%) as a colorless oil.

Entry 13. The reaction of **8c** (50 mg, 0.25 mmol) with K_2CO_3 (138 mg, 1.00 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **12c** (20 mg, 0.16 mmol, 65%).

Entry 14. The reaction of **9** (200 mg, 0.71 mmol) with K_2CO_3 (390 mg, 2.83 mmol) in H_2O (8 ml) afforded, after chromatography (AcOEt/hexane/acetone 5:5:3), **13** (50 mg, 0.17 mmol, 24%) as a colorless oil. No other products were isolated.

Entry 15. The reaction of **10a** (180 mg, 0.61 mmol) with K_2CO_3 (378 mg, 2.74 mmol) in H_2O (8 ml) afforded, after chromatography (hexane/acetone 6:4), **14** (70 mg, 0.28 mmol, 46%) as a colorless oil and recovered **10a** (36 mg, 0.12 mmol, 20%).

Entry 16. The reaction of **10b** (100 mg, 0.31 mmol) with K_2CO_3 (190 mg, 1.39 mmol) in H_2O (4 ml) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **11a** (50 mg, 0.20 mmol, 67%).

Entry 17. The reaction of **10c** (15 mg, 0.06 mmol) with K_2CO_3 (32 mg, 0.23 mmol) in H_2O (1 ml) afforded no new product; **10c** was recovered almost quantitatively.

1.2. *1-Hydroxybicyclo[9.3.1]pentadecane-12,15-dione* (**11a**, keto form). Racemic material from *Entries 1–7* and *16*. (+)-(*R*)-**11a** (35 mg, 1.4 mmol, 78%) of 98% ee was obtained by reaction of (+)-(*R*)-**7a** (50 mg, 0.18 mmol, 98% ee) with K_2CO_3 (100 mg, 0.75 mmol) in H_2O (1 ml) and workup as described above. $[\alpha]_D = +55.3$ ($c = 0.83$, AcOEt). CD: 249 (−0.36), 259 (0), 274 (+1.41), 286 (0), 300 (−1.53), 320 (0), 325 (+0.07).

Data of rac-**11a**: Slightly brownish crystals. M.p. 195–197° (CH_2Cl_2/hexane). IR (KBr): 3400*s*, 3130*m*, 2930*s*, 2860*m*, 1630*s*, 1620*s*, 1470*m*, 1400*m*, 1375*s*, 1330*m*, 1295*w*, 1265*w*, 1200*w*, 1150*w*. ^{1}H-NMR (enol form): 5.58, 4.01 (2 br. *s*, 2 OH); 2.82–2.64 (*m*, 2 H); 2.54–2.44 (*m*, 1 H); 2.17–1.87 (*m*, 3 H); 1.64–0.96 (*m*, 16 H). ^{13}C-NMR (enol form, (D_6)DMSO): 201.7 (*s*, CO); 167.3 (*s*, C(12)); 112.3 (*s*, C(11)); 74.6 (*s*, C(1)); 34.5, 33.3, 27.0, 26.2, 25.8, 23.7, 23.0, 22.2, 21.8, 21.7, 18.3 (11*t*). ^{17}O-NMR ((D_5)pyridine; *cf. Fig. 2*): 472.2 (*m*, CO); 147.0 (*w*, HOC=); 31.9 (*vw*, HOCCO). CI-MS: 270 (8, $[M + NH_4]^+$), 253 (100, $[M + H]^+$). EI-MS: 252 (100, $M^{+\cdot}$), 149 (30), 140 (51), 126 (35), 111 (22), 97 (19), 83 (18), 69 (21), 55 (41), 43 (58). EI-MS (20 eV): Isotopic pattern of $M^{+\cdot}$: 252 (100), 253 (16.8), 254 (1.7). Anal. calc. for $C_{15}H_{24}O_3$ (252.357): C 71.39, H 9.59; found: C 71.44, H 9.75.

A sample of **11a** recovered after ^{13}C-NMR spectroscopy (in (D_6)DMSO) was recrystallized from AcOEt/hexane to give colorless crystals of **11a** · DMSO (m.p. 197–198°). For its single-crystal X-ray analysis, see below.

1.3. *1-Hydroxybicyclo[7.3.1]tridecane-10,13-dione* (**11b**, keto form). Colorless oil. IR: 3500*m* (br.), 2935*s*, 2855*m*, 1785*s*, 1710*s*, 1650*w*, 1615*m*, 1465*w*, 1445*w*, 1400*w*, 1360*m*, 1260*m*, 1180*m*, 1155*w*, 1120*m*, 1100*m*, 1010*w*, 980*w*, 945*w*, 910*m*. ^{1}H-NMR (enol form): 7.15, 4.57 (2 br. *s*, 2 OH); 2.77–2.65 (*m*, 2 H); 2.55–2.47 (*m*, 1 H); 2.38–2.30 (*m*, 1 H); 2.30–2.17 (*m*, 1 H); 2.01–1.60 (*m*, 4 H); 1.53–0.83 (*m*, 9 H). ^{13}C-NMR (enol form): 203.0 (*s*, CO); 166.7 (*s*, C(10)); 113.0 (s, C(9)); 75.3 (*s*, C(1)); 33.2, 32.8, 27.5, 25.6, 25.5, 24.3, 23.9, 22.1, 17.8 (9*t*). CI-MS: 242 (22, $[M + NH_4]^+$), 225 (100, $[M + H]^+$).

1.4. *2,4-Diethyl-4-hydroxycyclohexane-1,3-dione* (**11c**, keto form). Slightly yellow oil. IR: 3500*m* (br.), 2950*s*, 2890*m*, 1785*s*, 1720*s*, 1650*m*, 1605*m*, 1460*m*, 1420*m*, 1380*w*, 1260*s*, 1175*m*, 1145*m*, 1100*s*, 1010*s*, 950*w*, 920*w*. ^{1}H-NMR (mixture of keto and enol form): 6.01, 3.94 (2 br. *s*, 2 OH); 2.74–2.24 (*m*, 4 H); 2.20–1.91 (*m*, 2 H); 1.62–1.58 (*m*, 2 H); 1.10–0.90 (*m*, 6 H). ^{13}C-NMR (mixture of keto and enol forms): 207.1, 204.9, 200.9, 167.8 (4*s*, CO and CO/HOC=); 95.5 (*s*, 0.5 COC=); 73.6 (*s*, HOCCO); 64.6 (*s*, 0.5 CCO); 37.6, 33.9, 30.8, 30.3, 29.9, 28.4, 27.6, 27,0 (8*t*, 4 CH_2); 15.3, 12.9, 7.3, 6.2 (4*q*, 2 Me). EI-MS: 184 (26, $M^{+\cdot}$), 156 (51), 112 (69), 99 (40), 84 (100), 69 (70), 57 (60), 55 (39).

1.5. *Bicyclo[6.3.0]undec-1(8)en-9-one* (**12a**). Colorless oil. IR: 3000*m*, 2930*s*, 2855*s*, 1690*s*, 1640*s*, 1570*m*, 1460*m*, 1455*m*, 1445*m*, 1410*w*, 1380*m*, 1360*w*, 1330*w*, 1310*w*, 1305*w*, 1280*w*, 1260*m*, 1120*w*, 1090*m*, 1025*w*, 975*w*, 910*w*. ^{1}H-NMR: 2.35–2.28 (*m*, 2 H); 2.21–2.13 (*m*, 4 H); 1.59–1.53 (*m*, 1 H); 1.37–1.30 (*m*, 1 H); 1.29–1.21 (*m*, 3 H); 1.13–1.05 (*m*, 3 H); 0.70–0.63 (*m*, 4 H). ^{13}C-NMR: 209.3 (*s*, CO); 175.4 (*s*, C(1)); 140.4 (*s*, C(8)); 34.0, 31.5, 30.3, 28.4, 27.2, 26.1, 25.6, 21.1 (8*t*). CI-MS: 329 (100, $[2M + H]^+$), 182 (9, $[M + NH_4]^+$), 165 (39, $[M + H]^+$).

1.6. *Bicyclo[5.3.0]dec-1(7)en-8-one* (**12b**). Colorless oil. IR: 2925*s*, 2860*m*, 1740*m*, 1695*s*, 1635*m*, 1510*w*, 1450*w*, 1410*w*, 1375*w*, 1290*w*, 1250*m*, 1100*w*, 1010*w*, 930*m*, 875*w*, 850*w*. ^{1}H-NMR: 2.50–2.44 (*m*, 4 H); 2.38–2.33 (*m*, 2 H); 2.31–2.03 (*m*, 2 H); 1.82–1.73 (*m*, 2 H); 1.69–1.60 (*m*, 2 H); 1.55–1.48 (*m*, 2 H). ^{13}C-NMR: 208.1 (*s*, CO); 175.8 (*s*, C(1)); 141.3 (*s*, C(7)); 34.5, 33.6, 31.5, 31.2, 26.6, 26.2, 23.3 (7*t*). CI-MS (isobutane): 301 (100, $[2M + H]^+$), 151 (40, $[M + H]^+$).

1.7. *Bicyclo[3.3.0]oct-1(5)en-2-one* (**12c**). Colorless oil. IR (film): 2950*s*, 2920*s*, 2855*s*, 2830*m*, 1695*s*, 1635*s*, 1460*w*, 1435*m*, 1405*w*, 1380*s*, 1325*m*, 1285*w*, 1235*w*, 1210*w*, 1185*w*, 1170*w*, 1125*w*, 1020*s*, 970*w*, 955*w*, 915*w*, 880*w*, 800*m*. ^{1}H-NMR: 2.75–2.71 (*m*, 2 H); 2.54–2.48 (*m*, 4 H); 2.37–2.32 (*m*, 4 H). ^{13}C-NMR: 203.9 (*s*, CO); 187.3 (*s*, C(5)); 148.8 (*s*, C(1)); 41.0, 31.9, 27.7, 25.5, 24.3 (5*t*). EI-MS: 122 (100, $M^{+\cdot}$), 121 (61), 94 (12), 93 (19), 91 (10), 85 (22), 80 (18), 79 (91), 77 (25), 66 (34), 65 (12), 39 (21).

1.8. *2-Hydroxy-5-nitrocyclotetradecane-1-carboxylic Acid* (**13**). Colorless oil. IR: 3000*s* (br.), 2940*s*, 2865*s*, 1710*s*, 1550*s*, 1460*s*, 1445*s*, 1410*w*, 1375*m*, 1290*m*, 1175*m*, 1120*w*, 1070*w*, 1050*w*, 1040*w*, 975*w*, 940*w*, 920*w*, 910*w*. ^{1}H-NMR (*ca.* 1:1 mixture of diastereoisomers): 7.65 (br. *s*, CO_2H); 4.56–4.52 (*m*, 1 H); 4.00–3.92 (*m*, C*H*(OH)); 2.57–2.45 (*m*, 1 H); 2.24–2.03 (*m*, 1 H); 1.98–1.83–1.03 (*m*, 2 H); 1.69–1.08 (*m*, 20 H). ^{13}C-NMR (*ca.* 1:1

mixture of diastereoisomers): 179.5, 179.4 (2*s*, COOH); 85.5, 85.2 (2*d*, C(5)); 70.7, 68.7 (2*d*, C(2)); 50.1, 48.2 (2*d*, C(1)); 41.2, 35.9, 34.5, 31.4, 29.5, 28.5, 26.7, 26.0, 25.7, 25.4, 25.2, 25.1, 24.6, 24.5, 24.4, 24.2, 23.6, 22.5, 22.4, 21.9, 21.7, 14.0 (22*t*, 11 CH_2). CI-MS: 319 (100, $[M + NH_4]^+$), 301 (4, $[M + NH_4 - H_2O]^+$), 274 (10), 253 (25).

1.9. *11-Methoxybicyclo[9.3.1]pentadeca-1(15),11,13-trien-11-ol* (**14**). IR: 3600*m*, 2920*s*, 2830*m*, 1730*s*, 1660*w*, 1610*w*, 1520*m*, 1490*s*, 1460*s*, 1390*s*, 1380*w*, 1220*m*, 1100*s*, 1060*m*, 1040*m*, 990*w*, 940*m*, 870*w*, 850*w*, 800*w*. ^{1}H-NMR: 8.85 (*d*, *J* = 8.3, arom. H); 6.42 (*d*, *J* = 8.3, arom. H); 4.84 (br. *s*, OH); 3.79 (*s*, Me); 3.02–2.89 (*m*, 2 H); 2.67–2.57 (*m*, 1 H); 2.45–2.35 (*m*, 1 H); 2.00–1.87 (*m*, 1 H); 1.87–1.72 (*m*, 1 H); 1.62–1.49 (*m*, 2 H); 1.49–1.39 (*m*, 1 H); 1.32–1.15 (*m*, 3 H); 1.12–0.92 (*m*, 4 H); 0.57–0.37 (*m*, 2 H). ^{13}C-NMR: 157.3, 153.1 (2*s*, 2 arom. C); 128.1 (*d*, arom. C); 120.5 (*s*, arom. C); 116.3 (*s*, arom. C); 103.1 (*d*, arom. C); 55.8 (*q*, MeO); 29.6, 25.9, 25.7, 25.5, 25.44, 25.39, 25.1, 24.1, 23.3 (9*t*). CI-MS: 249 (100, $[M + H]^+$), 150 (7), 58 (33).

2. **Incorporation of External Nucleophiles**. 2.1. *Reaction of* **7a** *in* ^{17}*O-Enriched* H_2O. Analogously to *1.1*, **7a** (25 mg, 0.09 mmol) delivered, after reaction with Et_3N (34 mg, 0.34 mmol) in ^{17}O-enriched H_2O (23.9% $H_2{}^{18}O$, 25.7% $H_2{}^{17}O$, 50.4% $H_2{}^{16}O$; 2 ml, *Dr. Glaser AG*, Basel (CH)) and chromatography, partially labeled **11a** (19 mg, 0.08 mmol, 85%). ^{17}O-NMR ((D_5)pyridine; *cf. Fig. 2*): 31.9 (*s*, HOCCO).

2.2. *Control Reaction of* **11a** *with* ^{17}*O-Enriched* H_2O. No exchange or only homogeneous exchange of all O-atoms of **11a** with the O-atoms of the solvent was observed when **11a** was treated analogously to **7a** in ^{17}O-enriched H_2O. The ^{17}O-NMR data were identical with those of a sample of **11a** obtained from a transformation that was performed in H_2O of natural composition.

2.3. *Reaction of* **7a** *in* ^{18}*O-Enriched* H_2O. EI-MS (20 eV): Analogously to *1.1*, **7a** (25 mg, 0.09 mmol) delivered, after reaction with Et_3N (34 mg, 0.34 mmol) in ^{18}O-enriched H_2O (97.4% $H_2{}^{18}O$, 1.0% $H_2{}^{17}O$, 1.6% $H_2{}^{16}O$; 1 ml, *Dr. Glaser AG*, Basel (CH)) and chromatography, partially labeled **11a** (17 mg, 0.07 mmol, 76%). Isotopic pattern of the $M^{+\cdot}$: 252 (40.4), 253 (6.9), 254 (100), 255 (15.6), 256 (8.5), 257 (1.1); 258 (0.1). This isotopic pattern corresponds to 67% mono- and 5% di-incorporation of O-atoms from the solvent, or overall *ca.* 72% incorporation of the O-atoms at the OH group in the α-position **11a**. *Fig. 1* shows the exper. MS result together with a calculated spectrum. The calculation is based on the spectrum of non-labeled **11a** and under consideration of the composition of ^{18}O-enriched H_2O. The MS of **7a** that was recovered after *ca.* 50% conversion showed only negligible incorporation of ^{18}O (< 5%) into the compound.

2.4. *Reaction of* **7a** *with MeONa/MeOH: 1-Methoxybicyclo[9.3.1]pentadecane-12,15-dione* (**18**, keto form). A soln. of **7a** (100 mg, 0.04 mmol) and MeONa (0.32 mmol) in MeOH (2 ml) was heated in a sealed tube at 120° for 2 h. After cooling to 23°, the solvent was evaporated, the residue dissolved in H_2O, acidified with 5% HCl soln., extracted with CH_2Cl_2, and chromatographed (CH_2Cl_2/acetone 9:1) to yield **18** (58 mg, 0.02 mmol, 58%) and recovered **7a** (36 mg, 0.014 mmol, 36%), both as colorless crystals. M.p. 72–74° (CH_2Cl_2/hexane). IR: 3400*m*, 2990*m*, 2930*s*, 2860*s*, 1625*s*, 1465*m*, 1445*m*, 1380*s*, 1350*m*, 1330*w*, 1280*w*, 1190*w*, 1150*w*, 1120*w*, 1090*m*, 1035*w*, 1000*w*, 980*w*, 920*w*, 905*w*. ^{1}H-NMR (enol form): 7.30 (br. *s*, OH); 3.34 (*s*, Me); 2.62–2.58 (*m*, 2 H); 2.34–2.25 (*m*, 2 H); 2.10–2.05 (*m*, 2 H); 1.89–1.70 (*m*, 2 H); 1.70–1.00 (*m*, 14 H). ^{13}C-NMR (enol form): 196.2 (*s*, CO); 172.3 (*s*, C(12)); 145.5 (*s*, C(11)); 116.7 (*s*, C(1)); 49.8 (*q*, MeO); 34.2, 33.2, 26.4, 25.8, 25.3, 25.0, 24.0, 23.4, 22.5, 21.8, 18.7 (11*t*). CI-MS: 267 (100, $[M + H]^+$), 253 (33).

3. Preparation of the Starting Materials. – 3.1. Michael *Reaction*. 3.1.1. *General Procedure*. A *ca.* 0.8–1M soln. of an α-nitro ketone of the type **25**, propenal (1.1 equiv.), and Ph_3P (cat. amount) in THF was stirred at 23° for 1 h. It was quenched by addition of MeI, filtered through SiO_2, and chromatographed or recrystallized.

3.1.2. *3-(1-Nitro-2-oxocyclododecyl)propanal* (**26a**). According to *3.1.1*, the reaction of *2-nitrocyclododecanone* (**25a**, 80.0 g, 352 mmol) afforded, after recrystallization (Et_2O/hexane), **26a** (90.5 g, 319 mmol, 91%) as colorless crystals. Data in agreement with [5].

3.1.3. *3-(1-Nitro-2-oxocyclodecyl)propanal* (**26b**). According to *3.1.1*, the reaction of *2-nitrocyclodecanone* (**25b**, 500 mg, 2.51 mmol) afforded, after chromatography (hexane/Et_2O 2:1), **26b** (430 mg, 1.68 mmol, 67%). Slightly yellow oil. IR: 2925*s*, 2840*m*, 2450*w*, 1730*s*, 1540*s*, 1470*m*, 1390*m*, 1350*m*, 1280*w*, 1200*w*, 1150*w*, 920*w*, 850*w*. ^{1}H-NMR: 9.73 (*t*, *J* = 0.8, CHO); 2.89–2.79 (*m*, 1 H); 2.62–2.47 (*m*, 2 H); 2.45–2.41 (*m*, 3 H); 2.34–2.15 (*m*, 1 H); 2.13–1.97 (*m*, 3 H); 1.83–1.20 (*m*, 10 H). ^{13}C-NMR: 202.1 (*s*, CO); 199.2 (*d*, CHO); 100.0 (*s*, CNO_2); 38.1, 35.3, 31.5, 30.6, 26.5, 25.2, 24.3, 22.8, 22.5, 19.8 (10*t*). CI-MS: 273 (100, $[M + NH_4]^+$), 237 (41), 220 (9).

3.1.4. *4-Ethyl-4-nitro-5-oxooctanal* (**26c**). According to *3.1.1*, the reaction of *5-nitroheptan-4-one* (**25c**, 35.0 g, 220 mmol) afforded, after chromatography (hexane/Et_2O 2:1), **26c** (29.0 g, 135 mmol, 61%). Slightly yellow liquid. IR: 3020*m*, 2935*s*, 2840*m*, 2820*w*, 2710*w*, 2320*w*, 1730*s*, 1540*s*, 1460*m*, 1390*w*, 1300*m*, 1280*w*, 1200*m*, 1140*w*, 1110*w*, 1060*w*, 920*w*, 890*w*, 850*w*. ^{1}H-NMR: 9.74 (*s*, CHO); 2.55–2.39 (*m*, 5 H); 2.37–2.10 (*m*, 3 H); 1.70–1.57 (*m*, 2 H); 1.00–0.87 (*m*, 2 Me). ^{13}C-NMR: 201.2 (*s*, CO); 199.1 (*d*, CHO); 100.0 (*s*, C(4)); 38.7, 37.8, 26.5, 25.9, 17.8 (5*t*); 13.5, 7.5 (2*q*). CI-MS: 216 ($[M + H]^+$).

3.1.5. *3-(1-Nitro-2-oxocyclononyl)propanal* (**26d**). According to *3.1.1*, the reaction of *2-nitrocyclononanone* (**25d**, 500 mg, 2.7 mmol) afforded, after chromatography (hexane/Et_2O 2:1), **26d** (500 mg, 2.1 mmol, 77%). Slightly yellow oil. IR: 3020*m*, 2920*s*, 2830*m*, 2710*w*, 2400*w*, 1725*s*, 2545*s*, 1470*m*, 1450*m*, 1340*m*, 1220*m*, 1140*w*, 1120*w*, 1080*m*, 1020*w*, 930*w*, 870*w*, 850*w*. ^{1}H-NMR: 9.73 (*s*, CHO); 2.75–2.65 (*m*, 1 H); 2.60–2.33 (*m*, 5 H); 2.28–2.20 (*m*, 1 H); 2.18–2.06 (*m*, 1 H); 1.98–1.86 (*m*, 1 H); 1.80–1.54 (*m*, 2 H); 1.49–1.20 (*m*, 7 H). ^{13}C-NMR: 203.7 (*s*, CO); 199.2 (*d*, CHO); 99.4 (*s*, CNO_2); 38.3, 36.8, 30.3, 26.5, 25.8, 24.6, 23.4, 22.0, 18.9 (9*t*). CI-MS: 259 ($[M + NH_4]^+$).

3.1.6. *3-(1-Nitro-2-oxocyclooctyl)propanal* (**26e**). According to *3.1.1*, the reaction of *2-nitrocyclooctanone* (**25e**, 1.0 g, 5.84 mmol) afforded, after chromatography (hexane/Et_2O 2:1), **26e** (1.1 g, 4.84 mmol, 83%). Colorless crystals. Data in agreement with [5].

3.1.7. *3-(1-Nitro-2-oxocyclohexyl)propanal* (**26f**). According to *3.1.1*, the reaction of *2-nitrocyclohexanone* (**25f**, 4.0 g, 28.3 mmol) afforded, after chromatography (hexane/Et_2O 2:1), **26f** (3.0 g, 15.1 mmol, 53%). Slightly yellow oil. Data in agreement with [5].

3.2. *Cyclization*. 3.2.1. *General Procedure*. A *ca.* 0.1M soln. of an aldehyde of the type **27** and DBU (2 equiv.) in THF was stirred at 23° until the starting material was consumed (1–2 d). It was neutralized with 5% HCl soln., extracted with CH_2Cl_2, and chromatographed.

3.2.2. *12-Hydroxy-1-nitrobicyclo[9.3.1]pentadecan-15-one* (**9**). According to *3.2.1*, the reaction of **26a** (1.0 g, 3.53 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **9** (0.7 g, 2.47 mmol, 70%) as colorless crystals. Data in agreement with [10]. For the single-crystal X-ray analysis of **9**, see below.

3.2.3. *10-Hydroxy-1-nitrobicyclo[7.3.1]tridecan-13-one* (**27b**). According to *3.2.1*, the reaction of **26b** (400 mg, 1.57 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **27b** (350 mg, 1.37 mmol, 88%). Colorless crystals. M.p. 144–146° (AcOEt/hexane). IR: 3600*m*, 3440*w* (br.), 2930*s*, 2880*m*, 1730*s*, 1550*s*, 1475*m*, 1445*m*, 1390*w*, 1355*m*, 1340*m*, 1315*w*, 1260*w*, 1175*w*, 1155*w*, 1120*w*, 1100*m*, 1060*w*, 1035*m*, 995*m*, 975*w*, 945*w*, 935*w*, 915*w*, 890*w*, 875*w*, 860*w*. ^{1}H-NMR: 4.30 (br. *s*, OH); 3.58–3.47 (*m*, H–C(10)); 3.01–2.88 (*m*, H–C(9)); 2.68–2.57 (*m*, 1 H); 2.27–1.12 (*m*, 17 H). ^{13}C-NMR: 202.5 (*s*, CO); 98.8 (*s*, C(1)); 76.0 (*d*, C(10)); 51.3 (*d*, C(9)); 34.4, 32.5, 30.6, 26.4 (4*t*); 25.9 (*t*, 2 CH_2); 23.4, 21.9, 20.9 (3*t*). CI-MS: 273 ($[M + NH_4]^+$).

3.2.4. *2,6-Diethyl-5-hydroxy-2-nitrocyclohexanone* (**27c**). According to *3.2.1*, the reaction of **26c** (2.0 g, 9.29 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **27c** (0.9 g, 4.18 mmol, 45%). Slightly yellow oil. IR: 3600*m*, 3430*w* (br.), 2980*m*, 2935*s*, 2875*m*, 1735*s*, 1680*m*, 1540*s*, 1460*m*, 1450*m*, 1440*m*, 1390*w*, 1360*m*, 1330*w*, 1260*w*, 1140*m*, 1095*w*, 1070*w*, 1035*w*, 965*m*, 940*m*, 880*w*, 850*m*. ^{1}H-NMR (*ca.* 70:30 mixture of diastereoisomers): 4.33 (br. *s*, H–C(5)); 3.57–3.42 (*m*, 0.3 H–C(5)); 2.87–2.71 (*m*, 1 H); 2.61–2.45 (*m*, 1 H); 2.29–2.07 (*m*, 2 H); 2.02–1.62 (*m*, 5 H); 1.53–1.31 (*m*, 1 H); 1.03–0.86 (*m*, 2 Me). ^{13}C-NMR: 199.2 (*s*, CO); 97.3 (*s*, C(2)); 72.1 (*d*, C(5)); 54.8 (*d*, C(6)); 30.0, 29.0, 28.9, 18.5 (4*t*); 11.2, 7.7 (2*q*). CI-MS (isobutane): 216 (100, $[M + H]^+$), 198 (28), 169 (19), 157 (18), 140 (30).

3.2.5. *9-Hydroxy-1-nitrobicyclo[6.3.1]dodecan-12-one* (**27d**). According to *3.2.1*, the reaction of **26d** (500 mg, 2.07 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **27d** (350 mg, 1.45 mmol, 70%). Colorless crystals. M.p. 104–107° (AcOEt/hexane). IR: 3600*m*, 3420*w* (br.), 2930*m*, 1740*s*, 1550*s*, 1470*m*, 1360*w*, 1340*m*, 1250*m*, 1130*w*, 1060*w*, 1030*w*, 950*w*, 930*w*, 830*w*. ^{1}H-NMR (*ca.* 85:15 mixture of diastereoisomers): 4.39, 4.13 (2 br. *s*, *H*COH); 3.20–3.03 (*m*, 2 H); 2.64–2.57 (*m*, 1 H); 2.37–2.26 (*m*, 1 H); 2.23–1.96 (*m*, 6 H); 1.85–1.55 (*m*, 4 H); 1.38–1.05 (*m*, 4 H). ^{13}C-NMR (*ca.* 85:15 mixture of diastereoisomers, major isomer described only): 202.4 (*s*, CO); 99.8 (*s*, C(1)); 75.9 (*d*, C(9)); 52.3 (*d*, C(8)); 37.3, 32.8, 32.0, 30.8, 28.5, 26.6, 25.8, 23.7 (8*t*). CI-MS: 259 ($[M + NH_4]^+$).

3.2.6. *8-Hydroxy-1-nitrobicyclo[5.3.1]undecan-11-one* (**27e**). According to *3.2.1*, the reaction of **26e** (2.5 g, 11.0 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **27e** (1.9 g, 8.3 mmol, 76%). Colorless crystals. M.p. 80–83° (CH_2Cl_2/hexane). IR: 3600*m*, 3410*w* (br.), 2930*m*, 2870*w*, 2850*w*, 1720*s*, 1550*s*, 1465*m*, 1455*w*, 1440*w*, 1430*w*, 1360*w*, 1335*m*, 1300*w*, 1260*m*, 1140*w*, 1090*m*, 1060*m*, 1020*w*, 1005*m*, 995*m*, 960*w*, 915*w*, 850*m*, 835*m*. ^{1}H-NMR (*ca.* 2:1 mixture of diastereoisomers): 4.14–3.99 (*m*, H–C(8)); 3.29–3.19, 2.99–2.92 (2*m*, H–C(7)); 2.83 (*s*, OH); 2.80–2.49 (*m*, 2 H); 2.26–1.09 (*m*, 12 H). ^{13}C-NMR (*ca.* 2:1 mixture of diastereoisomers, signals of major isomer in italics): *206.1*, 204.7 (2*s*, CO); *99.7*, 99.2 (2*s*, C(1)); *72.3*, 70.5 (2*d*, C(8)); *57.5*, 56.3 (2*d*, C(7)); 33.7, *33.4*, *31.9*, 31.6, *30.45*, 30.47, *29.3*, 25.5, *24.9*, 24.6, *23.8*, 23.5, 23.4, *23.3* (14*t*, 7 CH_2). CI-MS: 228 ($[M + H]^+$).

3.2.7. *6-Hydroxy-1-nitrobicyclo[3.3.1]nonan-9-one* (**27f**). According to *3.2.1*, the reaction of **26f** (1.95 g, 9.80 mmol) afforded, after chromatography (CH_2Cl_2/AcOEt 9:1), **27f** (1.52 g, 7.63 mmol, 78%). Colorless crystals. Data in agreement with [19].

3.3. *Oxidation*. 3.3.1. *General Procedure*. To a *ca.* 0.2M soln. of an alcohol of the type **9** or **27** *Jones* reagent (CrO_3/H_2SO_4, [27]) was added dropwise, until the orange color persisted (*ca.* 1.1 equiv.). The mixture was stirred

for another 2 h, and the excess of Cr(VI) was reduced with i-PrOH. The solvents were evaporated, the residue taken into H_2O, extracted with CH_2Cl_2, and chromatographed.

3.3.2. rac-*1-Nitrobicyclo[9.3.1]pentadecane-12,15-dione* (*rac*-**7a**, keto form) *and (+)-(R)-1-Nitrobicyclo[9.3.1]pentadecane-12,15-dione* ((+)-(*R*)-**7a**). According to *3.3.1*, the reaction of **9** (11.4 g, 40.2 mmol) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **7a** (5.83 g, 20.7 mmol, 52%) as colorless crystals. Enantiomerically enriched (+)-(*R*)-**7a** (46 mg, 0.16 mmol, 86%; 98% ee) was obtained by hydrolysis of (1*S*,1′*R*)-**15** (88 mg, 0.19 mmol) in 1N NaOH (490 ml) at 23° for 45 min. $[\alpha]_D = +36.1$ (0.81, AcOEt). CD: 264 (−8.50), 282 (0), 299 (+4.97).

Data of rac-**7a**: M.p. 162–164° (AcOEt/hexane 1:1). IR: 3540*w*, 3200*m* (br.), 2920*s*, 2855*m*, 1660*m*, 1625*s*, 1545*s*, 1465*m*, 1450*w*, 1425*w*, 1375*s*, 1340*m*, 1325*w*, 1290*w*, 1245*w*, 1230*w*, 1190*m*, 1180*m*, 1145*s*, 1130*s*, 1115*s*, 1035*m*, 1000*w*, 980*w*, 920*w*, 870*w*, 835*w*. ^{1}H-NMR (enol form): 6.30 (br., *s*, OH exchanged with D_2O); 3.07–2.82 (*m*, 1 H); 2.80–2.60 (*m*, 2 H); 2.28–1.85 (*m*, 4 H); 1.50–1.07 (*m*, 15 H). ^{13}C-NMR ((D$_6$)DMSO, enol form): 189.6 (*s*, CO); 171.4 (*s*, C(12)); 112.8 (*s*, C(11)); 96.0 (*s*, C(1)); 31.3, 30.5, 26.3, 26.1, 25.9, 23.2, 22.4, 22.3, 21.6, 21.0, 19.1 (11*t*). ^{17}O-NMR ((D$_5$)pyridine): 608.1 (*m*, NO_2); 492.8 (*m*, CO); 154.0 (*w*, HOC=). CI-MS: 299 (50, $[M + NH_4]^+$), 282 (10, $[M + H]^+$), 253 (100), 235 (30). EI-MS: 281 (5, $M^{+\cdot}$), 252 (25), 235 (100), 207 (17), 149 (29), 137 (40), 123 (29), 111 (20), 95 (26), 81 (29), 67 (30), 55 (55), 41 (48). ESI-MS: 320 (18, $[M + K]^+$), 304 (19, $[M + Na]^+$), 282 (80, $[M + H]^+$), 277 (100). Anal. calc. for $C_{15}H_{23}NO_4$ (281.355): C 64.04, H 8.24, N 4.98; found: C 64.26, H 7.92, N 4.74.

For the single-crystal X-ray analysis of *rac*-**7a**, see below.

3.3.3. *1-Nitrobicyclo[7.3.1]tridecane-10,13-dione* (**7b**, keto form). According to *3.3.1*, the reaction of **27b** (320 mg, 1.25 mmol) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **7b** (250 mg, 0.99 mmol, 79%). Colorless crystals. M.p. 105–116° (CH_2Cl_2/hexane). IR: 2935*m*, 2880*m*, 2850*w*, 1750*s*, 1725*s*, 1550*s*, 1475*m*, 1445*m*, 1405*w*, 1360*m*, 1345*m*, 1335*m*, 1320*w*, 1260*m*, 1140*m*, 1100*m*, 1010*m*, 960*w*, 950*w*, 940*w*, 910*w*, 875*w*. ^{1}H-NMR: 4.12 (*dd*, *J* = 10.4, 2.0, H–C(9)); 3.01–2.89 (*m*, 1 H); 2.78–2.57 (*m*, 4 H); 2.21–2.01 (*m*, 2 H); 1.99–1.80 (*m*, 2 H); 1.64–1.46 (*m*, 6 H); 1.27–1.14 (*m*, 3 H). ^{13}C-NMR: 201.2, 197.0 (2*s*, 2 CO); 96.9 (*s*, C(1)); 64.5 (*d*, C(9)); 36.8, 35.6, 29.8, 26.4, 24.4, 21.7, 20.8, 20.5, 19.9 (9*t*). CI-MS: 271 (100, $[M + NH_4]^+$), 254 (38, $[M + H]^+$), 179 (10).

For the single-crystal X-ray analysis of **7b**, see below.

3.3.4. *2,4-Diethyl-4-nitrocyclohexane-1,3-dione* (**7c**, keto form). According to *3.3.1*, the reaction of **27c** (200 mg, 0.93 mmol) afforded, after chromatography (CH_2Cl_2/acetone 98:2), **7c** (180 mg, 0.84 mmol, 91%). Colorless crystals. M.p. 105–110° (CH_2Cl_2/hexane). IR: 3655*m*, 3200*m* (br.), 2975*m*, 2945*m*, 2875*w*, 1750*w*, 1720*w*, 1630*s* (br.), 1545*s*, 1460*m*, 1440*m*, 1385*s*, 1345*m*, 1275*w*, 1185*w*, 1150*w*, 1110*w*, 965*w*, 950*w*, 860*w*, 835*m*. ^{1}H-NMR (enol form): 6.54 (br. *s*, OH); 2.87–2.70 (*m*, 2 H); 2.57–2.45 (*m*, 1 H); 2.40–2.19 (*m*, 4 H); 2.11–1.97 (*m*, 1 H); 1.05–0.90 (*m*, 2 Me). ^{13}C-NMR: 188.1 (*s*, CO); 168.9 (*s*, C(1)); 116.7 (*s*, C(2)); 93.0 (*s*, C(4)); 28.6, 27.8, 25.5, 15.6 (4*t*); 12.5, 8.6 (2*q*). CI-MS: 231 (100, $[M + NH_4]^+$), 214 (11, $[M + H]^+$). EI-MS: 214 (7, $[M + H]^+$), 167 (100), 139 (77), 125 (38), 109 (50), 97 (52), 69 (27).

For the single-crystal X-ray analysis of **7c**, see below.

3.3.5. *1-Nitrobicyclo[6.3.1]dodecane-9,12-dione* (**8a**). According to *3.3.1*, the reaction of **27d** (280 mg, 1.16 mmol) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **8a** (230 mg, 0.96 mmol, 83%). Colorless crystals. M.p. 96–100° (CH_2Cl_2/hexane). IR: 3020*w*, 2940*s*, 2875*w*, 1755*s*, 1730*s*, 1640*w*, 1555*s*, 1470*m*, 1445*m*, 1405*w*, 1360*m*, 1345*m*, 1335*m*, 1260*m*, 1160*m*, 1145*m*, 1090*m*, 1010*m*, 985*w*, 975*w*, 925*w*, 870*w*, 835*w*. ^{1}H-NMR: 3.95 (*dd*, *J* = 11.0, 1.9, H–C(8)); 3.04–2.87 (*m*, 1 H); 2.82–2.34 (*m*, 4 H); 2.29–1.96 (*m*, 3 H); 1.83–1.11 (*m*, 6 H); 1.01–0.83 (*m*, 2 H). ^{13}C-NMR: 201.6, 196.2 (2*s*, 2 CO); 96.5 (*s*, C(1)); 65.0 (*d*, C(8)); 38.6, 36.8, 30.3, 29.3, 27.3, 26.5, 25.8, 18.9 (8*t*). CI-MS: 257 (100, $[M + NH_4]^+$), 240 (6, $[M + H]^+$), 226 (10), 165 (10).

For the single-crystal X-ray analysis of **8a**, see below.

3.3.6. *1-Nitrobicyclo[5.3.1]undecane-8,11-dione* (**8b**). According to *3.3.1*, the reaction of **27e** (600 mg, 2.64 mmol) afforded, after chromatography (CH_2Cl_2/acetone 9:1), **8b** (250 mg, 1.11 mmol, 42%). Colorless crystals. M.p. 96–99° (CH_2Cl_2/hexane). IR: 3020*w*, 2935*m*, 2865*w*, 1740*s*, 1715*s*, 1665*w*, 1555*s*, 1460*m*, 1430*w*, 1360*w*, 1335*m*, 1325*w*, 1300*w*, 1260*s*, 1160*w*, 1125*w*, 1100*m*, 1035*w*, 1020*m*, 965*w*, 940*w*, 850*w*, 835*w*. ^{1}H-NMR: 3.38 (*t*, *J* = 7.7, H–C(7)); 2.90–2.73 (*m*, 3 H); 2.66–2.57 (*m*, 1 H); 2.43–1.97 (*m*, 4 H); 1.88–1.71 (*m*, 2 H); 1.64–1.41 (*m*, 4 H). ^{13}C-NMR: 204.0, 201.7 (2*s*, CO); 96.2 (*s*, C(1)); 63.6 (*d*, C(7)); 35.1, 34.0, 31.3, 28.2, 27.0, 23.8, 22.9 (7*t*). CI-MS (isobutane): 226 ($[M + H]^+$).

3.3.7. *1-Nitrobicyclo[3.3.1]nonane-6,9-dione* (**8c**). According to *3.3.1*, the reaction of **27f** (470 mg, 2.36 mmol) afforded, after chromatography (CH_2Cl_2/acctone 9:1), **8b** (400 mg, 2.02 mmol, 86%). Colorless crystals. Data in agreement with [19].

3.4. *Compounds of the Type* **10**. 3.4.1. *12-Methoxy-1-nitrobicyclo[9.3.1]pentadec-11-en-15-one* (**10a**) *and 11-Methyl-1-nitrobicyclo[9.3.1]pentadecane-12,15-dione* (**10a'**). A soln. of **7a** (200 mg, 0.71 mmol), MeI (5 µl, 0.8 mmol), and K_2CO_3 (100 mg, 0.72 mmol) in DMF (1.6 ml) was stirred at 23° for 24 h. The mixture was diluted with H_2O, extracted with AcOEt, and chromatographed (hexane/AcOEt 4:1) to give **10a** (30 mg, 0.10 mmol, 14%) and **10a'** (42 mg, 0.14 mmol, 20%), both as colorless crystals.

Data of **10a**: M.p. 153–155° (CH_2Cl_2/hexane). IR: 2930*s*, 2850*m*, 1665*s*, 1615*s*, 1545*s*, 1470*m*, 1430*w*, 1370*s*, 1345*m*, 1290*w*, 1260*m*, 1245*s*, 1200*m*, 1155*m*, 1120*m*, 1100*m*, 1035*w*, 1025*m*, 970*w*, 925*w*, 875*w*, 840*w*. ^{1}H-NMR: 3.84 (*s*, MeO); 2.99–2.91 (*m*, 1 H); 2.86–2.68 (*m*, 2 H); 2.50–2.41 (*m*, 1 H); 2.39–2.26 (*m*, 2 H); 2.20–2.08 (*m*, 1 H); 1.95–1.84 (*m*, 2 H); 1.46–0.86 (*m*, 13 H). ^{13}C-NMR: 189.0 (*s*, CO); 168.9 (*s*, C(12)); 117.5 (*s*, C(11)); 94.6 (*s*, C(1)); 54.8 (*q*, MeO); 31.0, 30.6, 25.9, 25.5, 22.9, 22.4, 22.2, 22.0, 21.6, 21.0, 18.9 (11*t*). CI-MS (isobutane): 296 (100, $[M + H]^+$), 249 (35). EI-MS: 296 (3, $M^{+\cdot}$), 249 (100), 221 (82), 137 (22).

For the single-crystal X-ray analysis of **10a**, see below.

Data of **10a'**: M.p. 158–160° (CH_2Cl_2/hexane). IR: 2930*s*, 2855*m*, 1735*m*, 1710*s*, 1550*s*, 1465*m*, 1460*m*, 1445*m*, 1410*w*, 1375*w*, 1360*w*, 1330*w*, 1260*m*, 1090*m*, 1010*m*, 950*w*, 860*w*. ^{1}H-NMR: 2.78–2.73 (*m*, 2 H); 2.65–2.61 (*m*, 2 H); 2.48–2.38 (*m*, 1 H); 2.17–2.07 (*m*, 1 H); 2.13–1.90 (*m*, 1 H); 1.64–1.55 (*m*, 1 H); 1.40–1.01 (*m*, 17 H, containing 1.38 (*s*, Me)). ^{13}C-NMR: 207.2, 201.6 (2*s*, 2 CO); 94.4 (*s*, C(1)); 64.5 (*s*, C(11)); 35.3, 33.8, 33.6, 29.2, 27.3, 26.3, 24.5, 24.3, 23.0, 20.8, 20.3 (11*t*); 19.5 (*q*). CI-MS (isobutane): 296 ($[M + H]^+$). EI-MS: 296 (5, $M^{+\cdot}$), 249 (34), 171 (14), 139 (17), 109 (25), 95 (48), 69 (65), 55 (100).

3.4.2. *1-Nitro-15-oxobicyclo[9.3.1]pentadec-11-en-12-yl Acetate* (**10b**). A soln. of **7a** (120 mg, 0.43 mmol) and 1-methylethenyl acetate (0.1 ml, 0.9 mmol) in pyridine (4 ml) was stirred at 23° for 2 d. The solvent was evaporated and the residue chromatographed (CH_2Cl_2/hexane 3:2) to yield **10b** (94 mg, 0.29 mmol, 68%). Colorless crystals. M.p. 124–126° (CH_2Cl_2/hexane). IR: 3200*w*, 2930*s*, 2865*m*, 2850*m*, 1765*s*, 1690*s*, 1650*s*, 1550*s*, 1470*m*, 1450*w*, 1430*m*, 1360*s*, 1340*m*, 1290*w*, 1185*s*, 1170*s*, 1155*s*, 1090*m*, 1010*m*, 975*w*, 960*w*, 930*w*, 915*w*, 895*w*, 890*w*, 880*w*, 850*w*, 840*w*, 830*w*. ^{1}H-NMR: 3.07–3.00 (*m*, 2 H); 2.67–2.53 (*m*, 2 H); 2.24–2.02 (*m*, 7 H, containing 2.23 (*s*, Me)); 2.00–1.86 (*m*, 1 H); 1.46–0.99 (*m*, 13 H). ^{13}C-NMR: 190.4, 167.5, 162.4 (3*s*, 2 CO, C(12)); 127.6 (*s*, C(11)); 95.6 (*s*, C(1)); 32.0, 30.7, 26.3, 25.9, 25.8, 23.04, 22.9, 22.8, 22.3, 21.9 (10*t*); 20.7 (*q*, MeO); 19.4 (*t*). CI-MS: 341 (100, $[M + NH_4]^+$), 324 (30, $[M + H]^+$), 235 (16).

3.4.3. *1-Nitrobicyclo[9.3.1]pentadec-11-en-15-one* (**10c**). A soln. of **9** (400 mg, 1.41 mmol) in conc. H_3PO_4 (20 ml) was refluxed for 12 h. The mixture was cooled to 23°, extracted with CH_2Cl_2, and chromatographed (hexane/AcOEt 9:1) to give **10c** (60 mg, 0.23 mmol, 16%). Colorless crystals. M.p. 118–119° (CH_2Cl_2/hexane). IR: 2920*s*, 2830*m*, 1730*s*, 1540*s*, 1470*m*, 1440*m*, 1350*m*, 1230*m*, 1170*w*, 1120*w*, 1090*w*, 920*w*, 850*w*. ^{1}H-NMR: 6.59 (*t*, J = 3.9, H–C(12)); 3.07–2.94 (*m*, 1 H); 2.90–2.89 (*m*, 1 H); 2.64–2.57 (*m*, 2 H); 2.33–2.25 (*m*, 1 H); 2.18–1.91 (*m*, 4 H); 1.73 (*td*, J = 7.5, 3.3, 1 H); 1.51–1.09 (*m*, 12 H). ^{13}C-NMR: 190.7 (*s*, CO); 144.5 (*d*, C(12)); 137.8 (*s*, C(11)); 96.5 (*s*, C(1)); 34.5, 30.7, 30.2, 26.3, 25.9, 23.9, 22.7, 22.6, 22.3, 21.9, 19.4 (11*t*). CI-MS: 266 ($[M + H]^+$).

3.5. *Enantiomerically Enriched Camphanic-Acid Derivatives*. 3.5.1. *(+)-(1R)-1-Nitro-15-oxobicyclo[9.3.1]pentadec-11-en-12-yl 4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptanecarboxylate* ((1*S*,1'*R*)-**15**). (−)-(*S*)-Camphanoyl chloride (227 mg, 1.05 mmol) was added at 23° to a soln. of *rac*-**7a** (300 mg, 1.07 mmol) and pyridine (86 mg, 1.09 mmol) in $CHCl_3$ (20 ml). After 2 h, the mixture was diluted with CH_2Cl_2 and extracted with H_2O, 6N HCl soln., sat. $NaHCO_3$ soln., and H_2O. Chromatography (CH_2Cl_2/hexane 9:1) gave a mixture of diastereoisomeric compounds of the type **15** (347 mg, 0.75 mmol, 71%), which was further separated by repetitive HPLC (*Spherisorb Si*, 5 µm, 250/12/20, *Bischoff*; hexane/6‰ EtOH, 20 ml min^{-1}) to give the first eluting isomer (1*S*,1'*R*)-**15** (143 mg, 0.31 mmol, 29%) in 98% de as colorless crystals. (1*S*,1'*R*)-**15** was used for the preparation of (+)-(*R*)-**7a** (see above): t_R 25–35 min, depending on the injection volume. $[\alpha]_D$ = + 32.5 (c = 1.14, $CHCl_3$). M.p. 126–127° (Et_2O/hexane). IR (KBr): 2930*s*, 2860*m*, 2840*m*, 1795*s*, 1760*s*, 1690*s*, 1655*m*, 1545*s*, 1465*m*, 1450*m*, 1420*m*, 1395*m*, 1370*m*, 1340*m*, 1305*m*, 1250*s*, 1230*m*, 1160*m*, 1140*s*, 1120*m*, 1080*s*, 1035*s*, 985*m*, 955*m*, 930*m*, 820*m*. ^{1}H-NMR: 3.13–2.93 (*m*, 2 H); 2.68–1.50 (*m*, 2 H); 2.49–2.35 (*m*, 1 H); 2.34–2.20 (*m*, 1 H); 2.20–2.00 (*m*, 4 H); 1.99–1.81 (*m*, 2 H); 1.78–1.64 (*m*, 1 H); 1.40–0.90 (*m*, 22 H, containing 1.09, 1.06, 1.00 (3*s*, 3 Me)). ^{13}C-NMR: 190.0 (*s*, CO); 177.2 (*s*, OC=); 164.7, 161.6 (2*s*, 2 COO); 128.1 (*s*, *C*OC=); 95.5 (*s*, CNO_2); 90.2, 54.8, 54.6 (3*s*); 31.7, 30.9, 30.5, 28.6, 26.2, 25.8, 25.7, 23.2, 23.0, 22.6, 22.1, 21.8, 19.3 (13*t*); 16.7, 16.6, 9.5 (3*q*). CI-MS: 479 (100, $[M + NH_4]^+$), 462 (15, $[M + H]^+$), 432 (11), 417 (26), 334 (37). Anal. calc. for $C_{25}H_{35}NO_7$ (461.560): C 65.06, H 7.64, N 3.03; found: C 64.78, H 7.88, N 3.17.

For the single-crystal X-ray analysis of (1*S*,1'*R*)-**15**, see below.

3.5.2. *(+)-(1R)-1-Hydroxy-15-oxobicyclo[9.3.1]pentadec-11-en-12-yl 4,7,7-Trimethyl-3-oxo-2-oxabicyclo-[2.2.1]heptanecarboxylate* ((1*S*,1'*R*)-**16**). To a soln. of (+)-(*R*)-**11a** (10 mg, 0.040 mmol, > 98% ee) was added NaH (tip of a spatula) and (−)-(*R*)-camphanoyl chloride (17 mg, 0.078 mmol). The mixture was stirred for 20 h at 23°, cooled to 0°, neutralized with AcOH, and extracted with Et_2O. Chromatography (hexane/AcOEt 55:25)

Table 2. *Crystallographic Data for* **7a, 7b, 7c, 8a, 9, 10a, 11a,** *(1S,1'R)*-**15,** *and (1S,1'R)*-**16**

	7a	**7b**	**7c**
Crystallized from	AcOEt/hexane	CH_2Cl_2/hexane	CH_2Cl_2/hexane
Empirical formula	$(C_{15}H_{23}NO_4)_2 \cdot C_4H_8O_2$	$C_{13}H_{19}NO_4$	$C_{10}H_{15}NO_4$
Formula weight	650.81	253.30	213.23
Crystal color, habit	colorless, prism	colorless, plate	colorless, needle
Crystal dimensions [mm]	0.25 × 0.35 × 0.50	0.10 × 0.25 × 0.45	0.15 × 0.20 × 0.40
Diffractometer	*Nicolet R3*	*Rigaku AFC5R*	*Rigaku AFC5R*
Radiation, wavelength [Å]	MoK_α, 0.71069	MoK_α, 0.71069	MoK_α, 0.71069
Crystal temp. [K]	133(1)	173(1)	173(1)
Scan type	*Wyckoff* ω	$\omega/2\theta$	$\omega/2\theta$
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/c$	*Pbca*	$P2_1/c$
Z	4	8	4
Reflections for cell determination	88	20	24
2θ Range for cell determination [°]	35–44	11–15	24–26
Unit cell parameters a [Å]	15.739(2)	17.153(6)	13.455(5)
b [Å]	16.061(2)	13.588(6)	7.324(4)
c [Å]	13.659(1)	11.065(6)	12.122(6)
α [°]	90	90	90
β [°]	91.71(1)	90	116.05(3)
γ [°]	90	90	90
V [Å^3]	3451(1)	2579(2)	1073.2(8)
$F(000)$	1408	1088	456
D_x [g cm^{-3}]	1.252	1.305	1.320
μ(MoK_α) [mm^{-1}]	0.0855	0.0963	0.1019
$2\theta_{(max)}$ [°]	55	60	60
Total reflections measured	8549	4860	3495
Symmetry-independent reflections	7921	3758	3115
Reflections used [$I > 2\sigma(I)$]	5342	1802	1732
Parameters refined	654	239	199
R	0.0473	0.0553	0.0552
wR	0.0428	0.0416	0.0458
Weights: p in $w = [\sigma^2(F_o) + (pF_o)^2]^{-1}$	0.015	0.005	0.005
Goodness of fit s	1.489	1.481	1.712
Secondary extinction coefficient	–	–	$1.8(2) \times 10^{-6}$
Final Δ_{max}/σ	0.003	0.0002	0.0001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.32; −0.24	0.30; −0.28	0.26; −0.27
$\sigma(d(C-C))$ [Å]	0.002–0.02	0.003–0.005	0.003–0.004

provided (1*S*,1'*R*)-**16** (14 mg, 0.032 mmol, 82%). Colorless crystals. M.p. 197–198° (Et_2O/hexane). IR: 3500*m*, 2950*m*, 2920*m*, 2860*m*, 1785*s*, 1770*s*, 1675*m*, 1650*m*, 1465*m*, 1400*w*, 1380*w*, 1350*w*, 1330*w*, 1300*w*, 1250*w*, 1220*m*, 1160*m*, 1140*s*, 1100*s*, 1080*s*, 1015*s*, 990*m*, 930*m*, 800*m*. ^{1}H-NMR: 3.84 (*s*, OH exchanged with D_2O); 3.10–2.96 (*m*, 1 H); 2.66–2.57 (*m*, 1 H); 2.54–2.42 (*m*, 2 H); 2.28–1.93 (*m*, 5 H); 1.82–1.70 (*m*, 1 H); 1.66–1.50 (*m*, 3 H); 1.42–0.99 (*m*, 22 H, containing 1.16, 1.13, 1.07 (3*s*, 3 Me)). CI-MS: 433 (100, $[M + H]^+$), 389 (18).

For the single-crystal X-ray analysis of (1*S*,1'*R*)-**16**, see below.

4. Crystal Structure Determination of 7a, 7b, 7c, 8a, 9, 10a, 11a, (1*S*,1'*R*)-15, and (1*S*,1'*R*)-16[7]. – All measurements were conducted on a *Rigaku AFC5R* diffractometer fitted to a 12-kW rotating anode generator, except for

[7]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Center* as supplementary publication No. CCDC-101281. Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0)1223-336033; email: deposit@ccdc.cam.ac.uk).

2 (cont.)

	9	**10a**	**11a**	(1S,1'R)-**15**	(1*S*,1'*R*)-**16**
$_2Cl_2$/hexane	AcOEt/hexane	CH_2Cl_2/hexane	AcOEt/hexane	Et_2O/pentane	Et_2O/pentane
$H_{17}NO_4$	$C_{15}H_{25}NO_4$	$C_{16}H_{25}NO_4$	$C_{15}H_{24}O_3 \cdot SO(CH_3)_2$	$C_{25}H_{35}NO_7$	$C_{25}H_{36}O_6$
.27	283.37	295.38	330.48	461.55	432.56
)rless, prism	colorless, prism	colorless, needle	colorless, prism	colorless, prism	colorless, prism
$\times 0.25 \times 0.45$	$0.27 \times 0.43 \times 0.50$	$0.15 \times 0.18 \times 0.45$	–	$0.15 \times 0.35 \times 0.44$	$0.18 \times 0.28 \times 0.30$
aku AFC5R	*Rigaku AFC5R*	*Rigaku AFC5R*	*Nicolet R3*	*Rigaku AFC5R*	*Rigaku AFC5R*
K_α, 0.71069	MoK_α, 0.71069	MoK_α, 0.71069	MoK_α, 0.71069	MoK_α, 0.71069	MoK_α, 0.71069
(1)	173(1)	173(1)	133(1)	173(1)	173(1)
θ	$\omega/2\theta$	$\omega/2\theta$	*Wyckoff* ω	ω	$\omega/2\theta$
linic	triclinic	monoclinic	triclinic	orthorhombic	orthorhombic
	$P\bar{1}$	$P2_1/c$	$P\bar{1}$	$P2_12_12_1$	$P2_12_12_1$
	4	4	2	4	4
	24	25	72	25	24
40	38–40	35–40	39–46	23–40	20–26
3207(9)	11.384(4)	5.842(2)	7.343(1)	8.278(3)	11.586(4)
372(1)	17.360(4)	13.809(2)	10.412(1)	40.038(5)	17.595(7)
9013(8)	8.360(2)	19.196(2)	11.744(1)	7.244(1)	11.263(9)
99.976(8)	99.57(2)	90	78.64(1)	90°	90°
3.516(9)	107.43(2)	92.03(2)	86.97(1)	90°	90°
3.316(9)	94.47(3)	90	83.90(1)	90°	90°
65.8(1)	1540.0(8)	1547.5(5)	874.8(3)	2400.7(9)	2296(2)
56	616	640	360	992	936
404	1.222	1.268	1.254	1.277	1.251
1052	0.0820	0.0901	0.1907	0.0867	0.0822
9	55	55	55	60	60
469	7432	4052	4034	4716	4340
285	7073	3551	4034	4572	4216
495	4923	2219	3499	3274	3007
23	561	291	320	439	425
0420	0.0458	0.0450	0.0346	0.0417	0.0436
0366	0.0379	0.0396	0.0440	0.0327	0.0335
005	0.005	0.005	0.015	0.005	0.005
941	2.062	1.480	2.034	1.397	1.429
$9(6) \times 10^{-6}$	–	$1.8(1) \times 10^{-6}$	$6(3) \times 10^{-7}$	$9(5) \times 10^{-8}$	$4(4) \times 10^{-8}$
0003	0.0003	0.0001	0.0005	0.001	0.0006
35; −0.18	0.34; −0.33	0.28; −0.21	0.34; −0.23	0.26; −0.17	0.26; −0.19
002	0.002–0.003	0.003	0.002	0.003–0.005	0.003–0.005

7a and **11a**, where a *Nicolet R3* diffractometer was used. The intensities of three standard reflections, which were measured after every 150 reflections (100 reflections for **7a** and **11a**), remained stable throughout each data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Each structure was solved by direct methods using SHELXS86 [28] which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. Except for the H-atoms of the disordered AcOEt molecules in **7a**, all H-atoms were located in difference-electron-density maps, and their positions were refined together with individual isotropic displacement parameters. The H-atoms of the AcOEt molecules in **7a** were fixed in geometrically calculated positions with a C–H distance of 0.95 Å, and they were assigned fixed isotropic displacement parameters with values equal to $1.2U_{eq}$ of the atom to which each was bonded. All refinements were carried out on *F* using full-matrix least-squares procedures which minimized the function $\sum w(|F_o| - |F_c|)^2$, where $1/w = [\sigma^2(F_o) + (pF_o)^2]$. The data collection and refinement parameters for each compound are listed in *Table 2*. Neutral atom scattering factors for non-H-atoms were taken from [29] and the scattering factors for H-atoms from [30]. Anomalous dispersion effects were included in F_c [31]; the values for f' and f'' were taken from [32]. All

calculations were performed using the TEXSAN [33] crystallographic software package and the figures were produced with ORTEPII [34].

Specific Remarks. In the crystals of the racemic **7a**, the asymmetric units contain two symmetry-independent molecules of the bicyclic compound plus one disordered solvent molecule of AcOEt. Two disordered positions were refined for each of the atoms of the AcOEt molecule, and the relative site occupation factors of the two orientations are *ca.* 3:1. The two overlapping orientations of the solvent molecule appear to be approximately the inverse of each other.

There are two symmetry-independent molecules with the connectivity of **9** in the asymmetric unit of the crystals of racemic **9**. The molecules differ in the configuration at two of the three stereogenic centers. Thus, there are four compounds, consisting of two enantiomeric pairs of diastereoisomers, in the crystal. The relative configuration at the ring junction of all molecules is *trans*; the diastereoisomeric structures differ in the configuration of the stereogenic center at the alcohol C-atom relative to the others.

The crystals of **11a** contain solvent molecules of DMSO in a 1:1 ratio with the compound of interest.

Although the samples were enantiomerically pure, the absolute configurations of (1*S*,1′*R*)-**15** and (1*S*,1′*R*)-**16** have not been determined by the crystallographic analyses. They were deduced, however, from the known absolute configuration of the camphanic-acid component, which is (1*S*).

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