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4-(1-Haloalkyl)-3-nitrotetrahydrofurans as versatile scaffolds for the synthesis of diversely functionalized tetrahydrofurans

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ABSTRACT

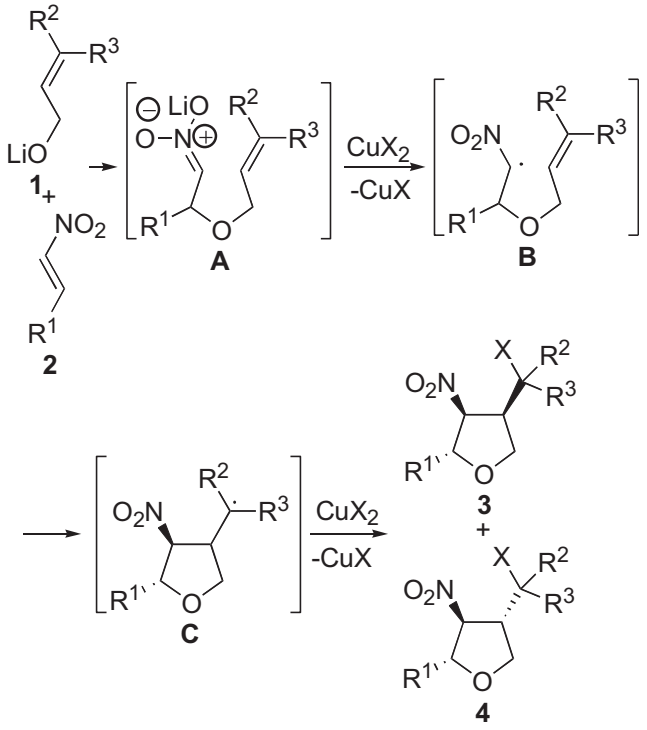
4-(1-Haloalkyl)-3-nitrotetrahydrofurans, which are accessible by tandem oxidative oxa-Michael addition/radical cyclization/ligand transfer reactions, can be processed to diversely substituted tetrahydrofuran derivatives. Selective epimerization at the nitro function provides tetrahydrofuran diastereomers, which cannot be prepared by the tandem process. Intramolecular alkylations furnish interesting bridgehead nitro oxabicyclo[3.1.0]hexane derivatives in high yields. Intermolecular substitution reactions of the halide functions succeed only with nucleophiles, which are not basic enough to trigger intramolecular alkylations. The aryl substituent in 2-aryl-3-nitrotetrahydrofurans can be selectively oxidatively transformed to carboxylic acid derivatives using catalytic Ru(III) and $NaIO_4$ without affecting the nitro group. Reduction and hydrogenation reactions provide differently substituted 3-aminotetrahydrofuran derivatives depending on the conditions with moderate to good chemoselectivity.

1. Introduction

Highly functionalized saturated heterocycles represent important targets in many applications, such as drug design, agricultural chemistry, and functional materials. An attractive strategy for generating such scaffolds is the design of generally applicable domino or tandem processes, which allow the time- and resource-efficient preparation of such platforms from very simple precursors.[1] Central to the success of this strategy is that the products can be easily processed further to diversely functionalized structures.

Recently, we reported a new general approach for the synthesis of halogenated nitrotetrahydrofurans based on a tandem reaction consisting of anionic conjugate addition of alkoxides **1** to nitroalkenes **2**, SET oxidation of the resulting nitronate **A** to α-nitro radical **B**, radical 5-*exo* cyclization to radical **C** and final ligand transfer to tetrahydrofuran diastereomers **3** and **4** mediated by cupric halides (Scheme 1).[2]

Nitrotetrahydrofurans **3** and **4** can be envisioned as versatile precursors to access functionalized ring systems via substitution and redox reactions (Fig. 1). The nitro group serves as a convenient hydrogen or amine surrogate and the developed method may thus serve as a strategy to approach natural products, such as tetrahydrofuran lignans **D**,[3] amino glycosides **E**,[4] or aminotetrahydrofuran



Scheme 1. Oxidative tandem anionic-radical reactions of allylic alkoxides and nitroalkenes to tetrahydrofurans **3** and **4**.

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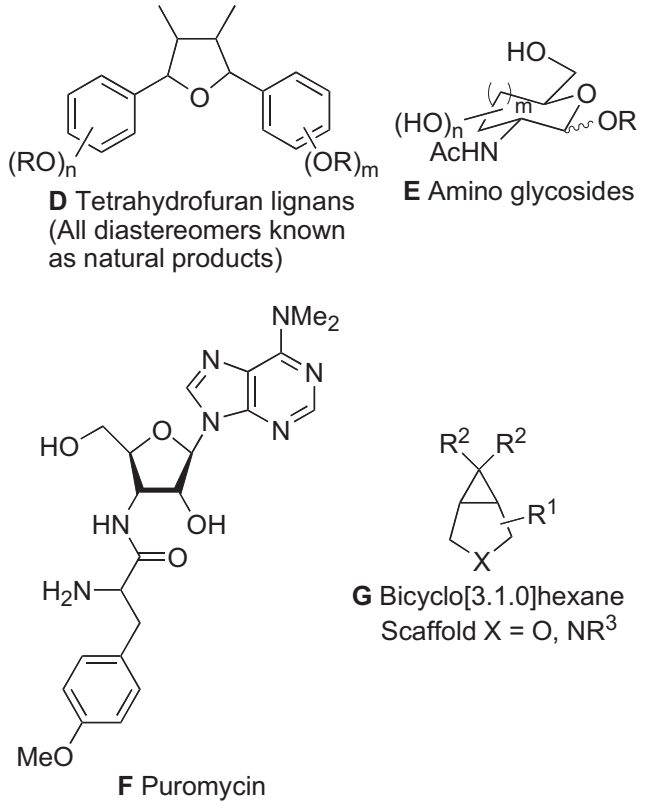


Fig. 1. Biologically interesting (amino)tetrahydrofuran and related structural motifs.

antibiotics, such as puromycin **F**.[5] They also represent interesting scaffolds **G** for medicinal chemistry and drug design, mimicking nucleosides[6] or acting as HCV protease inhibitors.[7]

In contrast to known nitrotetrahydrofurans,[8] the structural features of compounds **3** and **4** represent a special challenge for selective functionalization reactions, since the reactivity patterns of the individual functional groups are strongly coupled. Thus, the selectivity and order of steps has to be explored before target-oriented work can start. We present here a reactivity study of nitrotetrahydrofurans **3** and **4** (Fig. 2). Results on basic epimerization reactions at C-3 to tetrahydrofurans **I**, intramolecular alkylations at C-3 affording oxabicyclo[3.1.0]hexanes **II** or **III** and nucleophilic substitutions of the halide functions providing tetrahydrofurans **IV** are presented. It is shown that substituted tetrahydrofurans **3** and **4** can be converted oxidatively to tetrahydrofuran-2-carboxylic acids **V**. The reduction to 3-aminotetrahydrofurans of type **VI**–**VIII** was studied.

The access to new compound classes **I**–**VIII** represents an attractive and straightforward strategy since they can be prepared in only two steps from simple precursors by the tandem addition/cyclization process via **3** and **4** (Scheme 1).[2] These classes will find interest, since structurally similar derivatives are applied as HCV protease inhibitors,[7] constrained amino acids,[9] and modified nucleosides.[6] Compounds **V**–**VIII** represent interesting building blocks for new non-natural tetrahydrofuran-based β-amino acid derivatives,[10] which may become building blocks for new foldamers and related structures.[11]

2. Results and discussion

2.1. Epimerization reactions of nitrotetrahydrofurans

Under the conditions of their preparation 4-(1-chloroalkyl)-3-nitrotetrahydrofurans **3** were prone to epimerization.[2a] This

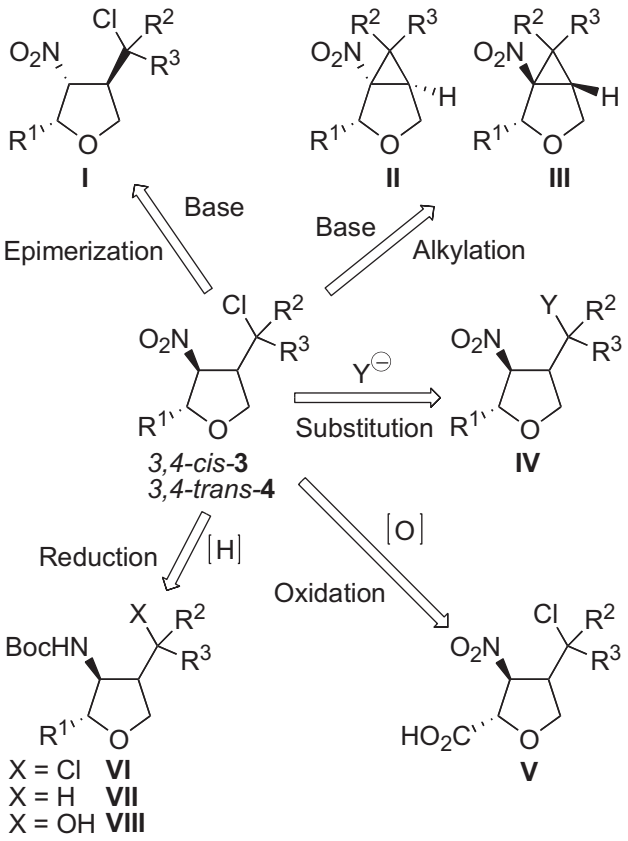
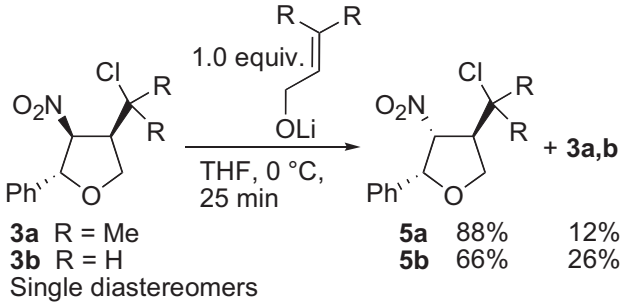


Fig. 2. Transformations of 4-(1-haloalkyl)-3-nitrotetrahydrofurans **3** and **4**.

undesired reaction can, however, be applied deliberately to synthesize nitrotetrahydrofuran diastereomers that are not accessible directly because of unfavorable transition state geometries.[2a] Thus, when **3a** or **3b** were subjected to their corresponding lithium allyloxides, a clean inversion at C-3 to nitrotetrahydrofurans **5a** and **5b** was observed (Scheme 2).



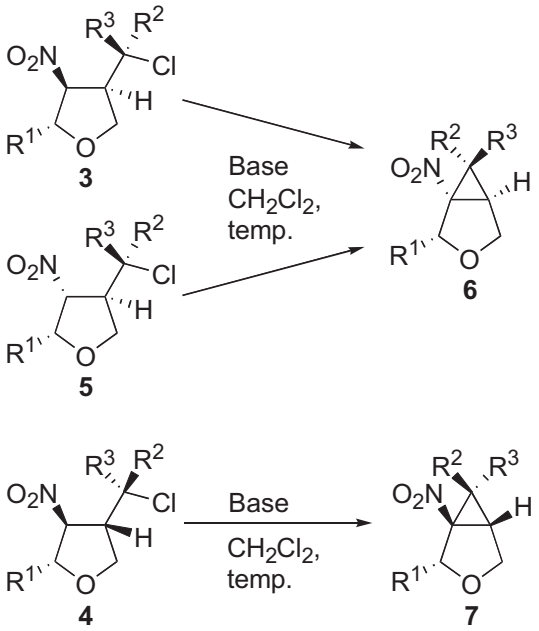
Scheme 2. Epimerization of **3a**,**b** induced by lithium alkoxides.

Other epimerization conditions, such as subjecting **3a** to sodium acetate in acetic acid, were less efficient. Amine bases also triggered epimerization, but were generally much better promoters of alkylations (vide infra). In contrast, the corresponding *trans*,*trans*-4-(1-chloroalkyl)-3-nitro-2-phenyltetrahydrofuran diastereomers **4** do not epimerize even after long reaction times and increased temperatures to the corresponding *cis*,*cis*-isomers.

2.2. Intramolecular alkylations

When nitrotetrahydrofurans **3** and **4** were treated with tertiary amines, the reaction outcome was dependent on their amounts (Scheme 3, Table 1). On treatment with catalytic amounts of DBU in dichloromethane, **3a** was recovered almost quantitatively without

noticeable epimerization, but trace amounts of cyclopropane derivative **6a** were detected (entry 1). With 1 equiv of DBU, the major reaction product was the bicyclic cyclopropane derivative **6a** isolated in 66% yield (entry 2). It was accompanied by 33% of **5a**. Quantitative conversion to oxabicyclo[3.1.0]hexane derivatives **6** or **7** was achieved in the presence of 2 equiv of DBU in refluxing dichloromethane.[12] The yields were good to excellent and reaction times were quite short for all substrates (entries 3–5, 8–11). The reaction conditions are compatible with epimerization-sensitive functionalities, such as in **6d** or **6e** (entries 6,7). For carboxylic acid derivative **3d**, it proved more convenient to treat it with a saturated sodium bicarbonate solution at room temperature for 10 min and to isolate **6d** after neutralization with hydrochloric acid (entry 6). The weaker base triethylamine can also be used in the cyclopropanation of **5b**, however, the reaction times increased considerably (entry 12).



Scheme 3. Synthesis of oxabicyclo[3.1.0]hexane derivatives **6** and **7** from 4-(1-chloroalkyl)-3-nitrotetrahydrofuran diastereomers **3**, **4**, and **5**.

Table 1
Base-mediated intramolecular alkylations of **3**, **4**, and **5**[a]

Entry	**3**,**4**,**5**	R^1	R^2	R^3	Base (equiv)	*T* (°C)	**6**,**7** (%, dr)[b]
1	**3a**	Ph	Me	Me	DBU (0.05)	25	**6a** (traces)
2	**3a**	Ph	Me	Me	DBU (1.0)	25	**6a** (66)[c]
3	**3a**	Ph	Me	Me	DBU (2.0)	40	**6a** (97)
4	**3b**	Ph	H	H	DBU (2.0)	40	**6b** (80)
5	**3c**/**4c** (3:1)	Ph	Ph	H	DBU (2.0)	40	**6c**/**7c** (70, 1.6:1)
6	**3d**	CO_2H	Me	H	$NaHCO_3$ (3.1)[d]	25	**6d** (94)
7	**3e**/**5e** (1:2.4)	CO_2Me	Me	H	DBU (3.0)	40	**6e** (98)
8	**3f**	Ph	Me	H	DBU (2.0)	40	**6f** (97)
9	**3g**/**4g** (2.4:1) **3g**	Ph	H	Me	DBU (2.0)	40	**6g** **6g**/**7g** (90, 2.2:1)
	4g	Ph	Me	H			**7g**
10	**4a**	Ph	Me	Me	DBU (2.0)	40	**7a** (96)
11	**5b**	Ph	H	H	DBU (2.0)	40	**6b** (80)
12[e]	**5b**	Ph	H	H	NEt_3 (7.0)	55	**6b** (95)

[a] Substrate (0.37 mmol) in dichloromethane at the given temp. Reaction times varied from 15 to 60 min.
[b] Isolated yields.
[c] In addition, 33% of **5a** was isolated.
[d] The reaction was carried out by dissolving acid **3d** in saturated $NaHCO_3$ solution. The characterization was performed after conversion into methyl ester **6e**.
[e] Reaction in acetonitrile/H_2O 3:1 at 55 °C for 5 h.

The configuration of bicycles **6** and **7** was determined by NOE or NOESY experiments. The structure of **6a** was unambiguously established by X-ray crystallography (Fig. 3).[13] The nitro and phenyl groups are oriented cis to each other on the convex face of the bicycle. The tetrahydrofuran ring adopts a flattened envelope conformation with the oxygen atom lying 0.28 Å out of the plane of the other four atoms.

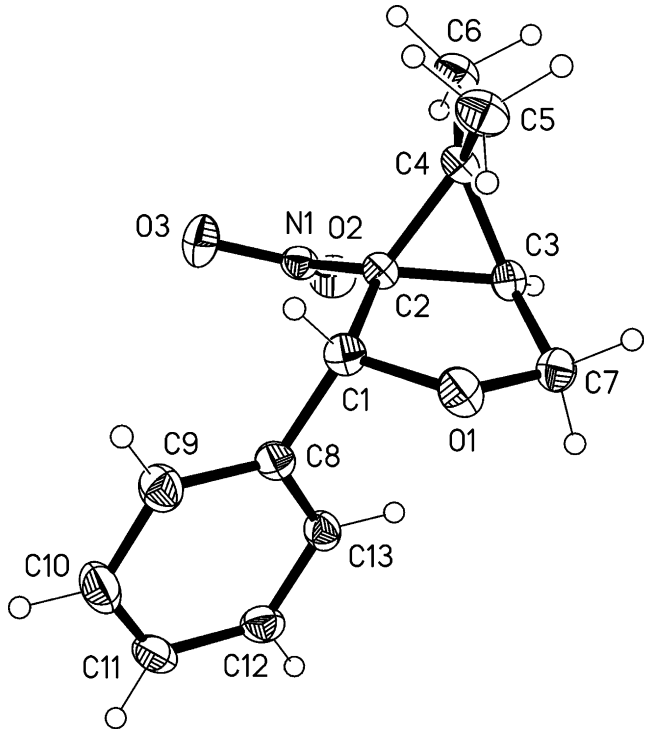
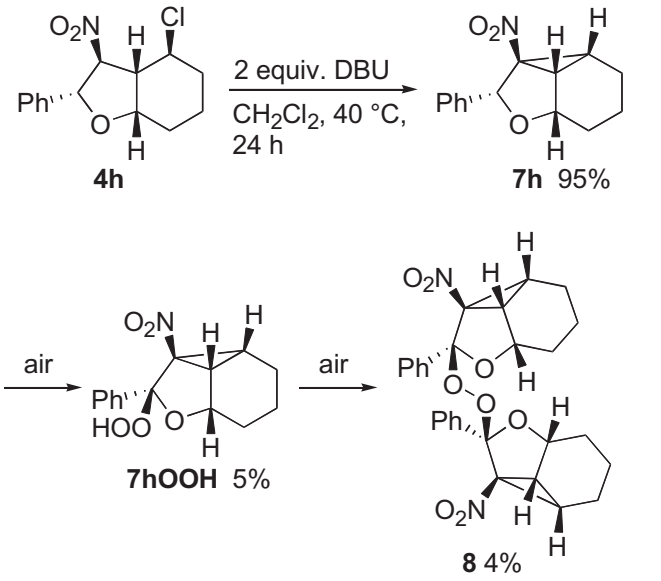


Fig. 3. X-ray crystal structure of **6a**. Relative configurations are *R**,*S**,*R** at C1, C2, and C3, respectively.

From all reactions, starting from single diastereomers **3** or **4**, single diastereomers of bicycles **6** and **7** were isolated. Since the substitution leading to **6** and **7** certainly occurs thus according to a S_N2 mechanism, inversion of configuration at the exocyclic stereocenter can be assumed and the configuration on this basis safely derived. Therefore, the intramolecular cyclopropanation is a very useful tool in assigning the exocyclic stereocenter in 4-(1-chloroalkyl)-3-nitrotetrahydrofurans **3c**, **3f**, **3g** and also of **4c** and **4g**. The stereoconvergent formation of **6** from **3** and **5** is also a safe way to detect epimerized products.[2a]

Even the bicyclic derivative **4h** underwent the cyclopropanation reaction cleanly in almost quantitative yield (Scheme 4). Because of the structural constraints of the bicyclic substrate, the reaction times for the synthesis of **7h** were much longer.

Tricycle **7h** is sensitive to air and converted slowly to hydroperoxide **7hOOH** on standing at room temperature in air. On prolonged exposure 4% of crystalline peroxide **8** was isolated by chromatography. Its structure was established by X-ray crystallography (Fig. 4), although the quality of the structure is not high (diffraction was weak and there was disorder of atom C6). Surprisingly, the peroxide displays a (2*R*)- and (2′*S*)-configuration at the tricyclic units in the molecule. The tetrahydrofuran rings adopt distorted envelope conformations. The trans-arrangement of the phenyl and nitro groups is retained in **8**. The benzylic hydrogen in the tricyclic derivative **7h** appears to be easily abstracted by molecular oxygen. Only the heterochiral peroxyl radical seems able to couple with the benzylic radical from the more accessible convex face. This structure confirms the stereochemical assignment of its precursor **7h**.



Scheme 4. Formation of tricyclic cyclopropane **7h** from oxabicyclo[4.3.0]nonane **4h** and its autoxidation to **8**.

2.3. Substitution reactions by nitrogen nucleophiles

The susceptibility of the halogenide function toward intermolecular substitution was examined briefly. When **3b** was treated with 2.5 equiv of *N*-methylaniline in refluxing acetonitrile in the presence of substoichiometric amounts of sodium iodide, a slow reaction occurred (Scheme 5) and a mixture of 4-(aminomethyl)tetrahydrofurans **11b** and **12b** was obtained in 56% yield. Thus, during the reaction extensive epimerization occurred. The reaction did not go to completion even after 8 days and 8–16% of epimerized **5b** was recovered. The corresponding bromides **9b** and **10b** proved to be more reactive, since no halide exchange by iodide was necessary to promote the substitution reaction. After four days of reflux in acetonitrile 72% and 70% of **11b** and **12b**, respectively, were formed. The results with **11b** and **12b** demonstrate that epimerization is bidirectional; however, **12b** and/or **10b** seem to be the thermodynamically favored diastereomers.

When the more basic dibenzylamine was reacted with **9b**, only traces of 4-(aminomethyl)tetrahydrofurans were detected, but bicyclic cyclopropane **6b** was formed in 62% yield. This divergent reactivity of **3b**, **9b** or **10b** toward secondary amines can be rationalized by taking into account that weakly basic methylaniline acts primarily as a nucleophile. Although it seems to be basic enough to deprotonate the α-position to the nitro function in **3b**, **9b**, and **10b**, the equilibrium lies on the left. This explains the occurrence of epimerization, the formation of **11b** and **12b** and the failure to detect **6b** in these reactions. Irreversible deprotonation of the hydrogen at C-3 is in contrast the preferred pathway for more basic aliphatic secondary and tertiary amines, resulting in cyclopropanation to **6** and **7**.

Since reactions with most amines did not successfully incorporate nitrogen in the exocyclic position, substitution of the halogenide function by sodium azide as an ammonia equivalent was investigated (Scheme 6). When **3b** was subjected to excess sodium azide in DMF at room temperature for 30 min, no trace of azidomethyltetrahydrofurans **13b**/**14b** was observed, but a clean epimerization to **5b** occurred in 73% yield, indicating that the azide acted primarily as a base to the hydrogen atom at the nitro function. Oxabicyclo[3.1.0]hexane derivative **6b** was formed in 6% yield and 15% of **3b** were recovered. Heating the reaction mixture to 60 °C for 4 h shifted the product spectrum. Bicyclic **6b** (52% yield) and also azides **13b** and **14b** (37% yield as a 1:4 mixture) proved to be the

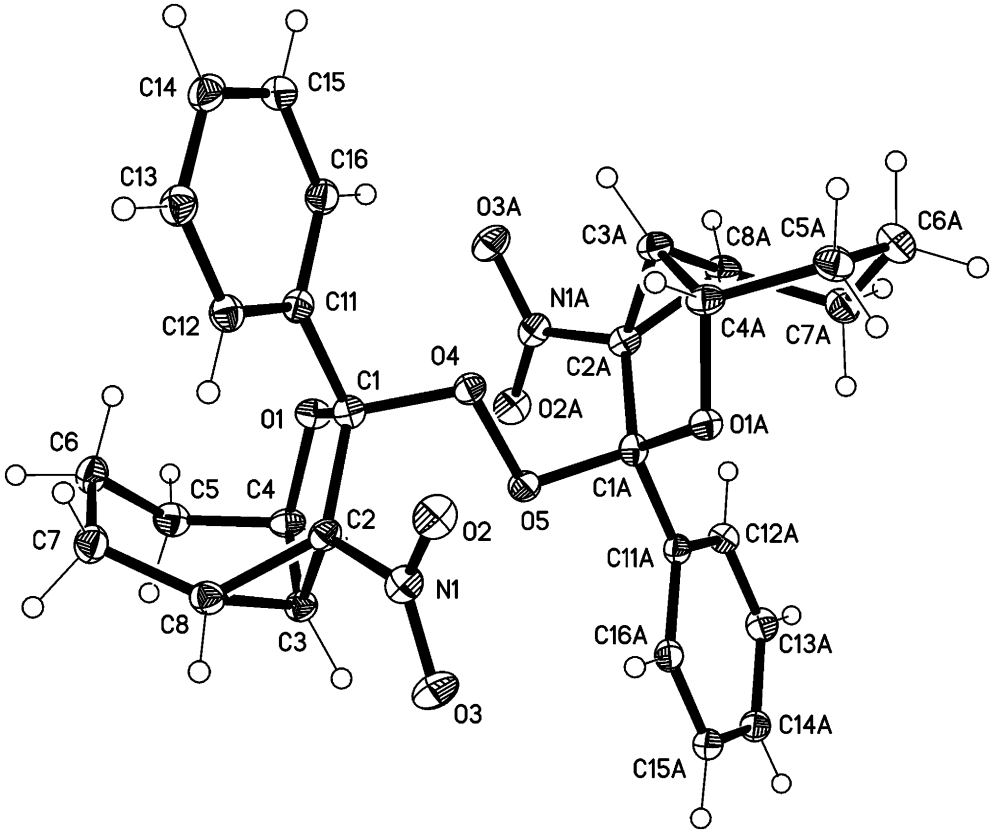
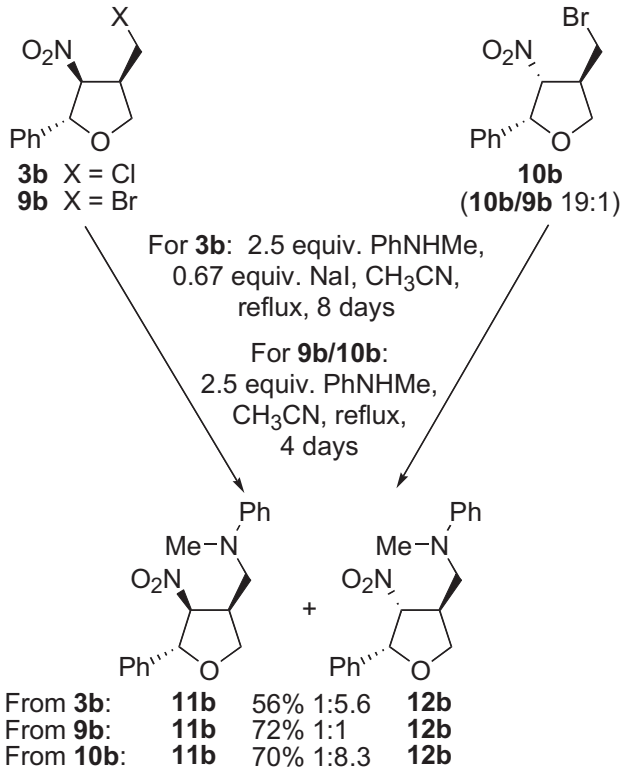


Fig. 4. X-ray crystal structure of the bis-tricyclic peroxide **8**. Only one of two independent molecules is shown. The ellipsoids correspond to 30% probability levels. The relative configurations are *R**,*R**,*R**,*S** at C1, C2, C3, C4, and C8, respectively, and are reversed in the other half of the molecule.



Scheme 5. Substitution of the halide in **3b**, **9b** or **10b** by *N*-methylaniline.

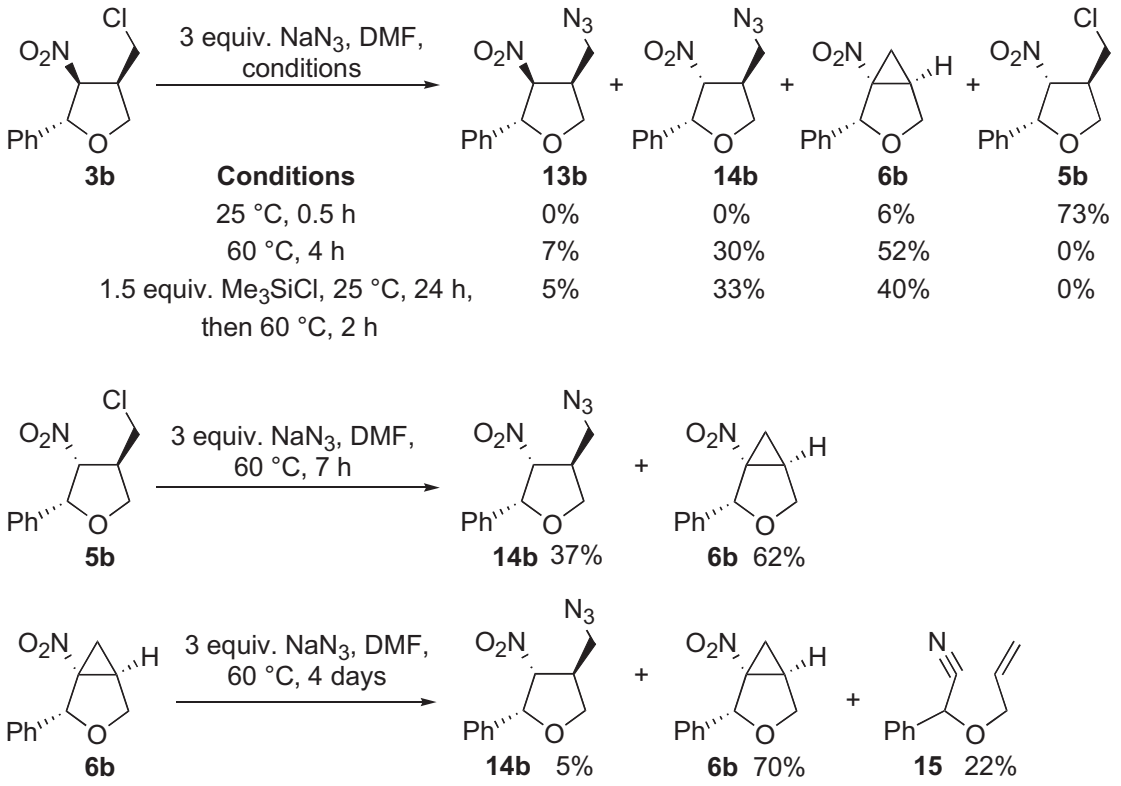
major products. To decrease the basicity of the reaction medium, chlorotrimethylsilane was added to the reaction mixture. The reaction with the in situ formed trimethylsilyl azide led to a similar product distribution of **6b**, **13b**, and **14b** as with NaN_3 alone. The configuration of **14b** was determined by reacting **5b** with sodium azide under similar reaction conditions, resulting in 37% of azide **14b**. The major product again proved to be **6b**, which was isolated in 62% yield.

4-(Azidomethyl)tetrahydrofuran **14b** may in principle form either by direct substitution of the chloride or by nucleophilic ring opening of the nitrocyclopropane **6b** by the azide ion. A control experiment, in which **6b** was treated with sodium azide under otherwise identical reaction conditions, ruled out the latter possibility. Azide **14b** was formed in only 5% yield after a very long reaction time of four days, but 70% of **5b** was recovered. Additionally, 22% of (α-allyloxy)phenylacetonitrile **15** was produced, which was not detected in the other experiments. Its formation cannot be explained satisfactorily at present.

To summarize this part, cyclopropanation under basic conditions is a very efficient reaction. Intermolecular substitutions at the halogen function of **3b** are strongly dependent on the basicity of the reagent. Only weakly basic nucleophiles, such as *N*-methylaniline substituted the halogenide. With more basic nucleophiles cyclopropanation and epimerization prevailed.

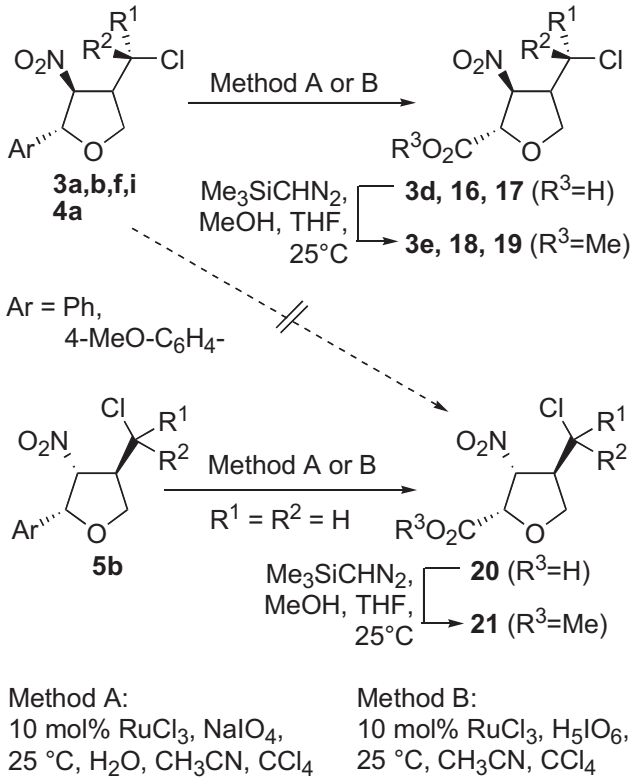
2.4. Oxidative degradation of the aryl ring in tetrahydrofurans 3, 4, 5

Aryl rings represent a convenient protected form of a carboxylate group.[14] It is however important to keep in mind that nitro compounds are amenable to Nef reactions under oxidative conditions.[15] Therefore, the oxidative degradation of the aryl ring in selected derivatives was investigated using ruthenium catalysis (Scheme 7, Table 2). The transformation was performed using 10 mol % of ruthenium trichloride and sodium periodate (Method A) or periodic acid (Method B) as the stoichiometric oxidants at room temperature. The arene units in diastereomeric **3**, **4**, and **5** were in all cases cleanly oxidatively cleaved to the carboxylic acid function (entries 1–5). Potential oxidations at the 5-position or Nef-type oxidations at the nitro group were not observed. The



Scheme 6. Reaction of **3b**, 5**b**, and **6b** with sodium azide.

reaction times were, however, rather long. Using $NaIO_4$ as the stoichiometric oxidant, it took a week to complete the reactions, whereas they were finished after two days when periodic acid was employed. An increase of the reaction temperature had no effect.



Scheme 7. Oxidative preparation of tetrahydrofuran-2-carboxylates.

compounds **3**, **4**, and **5** may be reduced. All three reduction modes to access the different products selectively are addressed.

(a) Metal-based reduction: nickel boride, generated in situ from 3 equiv of $NaBH_4$ and 1 equiv of $NiCl_2 \cdot 6H_2O$, was used initially as the mediator (Scheme 8).[16] A 1:1 mixture of compounds **3a** and **4a** was reduced smoothly (Table 3, entry 1). Products **22a** and **23a** were obtained after treatment of the crude amines with Boc anhydride in 75% yield as a separable 1:1 diastereomeric mixture. In addition, considerably more polar alcohol **24a** was isolated as a single diastereomer in 15% yield.

Using diastereomerically pure **3b** under similar conditions provided in contrast alcohol **24b** as the major product in 60% yield (entry 2). Some chlorine-containing derivative **25b** and minor amounts of fully reduced **22b** were also formed as single diastereomers. When a diastereomeric mixture of **3b** and **5b** was subjected to nickel boride, alcohol **24b** was isolated again as a single isomer in 52% yield, while fully reduced **26b** and **22b** were isolated as a diastereomeric mixture (entry 3). No trace of an alcohol resulting from **5b** was formed. A 1:3:8 diastereomeric mixture of 1-(chloroethyl)tetrahydrofurans **3g**, **4g**, and **5f** gave a mixture of fully reduced diastereomers **23g** and **26f** in 57% yield (entry 4). Moreover, 24% of chloro aminotetrahydrofuran **27f**, but no product corresponding to alcohols **24** was isolated.

When a mixture of **3a** and **4a** was treated with Zn dust in the presence of 10% HCl at 35 °C, the chloro oxime **28a** was obtained as the only significant product in 37% yield (Scheme 9). Attempts to employ Zn/acetic acid or lithium aluminum hydride for reduction of the nitro group were not successful.

(b) Catalytic hydrogenation: several catalytic systems are known.[17] When diastereomerically pure **4a** was hydrogenated using palladium on charcoal as the catalyst under 20 bar hydrogen, followed by protection with Boc anhydride, the fully reduced tetrahydrofuran **23a** was obtained as the major product in 60% yield (Scheme 10). Minor side products isolated were the chlorinated aminotetrahydrofuran **29a** and, surprisingly, the acyclic amino ether **30a**. When a 1.5:1 diastereomeric mixture of nitro-

Table 2
Oxidative transformation of 2-aryltetrahydrofurans **3**–**5** to acids **3d**, **16**, **17**, **20** and esters **3e**, **18**, **19**, **21**

Entry	Substrate (dr)	Ar	R^1	R^2	Method	**3d**,**16**,**17**,**20** (%, dr)	**3e**,**18**,**19**,**21** (%)
1	**3a**/**4a** (1.2:1)	Ph	Me	Me	A	**16a**/**17a** (61, 1.2:1)	**18a**/**19a** (95, 1.4:1)[a]
2	**3a**/**4a** (11:1)	Ph	Me	Me	B	(N.D.[b])	**18a**/**21a** (60, 2:1)[c]
3	**3b**/**5b** (1:6)	Ph	H	H	B	**16b**/**20b** (57, 1:3)	**18b**/**21b** (99, 1:2)
4	**3i**/**5i** (1:1)	4-$MeOC_6H_4$	H	H	B	N.D.[b]	**18b**/**21b** (34, 1:1.5)
5	**3f** (1:0)	Ph	Me	H	A	**3d** (77, 1:0)	**3e**/**5e** (95, 1:2.4)[c]

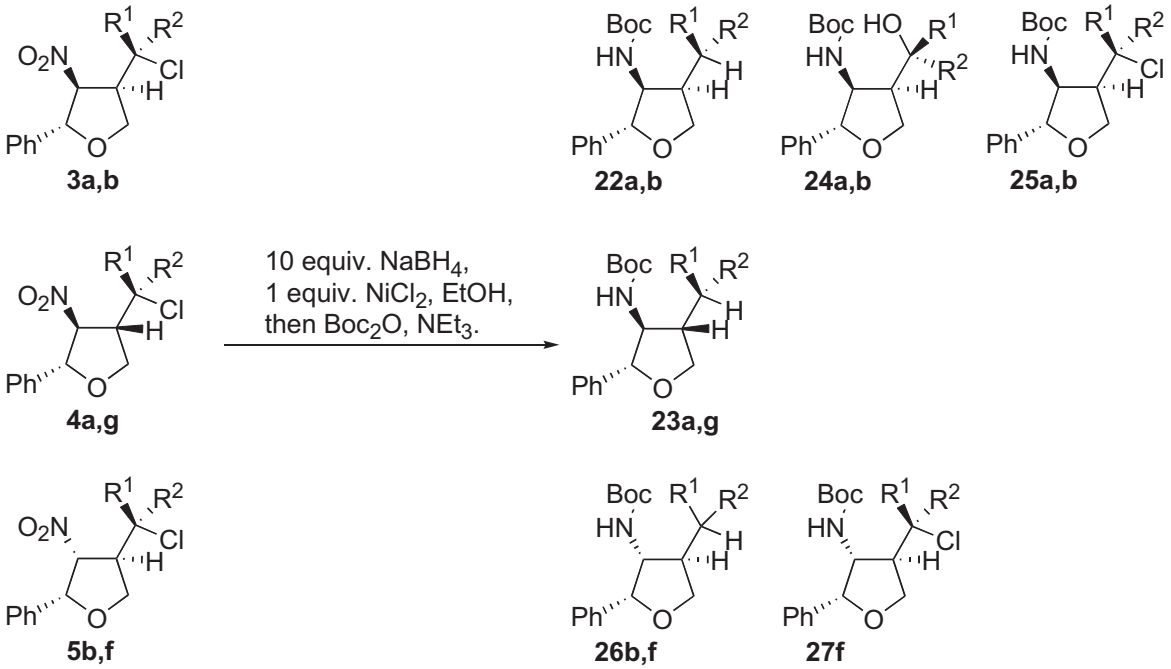
[a] Quick column purification.
[b] N.D.=Not determined.
[c] Long column, epimerization does not occur during the reaction, as determined by ^1H NMR of the crude mixture.

The carboxylic acids **3d**, **16**, **17**, and **20** were isolated as crude materials and converted immediately to the corresponding methyl esters **3e**, **18**, **19**, and **21** by treatment with trimethylsilyldiazomethane in THF/methanol solution. An exceptional case was tetrahydrofuran **3i**, bearing the more electron-rich anisyl group (entry 4). Methyl esters **18b** and **21b** were isolated in a moderate yield of only 34% applying periodic acid, while almost no conversion was observed with $NaIO_4$. It must be noted that epimerization was observed in methyl esters **18a**,**b**, and **3e**. This occurred on purification of crude esters **18** or **3e** by column chromatography, but not during esterification of the crude acids (entries 2–5). Thus purification must be performed as quickly as possible (entries 1 vs 2).

2.5. Reduction of the nitro group and/or the halogenide functions

The reduction of **3**, **4** or **5** presented a challenge since the nitro group as well as the halogen function and the benzylic ether unit in tetrahydrofurans **3a** and **4a** was subjected to similar conditions, **4a** gave **23a** exclusively, while diastereomer **3a** provided the oxygenated aminotetrahydrofuran **24a** and the fully reduced aminotetrahydrofuran **22a**. Since the overall yield was no better than the reduction of **3a**, **4a** with nickel boride, this reaction was not further optimized. Transfer hydrogenation using NH_4O_2CH in the presence of Pd–C as the catalyst was not successful, since a complex mixture of unidentified products was formed.

When the hydrogenation was performed with Raney nickel as the catalyst, the product spectrum was strongly dependent on the substrate and the conditions applied (Scheme 11, Table 4). Fully reduced tetrahydrofurans **22a** and **23a** were obtained as the major products on hydrogenation of a 6:1 mixture of **3a** and **4a** in moderate yield using 5 bar pressure. A small amount of alcohol **24a** and amino ether **30a**, but no chlorine-containing products **25a**, were additionally isolated (entry 1). Varying the conditions had only limited influence on the product distribution (entries 2–5). The product ratio is only slightly dependent on hydrogen pressure

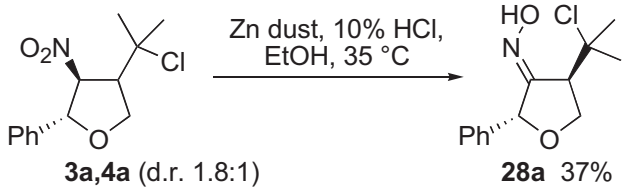


Scheme 8. Reduction of the nitro group in nitrotetrahydrofurans by nickel boride.

Table 3
Reduction of nitrotetrahydrofurans **3**,**4**,**5** with nickel boride in ethanol[a]

Entry	**3**/**4**/**5** (dr)	R^1	R^2	Temp (°C)	Time (min)	**22**, **23**, **26** (%, dr)	**24** (%)	**25**, **27** (%)
1	**3a**, **4a** (1:1)	Me	Me	0–37[a]	420[b]	**22a**, **23a** (75, 1:1)	15	—
2	**3b**	H	H	0–40[b]	130[c]	**22b** (3)	60	**25b** (8)
3	**3b**, **5b** (5:1)	H	H	0–40[c]	390[d]	**22b**, **26b** (30, 1:1.4)	52	—
4	**3g**, **4g**,**5f** (1:3:8)[f]	Me H	H Me	0–40[e]	290	**23g**, **26f** (57, 1:1.4)	—	**27f** (24)

[a] Substrate 0.7 mmol.
[b] 0 °C, 0.5 h, 25 °C, 4 h, then 37 °C, 2.5 h.
[c] 0 °C, 1 h, then 40 °C, 70 min.
[d] 0 °C, 1.0 h, then 40 °C, 5.5 h.
[e] 0 °C, 50 min, 40 °C, 240 min.
[f] Starting material was a 1:3:8 mixture of **3g**, **4g**, and **5f**. Products derived from **3g** were not isolated.



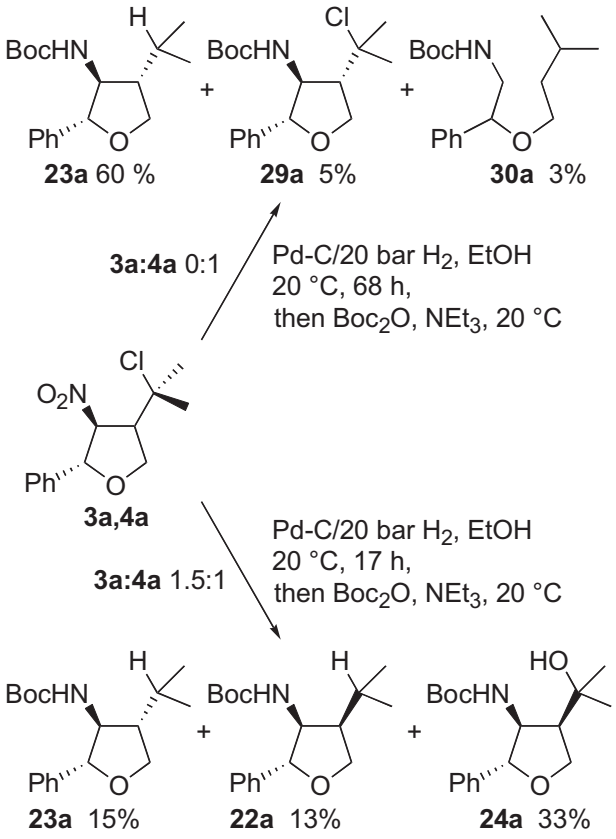
Scheme 9. Reduction of **3a** and **4a** by zinc and HCl.

(entries 1–3). With increasing temperature the yield of **22a** dropped at the expense of both **24a** and **30a** (entries 1–3 vs 4,5). Extended reaction times led to an overall decrease of the yield (entries 4,5). The best yield of **22a** (50%) was obtained applying 20 bar hydrogen pressure for 14 h at room temperature (entry 3).

The formation of **30a** was surprising, since pure cyclized **3a** was the starting material. Possible precursors may be β-nitro ether **32a** or the β-amino prenyl ether analog **33a**. To gain some insight, β-nitro ether **32a** was hydrogenated under identical conditions (Scheme 12). An almost equimolar mixture of **30a** and β-amino prenyl ether **33a** was obtained in good yield, suggesting that **30a** results from hydrogenation of a prenyl ether precursor (vide infra).

Compound **3b** behaved differently from **3a** under Raney nickel-catalyzed hydrogenation conditions. The hydrogenation was very slow at pressures lower than 5 bar. At 5 bar hydrogen pressure in a preheated autoclave at 37 °C, chlorinated aminotetrahydrofuran **25b** was the major product isolated in satisfactory 60% yield (entry 6). In addition, fully reduced aminotetrahydrofuran **22b** was formed in 36% yield. Reducing the reaction time further or applying lower temperatures did not have beneficial effects. With increasing reaction times of up to 8 h, the amount of **22b** increased at the expense of **25b** (entries 7–9). The chlorine function was removed essentially completely after 14 h, but at reaction times longer than 8 h benzylic cleavage of the tetrahydrofuran ring leading to γ-amino alcohol **31b** started to compete (entry 10). It was also possible to operate the hydrogenation with similar yields and ratios of **25b** and **22b** at 20 bar hydrogen pressure and 60 °C over much shortened reaction times (entries 12 and 13). After an extended reaction time of 17 h at 20 bar hydrogen pressure and a temperature of 60 °C, γ-amino alcohol **31b** was obtained in 70% yield as the major product of the hydrogenation reaction (entry 14).

The reactivity of tetrahydrofuran-2-carboxylates **18a** and **19a** was also investigated briefly. Carboxylate **18a** was hydrogenated at 60 °C at 20 bar hydrogen to fully reduced tetrahydrofuran-derived β-amino ester **22j** in 64% yield (entry 15). In addition 31% of fragmentation product **30j** was isolated. Nitrotetrahydrofuran ester **19a** gave a partially separable mixture of chlorinated and fully reduced tetrahydrofuran esters **29j** and **23j** at lower temperature and



Scheme 10. Catalytic hydrogenation of tetrahydrofurans **3a** and **4a** with Pd/C as the catalyst (substrate 0.36 mmol, 10 mg Pd/C).

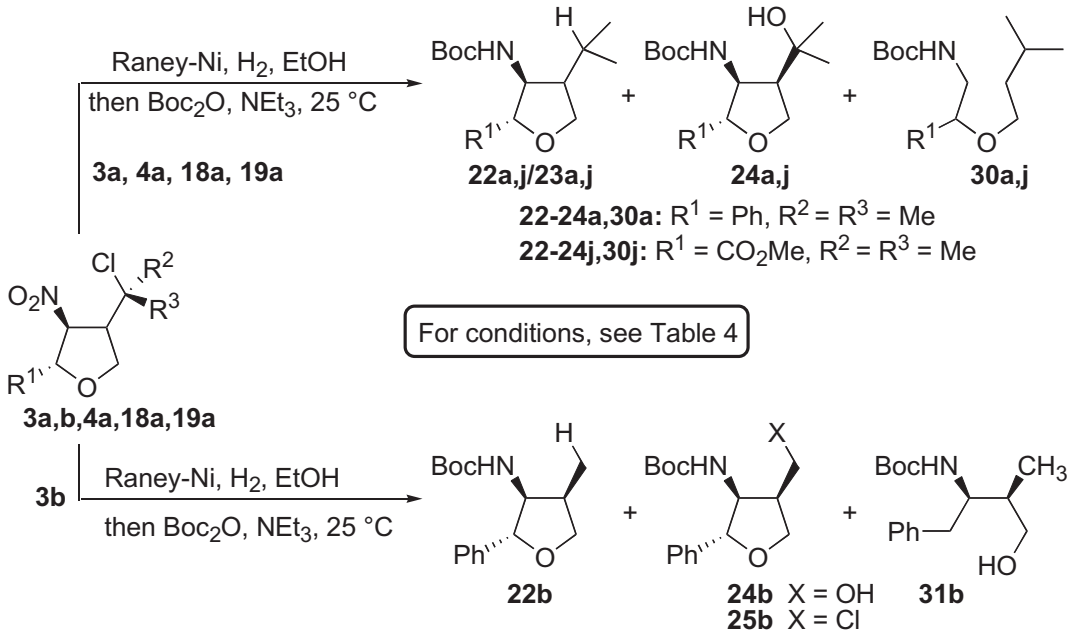
pressure (entry 16). A cleavage product comparable to **30j** was formed in 15% yield.

Although the method was not applied here, it should be mentioned that the nitro group can be completely removed reductively under radical conditions using tributyltin hydride.[3,8f,18] This method is suitable for the chemoselective reductive removal of the nitro group in the presence of the chloride function affording nitrogen-free chloro tetrahydrofuran derivatives.[3]

The relative configuration of all products was assigned based on that of the starting materials and on NOE or NOESY measurements. The relative configuration of 4-(1-chloroethyl)-3-nitrotetrahydrofurans **27f** was unequivocally established by X-ray crystallography (Fig. 5). The 2,3-*cis*-3,4-*trans*-configuration is clearly seen. The tetrahydrofuran ring has an envelope conformation, in which C4 lays 0.60 Å out of the plane of the other four atoms. The molecules are linked to form chains parallel to the *b* axis by classical hydrogen bonds N–H···O1.

Compound **22j** also crystallized and its structure was determined by X-ray crystallography (Fig. 6). The 2,3-*trans*-3,4-*cis*-arrangement of the substituents is confirmed. The methoxycarbonyl group and isopropyl groups occupy pseudo-equatorial positions in the molecule, while the NHBoc group is oriented axially. No intramolecular hydrogen bonding is seen in the β-amino ester unit (in fact the molecules are linked to form inversion-symmetric pairs by the interaction N–H···O4). The tetrahydrofuran ring adopts an envelope conformation C3 lying 0.58 Å out of the plane of the other four atoms. The relative configuration of **24b** was also unambiguously assigned by X-ray crystallography; the structure is, however, not publishable because of extensive disorder.

The outcome of the reductions reveals the following trends. Both the chlorine and the nitro functions are reduced competitively (Scheme 13). With all tested reduction systems, epimerization does not occur at any stage of the reduction process. The rate of chloride hydrogenation is dependent on the substitution degree at this carbon atom. In tertiary chlorides **3a** or **4a**, reduction of the chloride is fast and proceeds preferentially via intermediates **34** and **35** to fully reduced compounds **22a** or **23a**. The primary chloride in **3b** is reduced significantly more slowly than the tertiary chloride function in **3a**. The reduction of the nitro group occurs first via the corresponding nitroso compound **36** and to a hydroxylamine (not shown), which cyclizes to bicyclic intermediate **37**. Compound **37** may alternatively form via tautomerization of the nitroso compound **36** to oxime **28**. This can cyclize. The C=N double bond of

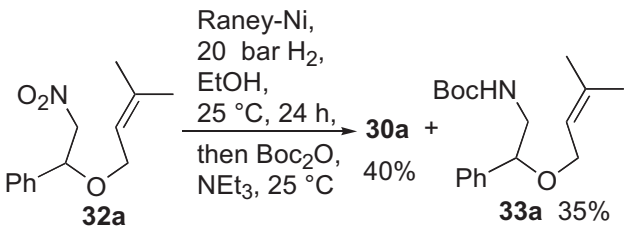


Scheme 11. Catalytic hydrogenation of 4-(1-chloroalkyl)-3-nitrotetrahydrofurans **3a**,**b**, **4a**, **18a**, and **19a**.

Table 4
Raney nickel-catalyzed hydrogenation of tetrahydrofurans **3a**,**b**, **4a**, **18a**, and **19a**[a]

Entry	Substrate	*p* (bar)	*T* (°C)	Time (h)	**22**,**23** (%, (dr))	**24** (%)	**25** (%)	**30a**,**j** (%)	**31b** (%)
1	**3a**/**4a** (6:1)	5	35	4	45 (6:1)	9	—	16	—
2	**3a**	5	25	8	42	9	—	20	—
3	**3a**	20	25	14	50	15	—	18	—
4[b]	**3a**	20	60	4	33	22	—	30	—
5	**3a**	20	60	18	22	21	—	15	—
6[b]	**3b**	5	37	0.5	36	2	60	—	—
7	**3b**	5	37	1	33	2	40	—	—
8	**3b**	5	37	3	54	—	36	—	—
9	**3b**	5	20–37[c]	8	64	—	16	—	4
10	**3b**	5	37	14	68	—	1	—	18
11	**3b**	20	25–40[d]	4	45	9	26	—	Traces
12	**3b**	20	60	1	66	2	12	—	6.5
13	**3b**	20	60	2	59	—	3	—	28
14[b]	**3b**	20	60	17	5	—	4	—	70
15	**18a**	20	60	4	**22j** 64	—	—	**30j** 31	—
16	**19a**	10	37	4	**23j** 36	—	**29j** 30	**30j** 15	—

[a] Substrate 0.29 mmol.
[b] Reaction was run in duplicate and gave almost identical results.
[c] 25–37 °C, 15 min, 37 °C, 7.5 h.
[d] 25–40 °C, 45 min, 40 °C, 3 h.



Scheme 12. Raney nickel-catalyzed hydrogenation of **32a**.

resulting isoxazoline will probably be hydrogenated further from the convex face, thus also providing **37** under the reduction conditions. This explains why only 3,4-*cis*-substituted alcohols are formed. Reductive N–O bond cleavage finally furnishes **24b**. The formation of alcohols **24** is thus an interesting indicator for the rates of chloride and nitro group reduction. The latter reaction course is also supported by the reduction of **3a** with the weaker reductant zinc/HCl, whereby the nitro group is reduced quickly but the reaction stops at the stage of the chloro oxime **28a**.

The formation of amino ethers **30** during hydrogenation can be rationalized by a Grob-type fragmentation of either chloro amine **25** or cyclic amino alcohol **24** to an acyclic alkenyl iminium ion, which is further reduced to **30**.

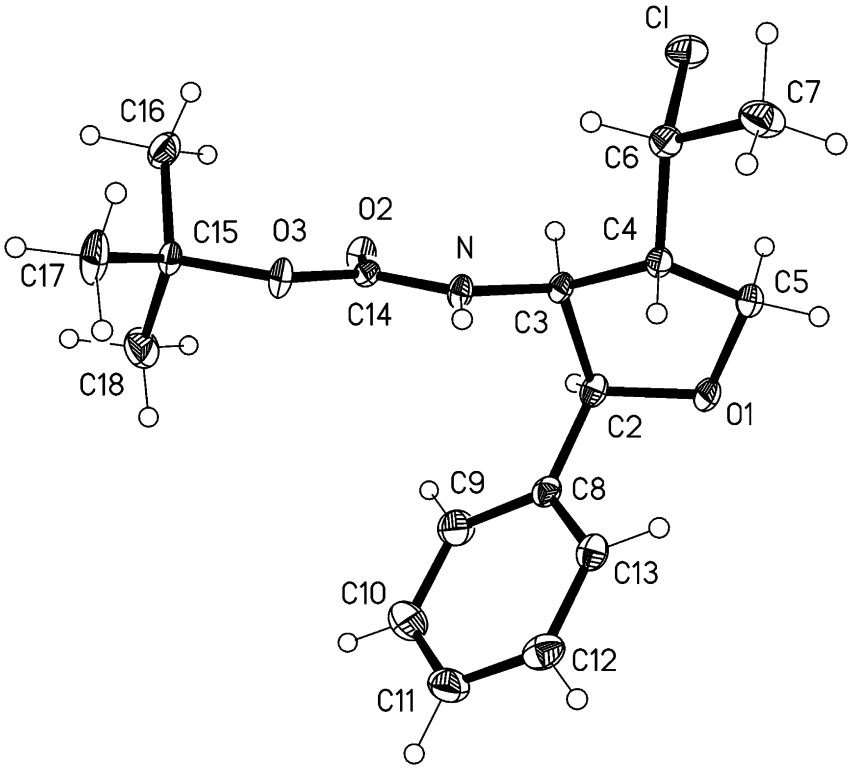


Fig. 5. X-ray crystal structure of 4-(1-chloroethyl)-3-nitrotetrahydrofuran **27f**. Relative configurations are *S**,*S**,*S**,*R** at C2, C3, C4, C6, respectively.

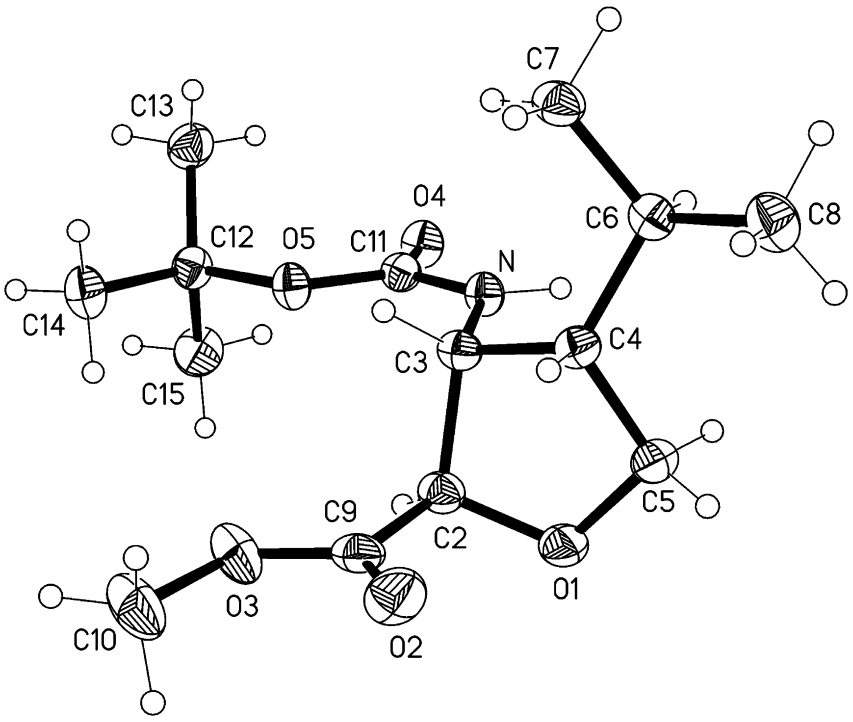
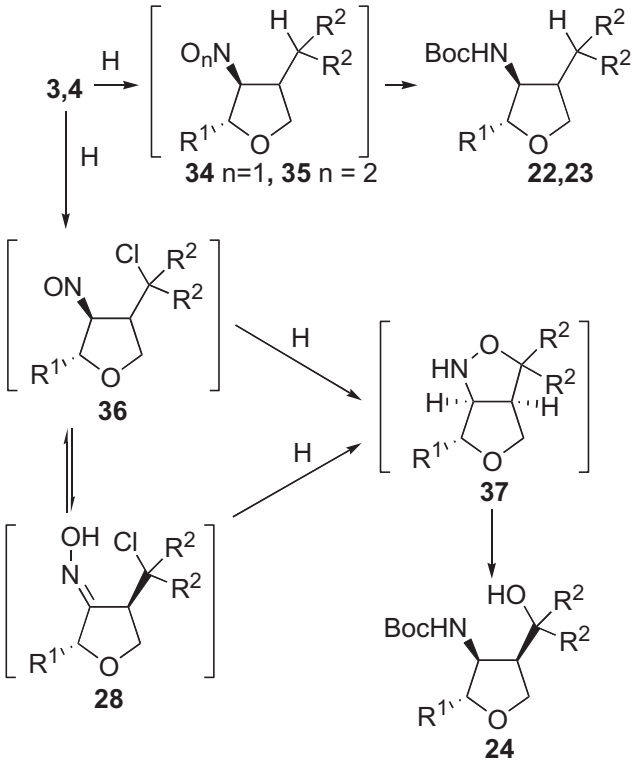


Fig. 6. X-ray crystal structure of 3-aminotetrahydrofuran-2-carboxylate **22j**. Relative configurations are *R**,*R**,*S** at C2, C3, and C4, respectively.



Scheme 13. Course of the reduction of tetrahydrofurans **3** and **4**.

3. Conclusion

The reactivity profile of several 3-nitrotetrahydrofurans **3**, **4**, and **5** was investigated. The compounds undergo very efficient intramolecular alkylations to bicyclic cyclopropanes. Intermolecular substitution reactions of the halogenide functions are slow. The range of nucleophiles is limited to such derivatives having low basicity to prevent competitive irreversible deprotonation of the very acidic α-position to the nitro group. The aryl units of 2-aryl-3-nitrotetrahydrofurans are cleanly degraded to carboxylic functions. Nef-type oxidative reactions do not compete significantly under the reaction conditions. Reduction reactions of the nitro and chloro groups were strongly dependent on the reactivity of the chloride function, the relative stereochemistry of the substrates and the applied catalysts. Depending on the conditions, amino hydroxy-, amino chloro- or amino alkyltetrahydrofurans can be synthesized with reasonable selectivity. Hydrogenative ring opening of tetrahydrofurans may offer interesting perspectives to synthesize amino alcohols with defined stereochemistry. All products can be envisaged as valuable platforms for the synthesis of new β-amino acid derivatives, amino alcohol ligands or bicyclic amines. Research along these lines is underway in these labs.

4. Experimental section

4.1. General

All reactions were conducted in flame dried glassware under nitrogen atmosphere. THF, DME, CH_2Cl_2, Et_2O, and EtOH were dried following standard methods under nitrogen atmosphere. TLC plates POLYGRAM SIL G/UV_{254} (Macherey–Nagel) were used for monitoring reactions. Flash column chromatographic separations were performed on silica gel 60 (Fluka, 230–400 mesh). IR spectra were taken on a Bruker Tensor 27 spectrometer (Dura Sample Diamant-ATR, 1 Reflexion). UV spectra were recorded on a Varian Cary 100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded, unless otherwise noted, in $CDCl_3$ on Bruker DRX 400, AV 300 or AC 200 spectrometers at 400, 300 or 200, and 100, 75 or 50 MHz, respectively. Connectivity was determined by ^{1}H–^{1}H COSY experiments. Relative configurations were determined by NOE or NOESY experiments. ^{13}C NMR assignments were obtained from DEPT and C,H-correlation experiments. EI-mass spectra were recorded on Finnigan MAT 95 spectrometers at 70 eV. ESI-mass spectra were obtained on a Finnigan MAT 95XLT, sample concentration approx. 50 μg/mL in MeOH,

spray voltage pos. mode: 1.3–1.8 kV, spray voltage neg. mode: 1.1–2.3 kV, HRMS resolution: 10,000 (10% valley definition). Combustion analyses were performed at the Microanalytical Laboratories of the Technical University of Braunschweig. The preparation of compounds **3a**, **3b**, **3f**, **3g**, **4a**, **4h**, **9b**, and **32a** is described in Ref. 2.

4.2. Typical procedure for epimerization of 3a or 3b

To the corresponding allylic alcohol (0.33 mmol) in 3 mL anhydrous THF was added *n*-BuLi (0.21 mL, 0.33 mmol, 1.6 M solution in hexane) via syringe at −78 °C. The mixture was stirred for 15 min and warmed to 0 °C. Nitrotetrahydrofuran **3a** or **3b** (0.33 mmol) was added and the mixture was stirred for 25 min. The reaction mixture was quenched with two drops of a saturated NH_4Cl solution, diluted with Et_2O, filtered through a pad of silica gel and concentrated under reduced pressure. The mixture of **3** and **5** was purified by column chromatography (hexane/EtOAc, gradient 10:1 to 5:1).

4.2.1. 4(R)-(1-Chloro-1-methylethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**5a**).* Colorless oil, yield 81 mg (88%). R_f=0.41, hexane/EtOAc 10:1; MS (CI) *m*/*z* 306/304 ($[M+NH_3+NH_4]^+$, 3/10), 289/287 ($[M+NH_4]^+$, 24/100), 273/271 (5/10), 256/254 (8/20), 237 (23), 220 (23), 202 (19), 145 (7); Anal. Calcd for $C_{13}H_{16}ClNO_3$ (269.72): C 57.89 H 5.98 N 5.19. Found: C 58.19 H 6.12 N 4.93. ^{1}H NMR (400 MHz) δ 1.57 (s, 3H), 1.63 (s, 3H), 3.39 (dt, *J*=8.8, 4.1 Hz, 1H), 3.94 (t, *J*=8.8 Hz, 1H), 4.52 (t, *J*=8.8 Hz, 1H), 5.11 (d, *J*=6.7 Hz, 1H), 5.36 (dd, *J*=6.7, 4.1 Hz, 1H), 7.27–7.31 (m, 5H); ^{13}C NMR (100 MHz) δ 31.0 (q), 32.4 (q), 57.1 (d), 68.6 (s), 69.2 (t), 84.7 (d), 93.2 (d), 126.1 (d), 128.4 (d), 128.9 (d), 133.9 (s).

4.2.2. 4(R)-(Chloromethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**5b**).* Colorless solid, yield 53 mg (66%). Mp 65 °C; R_f=0.29, hexane/EtOAc 5:1; MS (EI) *m*/*z* 243/241 (M^+, 1/3), 196/194 (5/14), 145 (100), 105 (50), 91 (19), 86 (13), 77 (28); Anal. Calcd for $C_{11}H_{12}ClNO_3$ (241.67): C 54.67 H 5.00 N 5.80. Found: C 54.84 H 4.91 N 5.65. ^{1}H NMR (400 MHz) δ 3.57–3.65 (m, 1H), 3.65 (dd, *J*=11.3, 6.2 Hz, 1H), 3.76 (dd, *J*=11.3, 5.1 Hz, 1H), 3.83 (dd, *J*=9.1, 7.2 Hz, 1H), 4.62 (dd, *J*=9.1, 8.0 Hz, 1H), 5.21 (d, *J*=6.3 Hz, 1H), 5.28 (dd, *J*=6.3, 3.1 Hz, 1H), 7.29–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 43.4 (t), 46.7 (d), 70.6 (t), 84.3 (d), 93.2 (d), 126.3 (d), 128.8 (d), 129.3 (d), 134.2 (s).

4.3. Oxabicyclo[3.1.0]hexanes 6 or 7 from 3, 4 or 5 using DBU (general procedure)

DBU (113 mg, 0.74 mmol) was added to a solution of compounds **3**, **4** or **5** (0.37 mmol) in 5 mL dry CH_2Cl_2 at 20 °C. The reaction mixture was warmed to 40 °C until complete according to TLC. The reaction mixture was acidified with 1 mL of 2 N HCl, 3 mL water was added and the aqueous layer was extracted three times with CH_2Cl_2. The organic solution was dried over Na_2SO_4 and concentrated in vacuum. The crude oils were purified by column chromatography (hexane/EtOAc, gradient 10:1 to 5:1).

*4.3.1. 6,6-Dimethyl-1-nitro-2-phenyl-3-oxabicyclo[3.1.0]hexanes (**6a**,**7a**).* The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3087, 3034, 2922, 2884, 1648, 1517, 1462, 1377, 1359, 1346, 1105, 1067, 1050, 1013, 891, 795, 763, 700 cm^{-1}; MS (EI) *m*/*z* 233 (M^+, 2), 186 (4), 145 (100), 141 (10), 129 (15), 127 (14), 117 (38), 115 (95), 105 (40), 91 (23), 81 (10), 79 (21), 77 (30), 53 (11), 51 (14); Anal. Calcd for $C_{13}H_{15}NO_3$ (233.26): C 66.94 H 6.48 N 6.00. Found: C 66.97 H 6.48 N 6.04.

4.3.1.1. 6,6-Dimethyl-1(S)-nitro-2(R*)-phenyl-3-oxabicyclo[3.1.0]hexane (**6a**).* Colorless solid, yield 84 mg (97%). Mp 102 °C; R_f=0.40, hexane/EtOAc 10:1; ^{1}H NMR (400 MHz) δ 1.23 (s, 3H), 1.35 (s, 3H), 2.63 (d, *J*=4.0 Hz, 1H), 3.86 (d, *J*=9.3 Hz, 1H), 4.47 (dd, *J*=9.3, 4.0 Hz, 1H), 5.16 (s, 1H), 7.26–7.32 (m, 5H); ^{13}C NMR (100 MHz) δ 13.4 (q), 20.7 (q), 30.4 (s), 35.5 (d), 67.5 (t), 80.0 (d), 83.2 (s), 127.1 (d), 128.7 (d), 128.8 (d), 138.4 (s).

4.3.1.2. 6,6-Dimethyl-1(R)-nitro-2(R*)-phenyl-3-oxabicyclo[3.1.0]hexane (**7a**).* Colorless oil, yield 83 mg (96%). R_f=0.45, hexane/EtOAc 10:1; ^{1}H NMR (400 MHz) δ 1.09 (s, 3H), 1.41 (s, 3H), 2.54 (d, *J*=4.2 Hz, 1H), 3.96 (d, *J*=9.4 Hz, 1H), 4.30 (dd, *J*=9.4, 4.2 Hz, 1H), 5.72 (s, 1H), 7.27–7.34 (m, 3H), 7.42–7.44 (m, 2H); ^{13}C NMR (100 MHz) δ 17.0 (q), 21.7 (q), 34.1 (s), 39.1 (d), 66.9 (t), 80.5 (s), 81.3 (d), 127.2 (d), 127.8 (d), 128.0 (d), 136.8 (s).

4.3.2. 1(R)-Nitro-2(R*)-phenyl-3-oxabicyclo[3.1.0]hexane (**6b**).* Colorless oil, yield 61 mg (80%). R_f=0.26, hexane/EtOAc 5:1; IR (neat) 3066, 3034, 2947, 2883, 1524, 1377, 1330, 1196, 1050, 1004, 894, 759, 700 cm^{-1}; MS (EI) *m*/*z* 205 (M^+, 13), 188 (23), 157 (12), 128 (11), 115 (17), 105 (100), 91 (13), 77 (35), 51 (14); Anal. Calcd for $C_{11}H_{11}NO_3$ (205.21): C 64.38 H 5.40 N 6.32. Found: C 64.31 H 5.50 N 6.68. ^{1}H NMR (400 MHz) δ 1.65 (t, *J*=5.6 Hz, 1H), 2.00 (dd, *J*=9.2, 5.6 Hz, 1H), 3.00 (ddd, *J*=9.2, 5.6, 2.9 Hz, 1H), 3.70 (d, *J*=9.2 Hz, 1H), 4.16 (dd, *J*=9.2, 2.9 Hz, 1H), 5.23 (s, 1H), 7.25–7.28 (m, 2H), 7.31–7.34 (m, 3H); ^{13}C NMR (100 MHz) δ 21.4 (t), 28.0 (d), 66.1 (t), 71.4 (s), 79.2 (d), 127.1 (d), 129.0 (d, 3C), 137.2 (s).

*4.3.3. 1-Nitro-2,6-diphenyl-3-oxabicyclo[3.1.0]hexanes (**6c**,**7c**).* The following analyses were performed before further separation. IR (neat) 3059, 3036, 2944, 2887, 1521, 1495, 1370, 1078, 1026, 1005, 891, 806, 763, 728, 697 cm^{-1}; MS (EI) *m*/*z* 281 (M^+, 4), 203 (10), 202 (10), 145 (85), 128 (30), 127 (22), 117 (35), 115 (45), 106 (50), 105 (100), 95 (20), 91 (35), 83 (11), 81 (25), 77 (75), 71 (15), 69 (20), 67 (23), 57 (27); Anal. Calcd for $C_{17}H_{15}NO_3$ (281.31): C 72.58 H 5.37 N 4.98. Found: C 72.28 H 5.31 N 4.92.

4.3.3.1. 1(R)-Nitro-2(R*),6(R*)-diphenyl-3-oxabicyclo[3.1.0]hexane (**6c**).* Colorless solid as a partly separable mixture with **7c**, yield 45 mg (43%). Mp 138 °C; R_f=0.33, hexane/EtOAc 10:1; ^{1}H NMR (300 MHz) δ 3.14 (d, *J*=6.1 Hz, 1H), 3.43 (dd, *J*=6.1, 3.1 Hz, 1H), 4.00 (d, *J*=9.1 Hz, 1H), 4.45 (dd, *J*=9.1, 3.1 Hz, 1H), 5.47 (s, 1H), 7.29–7.38 (m, 10H); ^{13}C NMR (75 MHz) δ 29.7 (d), 36.0 (d), 67.5 (t), 79.3 (s), 81.0 (d), 127.3 (d), 128.3 (d), 128.6 (d), 128.7 (d), 129.0 (d), 129.2 (d), 131.4 (s), 137.2 (s).

4.3.3.2. 1(S)-Nitro-2(R*),6(S*)-diphenyl-3-oxabicyclo[3.1.0]hexane (**7c**).* Colorless oil, yield 28 mg (27%). R_f=0.27, hexane/EtOAc 10:1; ^{1}H NMR (400 MHz, C_6D_6) δ 2.37 (dd, *J*=7.1, 3.1 Hz, 1H), 2.71 (d, *J*=7.1 Hz, 1H), 3.21 (d, *J*=8.8 Hz, 1H), 3.26 (dd, *J*=8.8, 3.1 Hz, 1H), 5.17 (s, 1H), 7.44–7.46 (m, 10H); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (d, *J*=7.4 Hz, 1H), 3.29 (dd, *J*=7.4, 2.6 Hz, 1H), 4.17 (d, *J*=9.1 Hz, 1H), 4.31 (dd, *J*=9.0, 2.5 Hz, 1H), 5.69 (s, 1H), 7.14–7.16 (m, 2H), 7.25–7.47 (m, 6H), 7.63–7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (d), 35.4 (d), 68.3 (t), 78.2 (s), 79.4 (d), 127.3 (d), 128.0 (d), 128.46 (d), 128.48 (d), 128.7 (d) 129.0 (d), 131.3 (s), 136.5 (s).

4.3.4. Methyl 6(R)-methyl-1(R*)-nitro-3-oxabicyclo[3.1.0]hexane-2(S*)-carboxylate (**6e**).* Colorless solid, yield 73 mg (98%). Mp 87 °C; R_f=0.25, hexane/EtOAc 10:1; IR (neat) 3061, 3011, 2968, 2901, 1730, 1523, 1446, 1357, 1240, 1212, 1182, 1089, 1066, 1039, 1008, 981, 907, 881, 803, 786, 731 cm^{-1}; MS (EI) *m*/*z* 142 (100), 95 (18), 67 (30); Anal. Calcd for $C_8H_{11}NO_5$ (201.18): C 47.76 H 5.51 N 6.96. Found: C 47.86 H 5.38 N 6.90. ^{1}H NMR (400 MHz) δ 1.38 (d, *J*=6.4 Hz, 3H), 1.82 (quint, *J*=6.4 Hz, 1H), 2.64 (dd, *J*=6.4, 3.1 Hz, 1H), 3.78 (s, 3H), 3.84 (d, *J*=8.6 Hz, 1H), 4.30 (dd, *J*=8.6, 3.1 Hz, 1H), 4.70 (s, 1H); ^{13}C NMR (100 MHz) δ 10.0 (q), 27.2 (d), 33.9 (d), 52.6 (q), 69.4 (t), 76.8 (d), 77.2 (s), 168.8 (s).

*4.3.5. 6-Methyl-1-nitro-2-phenyl-3-oxabicyclo[3.1.0]hexanes (**6f**,**6g**,**7g**).* The following analyses were performed before further

separation. IR (neat) 3062, 3033, 3009, 2942, 2885, 1521, 1496, 1456, 1362, 1336, 1203, 1107, 1061, 1018, 995, 925, 895, 786, 743, 699 cm^{-1}; MS (EI) *m/z* 219 (M^+, 38), 202 (50), 128 (14), 115 (15), 105 (100), 91 (10), 77 (30), 55 (17), 51 (13); Anal. Calcd for $C_{12}H_{13}NO_3$ (219.24): C 65.74 H 5.98 N 6.39. Found: C 65.85 H 6.19 N 6.53.

4.3.5.1. 6(R)-Methyl-1(R*)-nitro-2(R*)-phenyl-3-oxabicyclo [3.1.0]hexane (**6f**).* Colorless solid, yield 79 mg (97%). Mp 51 °C; R_f=0.30, hexane/EtOAc 10:1; IR (neat) 3065, 3034, 2970, 2939, 2882, 1522, 1456, 1371, 1279, 1207, 1089, 1056, 1031, 1008, 992, 898, 885, 759, 699 cm^{-1}; MS (EI) *m/z* 219 (M^+, 24), 128 (24), 117 (10), 115 (30), 107 (10), 105 (100), 91 (22), 79 (11), 77 (35), 69 (14), 67 (14), 55 (17), 51 (19); ^{1}H NMR (400 MHz) δ 1.32 (d, *J*=6.2 Hz, 3H), 1.89 (quint, *J*=6.2 Hz, 1H), 2.70 (dd, *J*=6.2, 3.0 Hz, 1H), 3.81 (d, *J*=9.0 Hz, 1H), 4.26 (dd, *J*=9.0, 3.0 Hz, 1H), 5.25 (s, 1H), 7.29–7.39 (m, 5H); ^{13}C NMR (100 MHz) δ 10.5 (q), 26.4 (d), 32.6 (d), 67.2 (t), 78.2 (s), 80.6 (d), 127.2 (d), 128.96 (d), 129.02 (d), 137.6 (s).

4.3.5.2. 6(S)-Methyl-1(R*)-nitro-2(R*)-phenyl-3-oxabicyclo [3.1.0]hexane (**6g**).* Colorless oil, yield 50 mg (62%). R_f=0.24, hexane/EtOAc 5:1; MS (EI) *m/z* 219 (M^+, 13), 202 (65), 157 (10), 128 (27), 117 (10), 115 (30), 105 (100), 91 (23), 77 (31), 67 (11), 65 (12), 55 (17), 51 (16); ^{1}H NMR (300 MHz) δ 1.39 (d, *J*=6.5 Hz, 3H), 2.32 (dq, *J*=9.7, 6.5 Hz, 1H), 3.10 (dd, *J*=9.7, 3.6 Hz, 1H), 3.87 (dd, *J*=9.5, 0.4 Hz, 1H), 4.44 (dd, *J*=9.5, 3.6 Hz, 1H), 5.22 (s, 1H), 7.30–7.40 (m, 5H); ^{13}C NMR (75 MHz) δ 6.2 (q), 29.3 (d), 31.4 (d), 65.3 (t), 75.8 (s), 78.1 (d), 127.0 (d), 128.8 (d), 128.9 (d), 138.3 (s).

4.3.5.3. 6(S)-Methyl-1(S*)-nitro-2(R*)-phenyl-3-oxabicyclo [3.1.0]hexane (**7g**).* Colorless solid, yield 23 mg (28%). Mp 70 °C; R_f=0.26, hexane/EtOAc 5:1; ^{1}H NMR (400 MHz) δ 1.44 (d, *J*=6.5 Hz, 3H), 2.03 (quint, *J*=6.5 Hz, 1H), 2.58 (dd, *J*=6.5, 3.2 Hz, 1H), 4.00 (d, *J*=9.0 Hz, 1H), 4.13 (dd, *J*=9.0, 3.2 Hz, 1H), 5.59 (s, 1H), 7.34–7.42 (m, 3H), 7.50–7.53 (m, 2H); ^{13}C NMR (100 MHz) δ 10.4 (q), 26.2 (d), 37.6 (d), 68.3 (t), 77.2 (s), 79.5 (d), 127.3 (d), 128.4 (d), 128.5 (d), 136.5 (s).

4.3.6. (2R,2aS*,2bR*,5aS*,5bS*)-2a-Nitro-2-phenyloctahydro-1-oxacyclopropa[cd]indene (**7h**).* Colorless oil, yield 86 mg (95%). R_f=0.36, hexane/EtOAc 10:1; IR (neat) 3034, 2927, 1522, 1495, 1451, 1349, 1260, 1090, 1042, 1027, 934, 800, 776, 732, 696 cm^{-1}; MS (EI) *m/z* 245 (M^+, 1), 228 (100), 198 (16), 170 (17), 157 (28), 141 (34), 128 (34), 115 (67), 105 (99), 91 (57), 81 (35), 79 (32), 77 (97), 67 (13), 65 (22), 63 (11), 53 (13), 51 (34); HRMS (EI) calcd for $C_{14}H_{15}NO_3$ 245.1052, found 245.1053; ^{1}H NMR (400 MHz) δ 1.25 (m, 1H), 1.36 (m, 1H), 1.41 (m, 1H), 1.62 (m, 1H), 1.70 (m, 1H), 1.82 (m, 1H), 2.87 (dd, *J*=9.9, 4.6 Hz, 1H), 2.95 (dt, *J*=9.1, 4.6 Hz, 1H), 4.75 (m, 1H), 6.09 (s, 1H), 7.31–7.38 (m, 3H), 7.41–7.45 (m, 2H); ^{13}C NMR (100 MHz) δ 15.7 (t), 16.4 (t), 25.2 (t), 29.7 (d), 34.6 (d), 73.4 (d), 74.1 (s), 79.1 (d), 126.9 (d), 127.9 (d) 128.3 (d), 137.0 (s).

4.3.7. (2R,2aR*,2bS*,5aR*,5bR*,2′S*,2a′S*,2b′R*,5a′S*,5b′R*)-2,2′-Dioxybis(2a-nitro-2-phenyloctahydro-1-oxacyclopropa[cd]indene) (**8**).* Colorless solid, yield 8 mg (4%). Mp 135 °C; R_f=0.30, hexane/EtOAc 10:1; IR (neat) 3064, 2950, 1529, 1451, 1359, 1233, 1095, 1016, 974, 938, 910, 789, 762, 695 cm^{-1}; MS (EI) *m/z* 244 (100), 202 (35), 198 (8), 141 (10), 128 (14), 115 (20); HRMS (EI) calcd for $C_{14}H_{14}NO_3$ ($M^+-O_2-C_{14}H_{14}NO_3$) 244.0974, found 244.0968; ^{1}H NMR (200 MHz) δ 1.19–1.44 (m, 4H), 1.59 (m, 1H), 1.80 (m, 1H), 2.58 (dt, *J*=9.2, 4.7 Hz, 1H), 3.05 (dd, *J*=9.6, 4.7 Hz, 1H), 4.75 (m, 1H), 7.36–7.43 (m, 3H), 7.57–7.62 (m, 2H).

4.4. 6(*R**)-Methyl-1(*R**)-nitro-3-oxabicyclo[3.1.0]hexane-2(*S**)-carboxylic acid (6d) from 3d using $NaHCO_3$

Crude **3d** (54 mg, 0.22 mmol) was dissolved in a saturated aqueous solution of $NaHCO_3$ (0.6 mL, 0.69 mmol) at 20 °C and stirred for 10 min. The mixture was extracted with 3 mL diethyl ether and phases were separated. To the water phase was added concd HCl (0.1 mL, 1.2 mmol) and it was stirred for 10 min. The mixture was extracted three times with 10 mL diethyl ether. Concentration of the combined organic layers in vacuum and drying yielded **6d**. Colorless solid, yield 30 mg (72%). ^{1}H NMR (200 MHz) δ 1.38 (d, *J*=6.4 Hz, 3H), 1.82 (quint, *J*=6.4 Hz, 1H), 2.63 (dd, *J*=6.4, 3.1 Hz, 1H), 3.86 (d, *J*=8.7 Hz, 1H), 4.30 (dd, *J*=8.7, 3.1 Hz, 1H), 4.71 (s, 1H), 10.55 (br s, 1H); ^{13}C NMR (50 MHz) δ 9.9 (q), 27.3 (d), 34.0 (d), 69.6 (t), 76.0 (s), 77.0 (d), 173.8 (s).

4.5. 4-((*N*-Methyl-*N*-phenylamino)methyl)-3-nitro-2-phenyltetrahydrofurans 11b, 12b (general procedure)

To a solution of **3b**, **9b** or **10b** (0.3 mmol) in 2 mL dry CH_3CN was added a solution of *N*-methylaniline (80 mg, 0.75 mmol) in 1 mL dry CH_3CN and NaI (30 mg, 0.2 mmol) at 20 °C. The reaction mixture was heated to reflux until the starting material was consumed as indicated by TLC. The reaction mixture was concentrated in vacuum, diluted with 10 mL diethyl ether and filtered. The ethereal solution was concentrated and the residual oil was purified by column chromatography (hexane/EtOAc, gradient 10:1 to 5:1). The same substitution of **9b** and **10b** was performed in the absence of NaI. The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 2955, 2923, 2854, 1599, 1552, 1503, 1464, 1377, 1345, 1100, 1072, 992, 967, 744, 693 cm^{-1}; MS (EI) *m/z* 312 (M^+, 7), 266 (25), 248 (16), 159 (21), 145 (81), 120 (100), 117 (11), 115 (14), 105 (55), 91 (24), 77 (48), 51 (21); Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.36): C 69.21 H 6.45 N 8.97. Found: C 69.21 H 6.42 N 8.92.

4.5.1. 4(R)-((N-Methyl-N-phenylamino)methyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**11b**).* Colorless oil, yield starting from **3b** 8 mg (8%); yield starting from **9b** 34 mg (36%). R_f=0.33, hexane/EtOAc 5:1; ^{1}H NMR (400 MHz) δ 2.96 (s, 3H), 3.04 (m, 1H), 3.37 (dd, *J*=15.0, 8.5 Hz, 1H), 3.59 (dd, *J*=15.0, 5.6 Hz, 1H), 4.18 (dd, *J*=10.5, 8.5 Hz, 1H), 4.36 (dd, *J*=8.5, 7.5 Hz, 1H), 5.00 (dd, *J*=7.5, 3.0 Hz, 1H), 5.53 (d, *J*=3.0 Hz, 1H), 6.61–6.83 (m, 3H), 7.16–7.44 (m, 7H); ^{13}C NMR (100 MHz) δ 39.5 (q), 42.1 (d), 49.5 (t), 71.9 (t), 85.0 (d), 94.2 (d), 112.9 (d), 117.6 (d), 125.3 (d), 128.6 (d), 128.9 (d), 129.42 (d), 139.0 (s), 148.5 (s).

4.5.2. 4(R)-((N-Methyl-N-phenylamino)methyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**12b**).* Colorless solid, yield starting from **3b** 46 mg (48%); yield starting from **9b** 34 mg (36%). Mp 87 °C; R_f=0.18, hexane/EtOAc 5:1; ^{1}H NMR (400 MHz) δ 2.91 (s, 3H), 3.35 (dd, *J*=17.4, 10.7 Hz, 1H), 3.50 (m, 2H), 3.74 (dd, *J*=8.9, 5.8 Hz, 1H), 4.56 (dd, *J*=8.9, 7.1 Hz, 1H), 5.09 (dd, *J*=6.4, 2.9 Hz, 1H), 5.25 (d, *J*=6.4 Hz, 1H), 6.72–6.79 (m, 3H), 7.20–7.30 (m, 7H); ^{13}C NMR (100 MHz) δ 39.2 (q), 44.4 (d), 53.8 (t), 71.4 (t), 83.1 (d), 92.9 (d), 113.4 (d), 118.2 (d), 126.0 (d), 128.4 (d), 128.8 (d), 129.44 (d), 134.4 (s), 149.3 (s).

4.6. 4-(Azidomethyl)-3-nitro-2-phenyltetrahydrofurans 13, 14 (general procedure)

To a solution of **3b** or **5b** (115 mg, 0.46 mmol) in 2 mL dry DMF was added NaN_3 (90 mg, 1.38 mmol) at 20 °C. The reaction mixture was warmed to 60 °C with stirring until complete according to TLC. The reaction mixture was concentrated in vacuum, diluted with 10 mL diethyl ether and filtered. The ethereal solution was concentrated and the residual oil was purified by column chromatography (hexane/EtOAc, gradient 10:1 to 5:1). The following analyses were performed on the diastereomeric mixture of **13b** and **14b** before further separation. IR (neat) 3067, 3034, 2980, 2929, 2871, 2100, 1547, 1453, 1359, 1333, 1276, 1097, 1069, 1029, 983, 747, 698 cm^{-1}; MS (CI) *m/z* 266 ([M+NH_4^+], 100), 240 (12), 233 (10), 223

(14), 221 (16), 219 (16), 207 (13), 202 (25), 196 (44), 193 (18), 191 (11), 178 (30), 176 (55), 174 (25), 164 (100), 162 (25), 147 (12), 145 (19), 61 (18); Anal. Calcd for $C_{11}H_{12}N_4O_3$ (248.24): C 53.22 H 4.87 N 22.57. Found: C 53.12 H 4.89 N 22.59.

4.6.1. 4(R)-(Azidomethyl)-3(S*)-nitro-2(R*)-phenyltetrahydrofuran (**13b**).* Colorless oil, for yields see Scheme 6. R_f=0.26, hexane/EtOAc 5:1; ^{1}H NMR (200 MHz) δ 2.92 (dq, J=10.3, 7.6 Hz, 1H), 3.47 (dd, J=12.5, 7.6 Hz, 1H), 3.56 (dd, J=12.5, 7.6 Hz, 1H), 4.05 (dd, J=10.3, 8.6 Hz, 1H), 4.44 (dd, J=8.6, 7.6 Hz, 1H), 5.02 (dd, J=7.6, 3.2 Hz, 1H), 5.54 (d, J=3.2 Hz, 1H), 7.26–7.38 (m, 5H); ^{13}C NMR (100 MHz) δ 34.8 (d), 48.0 (t), 70.9 (t), 86.0 (d), 93.0 (d), 125.3 (d), 128.9 (d), 129.6 (d), 137.5 (s).

4.6.2. 4(R)-(Azidomethyl)-3(R*)-nitro-2(R*)-phenyltetrahydrofuran (**14b**).* Colorless oil, for yields see Scheme 6. R_f=0.15, hexane/EtOAc 5:1; ^{1}H NMR (200 MHz) δ 3.31 (m, 1H), 3.51 (dd, J=12.4, 6.3 Hz, 1H), 3.65 (dd, J=12.4, 5.6 Hz, 1H), 3.73 (dd, J=8.9, 7.1 Hz, 1H), 4.58 (dd, J=8.9, 8.1 Hz, 1H), 5.15 (dd, J=6.3, 2.7 Hz, 1H), 5.19 (d, J=6.3 Hz, 1H), 7.30–7.34 (m, 5H); ^{13}C NMR (50 MHz) δ 44.3 (d), 51.0 (t), 70.1 (t), 83.7 (d), 92.6 (d), 126.0 (d), 128.4 (d), 128.9 (d), 134.0 (s).

4.7. Oxidative degradation of the phenyl ring using $NaIO_4$/$RuCl_3$ (method A)

To a mixture of **3**, **4**, or **5** (0.54 mmol) in 4 mL CH_3CN, 4 mL CCl_4, and 6 mL H_2O were added subsequently with vigorous stirring $NaIO_4$ (797 mg, 3.72 mmol) and $RuCl_3\cdot 1H_2O$ (9 mg, 0.04 mmol) at 20 °C. The white-yellow reaction mixture was stirred at room temperature until the starting material was consumed. When the reaction mixture changed its color to gray-brown and the starting material was not completely consumed, additional $NaIO_4$ (797 mg, 3.72 mmol) and 4 mL H_2O was added. The reaction mixture was extracted three times with 20 mL CH_2Cl_2 and then three times with 20 mL EtOAc. The organic extracts were combined, dried over Na_2SO_4, and concentrated in vacuum. The crude acids **3d**, **16**, **17**, or **20** were analyzed by NMR and then immediately converted to the corresponding methyl esters **3e**, **18**, **19**, or **21** by dissolving them in 4 mL anhydrous THF and 0.2 mL dry MeOH and adding trimethylsilyldiazomethane (0.243 mL, 0.486 mmol, 2 M solution in Et_2O). The reaction mixture was stirred for 2 h at room temperature, concentrated in vacuum and purified by column chromatography (hexane/EtOAc, gradient 10:1 to 2:1).

4.8. Oxidative degradation of the phenyl ring using H_5IO_6/$RuCl_3$ (method B)

A mixture of **3**, **4**, or **5** (0.33 mmol) in 3 mL CCl_4 and $RuCl_3\cdot 1H_2O$ (7.6 mg, 0.033 mmol) in 1 mL CH_3CN was added to a stirred solution of H_5IO_6 (753 mg, 3.3 mmol) in 10 mL CH_3CN at 20 °C. The reaction mixture was stirred at room temperature until the reaction was complete according to TLC, and concentrated in vacuum. The residue was mixed with a small amount of water and extracted three times with Et_2O. The combined extracts were dried over Na_2SO_4 and concentrated in vacuum. The crude products **3d**, **16**, **17**, or **20** were transformed to the methyl esters **3e**, **18**, **19**, or **21** by the procedure described above.

4.8.1. 4(R)-(1(S*)-Chloroethyl)-3(S*)-nitrotetrahydrofuran-2(S*)-carboxylic acid (**3d**).* Colorless oil, yield 93 mg (77%). R_f=0.20, hexane/EtOAc 2:1; ^{1}H NMR (200 MHz) δ 1.60 (d, J=6.5 Hz, 3H), 2.87 (m, 1H), 3.85 (dq, J=10.4, 6.5 Hz, 1H), 4.12 (dd, J=10.9, 8.8 Hz, 1H), 4.47 (dd, J=8.8, 7.9 Hz, 1H), 5.06 (d, J=1.5 Hz, 1H), 5.23 (dd, J=6.6, 1.5 Hz, 1H), 9.50 (br s, 1H); ^{13}C NMR (50 MHz) δ 24.6 (q), 51.9 (d), 53.1 (d), 72.9 (t), 81.7 (d), 88.5 (d), 172.1 (s).

*4.8.2. Methyl 4-(1-chloro-1-methylethyl)-3-nitrotetrahydrofuran-2-carboxylates (**18a**,**19a**,(**21a**)).* The following analyses were performed on the diastereomeric mixture of **18a** and **19a** before further separation. IR (neat) 3047, 2969, 2893, 1744, 1732, 1553, 1440, 1375, 1223, 1132, 1102, 1083, 1032, 939, 923, 785 cm^{-1}; MS (EI) m/z 194/192 (25/75), 169 (12), 151 (15), 148/146 (14/42), 145 (20), 141 (13), 127 (100), 109 (55), 97 (38), 95 (18), 83 (15), 81 (55), 79 (35), 77 (40); HRMS (EI) calcd for $C_7H_{11}{}^{35}ClNO_3$ ($M^+-CH_3O(O)C$) 192.0427, found 192.0424.

4.8.2.1. Methyl 4(R)-(1-chloro-1-methylethyl)-3(S*)-nitrotetrahydrofuran-2(S*)-carboxylate (**18a**).* Colorless solid, yield according to method A 79 mg (58%, **18a**/**19a** 1.4:1); yield according to method B 55 mg (40%). Mp 109 °C; R_f=0.30, hexane/EtOAc 2:1; ^{1}H NMR (400 MHz) δ 1.67 (s, 3H), 1.701 (s, 3H), 2.95 (ddd, J=11.4, 8.0, 6.2 Hz, 1H), 3.82 (s, 3H), 4.35 (dd, J=11.4, 8.0 Hz, 1H), 4.44 (t, J=8.0 Hz, 1H), 5.02 (d, J=1.0 Hz, 1H), 5.28 (dd, J=6.2, 1.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 30.5 (q), 32.4 (q), 53.1 (q), 56.0 (d), 65.0 (s), 69.5 (t), 81.4 (d), 87.4 (d), 169.4 (s).

4.8.2.2. Methyl 4(S)-(1-chloro-1-methylethyl)-3(S*)-nitrotetrahydrofuran-2(S*)-carboxylate (**19a**).* Colorless oil. R_f=0.35, hexane/EtOAc 2:1; ^{1}H NMR (400 MHz) δ 1.55 (s, 3H), 1.695 (s, 3H), 3.26 (dt, J=8.7, 4.8 Hz, 1H), 3.83 (s, 3H), 4.11 (dt, J=8.7, 0.6 Hz, 1H), 4.37 (t, J=8.7 Hz, 1H), 5.10 (d, J=3.0 Hz, 1H), 5.33 (dd, J=4.8, 3.0 Hz, 1H); ^{13}C NMR (100 MHz) δ 31.1 (q), 32.1 (q), 53.0 (q), 57.2 (d), 68.4 (s), 70.6 (t), 81.6 (d), 90.5 (d), 168.8 (s).

4.8.2.3. Methyl 4(R)-(1-chloro-1-methylethyl)-3(R*)-nitrotetrahydrofuran-2(S*)-carboxylate (**21a**).* Colorless oil, yield according to method B 28 mg (20%). R_f=0.44, hexane/EtOAc 2:1; ^{1}H NMR (400 MHz) δ 1.57 (s, 3H), 1.75 (s, 3H), 3.08 (dt, J=8.2, 4.2 Hz, 1H), 3.80 (s, 3H), 3.96 (dd, J=9.1, 8.2 Hz, 1H), 4.50 (t, J=8.7 Hz, 1H), 4.65 (d, J=6.3 Hz, 1H), 5.40 (dd, J=6.3, 4.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 31.0 (q), 32.2 (q), 52.9 (q), 57.6 (d), 69.0 (s), 69.7 (t), 80.2 (d), 89.0 (d), 166.8 (s).

*4.8.3. Methyl 4-(chloromethyl)-3-nitrotetrahydrofuran-2-carboxylates (**18b**,**21b**).* The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3011, 2958, 2898, 1757, 1740, 1554, 1440, 1363, 1289, 1263, 1215, 1182, 1118, 1066, 1022, 929, 850, 736 cm^{-1}; MS (EI) m/z 178/176 (1/3), 166/164 (15/45), 127 (18), 120/118 (17/55), 119/117 (5/12), 69 (100), 59 (35), 53 (14); HRMS (EI) calcd for $C_5H_7{}^{35}ClNO_3$ (M^+-CH_3OOC) 164.0114, found 164.0112.

4.8.3.1. Methyl 4(R)-(chloromethyl)-3(S*)-nitrotetrahydrofuran-2(S*)-carboxylate (**18b**).* Colorless oil, yield 42 mg (56%, **18b**/**21b** 1:2). R_f=0.44, hexane/EtOAc 2:1; ^{1}H NMR (400 MHz) δ 3.14 (m, 1H), 3.48 (dd, J=11.4, 8.3 Hz, 1H), 3.62 (dd, J=11.4, 7.1 Hz, 1H), 3.83 (s, 3H), 4.03 (t, J=8.8 Hz, 1H), 4.40 (dd, J=8.8, 7.5 Hz, 1H), 5.08 (d, J=2.5 Hz, 1H), 5.35 (dd, J=7.2, 2.5 Hz, 1H); ^{13}C NMR (100 MHz) δ 39.2 (t), 45.9 (d), 53.2 (q), 71.6 (t), 80.9 (d), 88.8 (d), 168.9 (s).

4.8.3.2. Methyl 4(R)-(chloromethyl)-3(R*)-nitrotetrahydrofuran-2(S*)-carboxylate (**21b**).* Colorless oil. R_f=0.40, hexane/EtOAc 2:1; ^{1}H NMR (400 MHz) δ 3.40 (m, 1H), 3.66 (dd, J=11.9, 5.8 Hz, 1H), 3.79 (s, 3H), 3.82 (dd, J=11.9, 5.4 Hz, 1H), 3.89 (dd, J=9.2, 6.2 Hz, 1H), 4.51 (dd, J=9.2, 7.8 Hz, 1H), 4.77 (d, J=6.6 Hz, 1H), 5.32 (dd, J=6.6, 4.3 Hz, 1H); ^{13}C NMR (100 MHz) δ 43.1 (t), 46.9 (d), 52.9 (q), 70.5 (t), 79.2 (d), 88.3 (d), 167.2 (s).

4.8.4. Methyl 4(R)-(1(S*)-chloroethyl)-3(S*)-nitrotetrahydrofuran-2(S*)-carboxylate (**3e**).* Colorless oil as a partially separable mixture with **5e**, yield 94 mg (73%, **3e**/**5e** 1:2.4). R_f=0.20, hexane/EtOAc 10:1; IR (neat) 2960, 2939, 2902, 1714, 1551, 1454, 1368, 1268, 1221, 1130, 1097, 1034, 935, 908, 802 cm^{-1}; MS (EI) m/z 178/176 (9/27), 132 (30), 127 (10), 95 (11), 69 (100), 59 (20), 55 (10); ^{1}H NMR (400 MHz) δ 1.66 (d, J=6.4 Hz, 3H), 2.96 (m, 1H), 3.84 (s, 3H), 3.92

(m, 1H), 4.17 (dd, *J*=10.8, 8.6 Hz, 1H), 4.51 (t, *J*=8.6 Hz, 1H), 5.05 (d, *J*=1.6 Hz, 1H), 5.23 (dd, *J*=6.5, 1.6 Hz, 1H); ^{13}C NMR (100 MHz) δ 24.6 (q), 51.98 (d), 53.2 (q), 53.3 (d), 72.8 (t), 82.1 (d), 88.6 (d), 169.0 (s).

4.8.5. Methyl 4(R)-(1(S*)-chloroethyl)-3(R*)-nitrotetrahydrofuran-2(S*)-carboxylate (**5e**).* Colorless oil as a partially separable mixture with **3e**, yield 94 mg (73%, **3e**/**5e** 1:2.4). R_f=0.17, hexane/EtOAc 10:1; IR (neat) 2960, 2939, 2902, 1714, 1551, 1454, 1368, 1268, 1221, 1130, 1097, 1034, 935, 908, 802 cm^{-1}; MS (EI) *m*/*z* 178/176 (9/27), 132 (30), 127 (10), 95 (11), 69 (100), 59 (20), 55 (10); ^{1}H NMR (400 MHz) δ 1.56 (d, *J*=6.8 Hz, 3H), 3.27 (tt, *J*=8.1, 4.8 Hz, 1H), 3.79 (s, 3H), 3.98 (dd, *J*=9.1, 7.7 Hz, 1H), 4.44 (dq, *J*=6.8, 4.8 Hz, 1H), 4.48 (t, *J*=8.8 Hz, 1H), 4.71 (d, *J*=6.6 Hz, 1H), 5.27 (dd, *J*=6.6, 4.8 Hz, 1H); ^{13}C NMR (100 MHz) δ 23.4 (q), 52.04 (d), 52.9 (q), 56.8 (d), 68.7 (t), 79.3 (d), 88.8 (d), 167.2 (s).

4.9. Reduction of tetrahydrofurans 3a,b,g, 4a,g, and 5b,f by $NiCl_2$/$NaBH_4$ (general procedure)

(a) Preparation of the Ni_2B catalyst: to a solution of $NiCl_2 \cdot 6H_2O$ (166 mg, 0.7 mmol) in 6 mL dry EtOH was added $NaBH_4$ (83 mg, 2.2 mmol) at 0 °C and the mixture was stirred for 30 min. (b) Reduction of the NO_2 group: To a mixture of **3**, **4** or **5** (0.7 mmol), $NaBH_4$ (265 mg, 7.0 mmol) and 13 mL dry EtOH was added the freshly prepared Ni_2B catalyst suspension at the given starting temperature (see Table 3). The mixture was stirred for the indicated time at 0 °C and subsequently warmed to 40 °C with stirring for the given time. After completion of the reaction, the mixture was cooled to room temperature and Et_3N (0.142 mL, 1.4 mmol) followed by Boc_2O (327 mg, 1.5 mmol) was added. The reaction mixture was stirred overnight, filtered, and concentrated in vacuum. The residual oil was purified by column chromatography (hexane/EtOAc, gradient 10:1 to 2:1).

*4.9.1. 3-(N-tert-Butoxycarbonylamino)-4-isopropyl-2-phenyltetrahydrofurans (**22a**,**23a**).* The combustion analysis was performed on the diastereomeric mixture before further separation. Anal. Calcd for $C_{18}H_{27}NO_4$ (305.41): C 70.79 H 8.91 N 4.59. Found: C 70.62 H 8.92 N 4.68.

4.9.1.1. 3(S)-(N-tert-Butoxycarbonylamino)-4(R*)-isopropyl-2(R*)-phenyltetrahydrofuran (**22a**).* Colorless solid, for yields and ratios, see Tables 3 and 4 and Scheme 10. Mp 124 °C; R_f=0.55, hexane/EtOAc 5:1; IR (neat) 3334, 3271, 3146, 3064, 2961, 2926, 2872, 1702, 1533, 1449, 1388, 1365, 1348, 1164, 1085, 1059, 1027, 991, 971, 928, 776, 734, 699, 681 cm^{-1}; MS (EI) *m*/*z* 305 (M$^+$, 4), 290 (25), 249 (11), 248 (64), 188 (5), 99 (14), 56 (100); ^{1}H NMR (400 MHz) δ 0.87 (d, *J*=6.6 Hz, 3H), 0.89 (d, *J*=6.6 Hz, 3H), 1.49 (s, 9H), 1.61 (m, 1H), 1.92 (m, 1H), 3.68 (dd, *J*=11.1, 8.6 Hz, 1H), 4.19 (dd, *J*=8.6, 6.0 Hz, 1H), 4.31 (t, *J*=8.6 Hz, 1H), 4.88 (br d, *J*=8.6 Hz, 1H), 5.07 (br s, 1H), 7.23–7.52 (m, 5H); ^{13}C NMR (100 MHz) δ 21.5 (q), 21.8 (q), 26.8 (d), 28.4 (q), 47.1 (d), 59.5 (d), 71.7 (t), 79.7 (s), 88.1 (d), 125.0 (d), 127.1 (d), 128.275 (d), 141.6 (s), 155.5 (s).

4.9.1.2. 3(S)-(N-tert-Butoxycarbonylamino)-4(S*)-isopropyl-2(R*)-phenyltetrahydrofuran (**23a**).* Colorless solid, for yields and ratios, see Tables 3 and 4 and Scheme 10. Mp 102 °C; R_f=0.30, hexane/EtOAc 5:1; IR (neat) 3361, 3033, 3008, 2959, 2934, 2874, 1684, 1525, 1456, 1368, 1291, 1236, 1167, 1091, 1042, 1021, 975, 872, 862, 759, 699 cm^{-1}; MS (EI) *m*/*z* 248 (7), 188 (33), 174 (14), 145 (42), 107 (30), 105 (15), 99 (11), 97 (18), 91 (13), 82 (14), 79 (14), 77 (16), 59 (20), 56 (100); ^{1}H NMR (400 MHz) δ 0.89 (d, *J*=6.3 Hz, 3H), 0.96 (d, *J*=6.7 Hz, 3H), 1.40 (s, 9H), 1.72 (m, 1H), 1.96 (m, 1H), 3.85 (m, 1H), 3.93 (m, 1H), 4.13 (t, *J*=8.7 Hz, 1H), 4.61 (br d, *J*=5.9 Hz, 1H), 4.72 (br d, *J*=7.9 Hz, 1H), 7.24–7.46 (m, 5H); ^{13}C NMR (100 MHz) δ 20.3 (q), 20.7 (q), 28.5 (q), 30.1 (d), 52.9 (d), 62.9 (d), 70.5 (t), 79.4 (s), 85.6 (d), 125.1 (d), 128.1 (d), 128.283 (d), 140.0 (s), 154.9 (s).

4.9.2. 3(S)-(N-tert-Butoxycarbonylamino)-4(R*)-(1-hydroxy-1-methylethyl)-2(R*)-phenyltetrahydrofuran (**24a**).* Colorless solid, for yields and ratios, see Tables 3 and 4 and Scheme 10. Mp 157 °C; R_f=0.23, hexane/EtOAc 2:1; UV (CH_2Cl_2, 6.0×10^{-5} M): λ_{max} 258, 227 nm; IR (neat) 3435, 3330, 2974, 2933, 2887, 1679, 1450, 1385, 1364, 1345, 1328, 1127, 1091, 1064, 988, 928, 815, 779, 737, 715 cm^{-1}; MS (ESI) *m*/*z* 344 ([M+Na$^+$], 100); MS (EI) *m*/*z* 321 (M$^+$, 1), 264 (6), 190 (13), 186 (20), 176 (10), 146 (76), 144 (21), 141 (13), 120 (50), 118 (15), 116 (13), 107 (43), 105 (25), 101 (26), 97 (42), 91 (22), 82 (100), 79 (18), 77 (26), 70 (34); Anal. Calcd for $C_{18}H_{27}NO_4$ (321.41): C 67.26 H 8.47 N 4.36. Found: C 67.03 H 8.28 N 4.32; ^{1}H NMR (400 MHz) δ 1.22 (s, 3H), 1.31 (s, 3H), 1.49 (s, 9H), 1.94 (br s, 1H), 2.19 (m, 1H), 4.08 (m, 1H), 4.27 (m, 2H), 5.22 (br s, 1H), 6.62 (br s, 1H), 7.24 (m, 1H), 7.34 (m, 2H), 7.48 (m, 2H); ^{13}C NMR (100 MHz) δ 28.8 (q), 29.6 (q), 31.7 (q), 47.8 (d), 60.8 (d), 68.1 (t), 71.0 (s), 79.7 (s), 85.3 (d), 125.4 (d), 127.3 (d), 128.5 (d), 142.0 (s), 156.5 (s).

4.9.3. 3(S)-(N-tert-Butoxycarbonylamino)-4(R*)-methyl-2(R*)-phenyltetrahydrofuran (**22b**).* Colorless solid, for yields and ratios, see Tables 3 and 4. Mp 102 °C; R_f=0.30, hexane/EtOAc 5:1; IR (neat) 3370, 3066, 3032, 2980, 2965, 2941, 2874, 1680, 1517, 1454, 1389, 1366, 1278, 1248, 1167, 1090, 1055, 1008, 980, 929, 871, 755, 740, 698 cm^{-1}; MS (EI) *m*/*z* 220 (29), 160 (64), 146 (16), 115 (25), 107 (12), 91 (11), 77 (10), 70 (40), 57 (100); Anal. Calcd for $C_{16}H_{23}NO_3$ (277.36): C 69.29 H 8.36 N 5.05. Found: C 69.07 H 8.51 N 5.37. ^{1}H NMR (300 MHz) δ 1.00 (d, *J*=6.9 Hz, 3H), 1.46 (s, 9H), 2.49 (m, 1H), 3.58 (t, *J*=8.7 Hz, 1H), 4.14 (m, 1H), 4.29 (dd, *J*=8.7, 7.7 Hz, 1H), 4.75 (br s, 1H), 4.77 (br d, *J*=3.9 Hz, 1H), 7.23–7.39 (m, 5H); ^{13}C NMR (75 MHz) δ 11.1 (q), 28.3 (q), 34.8 (d), 61.0 (d), 73.9 (t), 77.2 (s), 85.8 (d), 125.4 (d), 127.5 (d), 128.4 (d), 141.0 (s), 155.5 (s).

4.9.4. 3(S)-(N-tert-Butoxycarbonylamino)-4(S*)-(hydroxymethyl)-2(R*)-phenyltetrahydrofuran (**24b**).* Colorless solid, for yields and ratios, see Tables 3 and 4. Mp 130 °C; R_f=0.26, hexane/EtOAc 2:1; IR (neat) 3483, 3418, 3376, 3067, 3035, 2980, 2933, 2904, 2868, 1681, 1516, 1389, 1254, 1165, 1094, 1046, 1014, 981, 951, 873, 755, 740, 698 cm^{-1}; MS (ESI) *m*/*z* 316 ([M+Na$^+$], 100); MS (EI) *m*/*z* 236 (7), 220 (5), 176 (30), 145 (35), 131 (15), 107 (13), 91 (12), 86 (15), 77 (20), 68 (25), 59 (14), 57 (90), 56 (100); Anal. Calcd for $C_{16}H_{23}NO_4$ (293.36): C 65.51 H 7.90 N 4.77. Found: C 65.63 H 7.93 N 4.81. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (s, 9H), 2.44 (m, 1H), 3.43 (m, 1H), 3.52 (m, 1H), 3.86 (m, 2H), 4.16 (dd, *J*=8.5, 7.5 Hz, 1H), 4.55 (t, *J*=5.0 Hz, 1H), 4.60 (d, *J*=6.4 Hz, 1H), 7.12 (d, *J*=8.5 Hz, 1H), 7.24–7.29 (m, 1H), 7.31–7.36 (m, 4H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.1 (q), 42.6 (d), 58.7 (t), 59.8 (d), 70.3 (t), 78.0 (s), 83.2 (d), 125.5 (d), 127.3 (d), 128.1 (d), 141.6 (s), 155.4 (s).

4.9.5. 3(S)-(N-tert-Butoxycarbonylamino)-4(R*)-(chloromethyl)-2(R*)-phenyltetrahydrofuran (**25b**).* Colorless solid, for yields and ratios, see Tables 3 and 4. Mp 124 °C; R_f=0.50, hexane/EtOAc 5:1; IR (neat) 3360, 3037, 2978, 2935, 2880, 1672, 1517, 1454, 1370, 1352, 1274, 1250, 1157, 1054, 1013, 968, 900, 756 cm^{-1}; MS (EI) *m*/*z* 256/254 (3/8), 158 (11), 145 (13), 107 (14), 105 (30), 91 (17), 77 (25), 70 (100), 68 (30), 57 (48); Anal. Calcd for $C_{16}H_{22}ClNO_3$ (311.80): C 61.63 H 7.11 N 4.49. Found: C 61.65 H 6.98 N 4.22. ^{1}H NMR (300 MHz) δ 1.44 (s, 9H), 2.84 (m, 1H), 3.54 (dd, *J*=11.0, 8.6 Hz, 1H), 3.71 (dd, *J*=11.0, 5.1 Hz, 1H), 3.91 (t, *J*=8.8 Hz, 1H), 4.30 (m, 1H), 4.40 (dd, *J*=8.8, 8.2 Hz, 1H), 4.79 (d, *J*=3.9 Hz, 1H), 4.85 (br d, *J*=7.9 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (75 MHz) δ 28.3 (q), 42.6 (t), 42.9 (d), 59.8 (d), 70.8 (t), 77.2 (s), 85.8 (d), 125.4 (d), 127.9 (d), 128.6 (d), 139.8 (s), 155.3 (s).

4.9.6. 3(R)-(N-tert-Butoxycarbonylamino)-4(R*)-methyl-2(R*)-phenyltetrahydrofuran (**26b**).* Colorless solid, as an inseparable mixture with **22b**, yield 58 mg (30%, **26b**/**22b** 1.4:1). R_f=0.30, hexane/EtOAc 5:1; ^{1}H NMR (200 MHz) δ 1.14 (d, *J*=6.8 Hz, 3H), 1.31 (s, 9H), 2.17 (m,

1H), 3.52 (t, *J*=8.5 Hz, 1H), 4.07 (m, 2H), 4.29 (t, *J*=8.5 Hz, 1H), 5.11 (br d, *J*=6.0 Hz, 1H), 7.21–7.37 (m, 5H); ^{13}C NMR (50 MHz) δ 15.4 (q), 28.2 (q), 39.4 (d), 60.5 (d), 73.4 (t), 77.0 (s), 81.0 (d), 126.4 (d, 3C), 128.3 (d), 141.5 (s), 156.0 (s).

*4.9.7. 3-(N-tert-Butoxycarbonylamino)-4-ethyl-2-phenyltetrahydrofurans (**23g**,**26f**).* The combustion analysis was performed on the diastereomeric mixture before further separation. Anal. Calcd for $C_{17}H_{25}NO_3$ (291.39): C 70.07 H 8.65 N 4.81. Found: C 69.58 H 8.92 N 4.81.

4.9.7.1. 3(S)-(N-tert-Butoxycarbonylamino)-4(S*)-ethyl-2(R*)-phenyltetrahydrofuran (**23g**).* Colorless solid, yield 49 mg (24%). Mp 107 °C; R_f=0.35, hexane/EtOAc 5:1; IR (neat) 3325, 3059, 3032, 2962, 2933, 2877, 2858, 1699, 1689, 1532, 1458, 1365, 1269, 1248, 1166, 1048, 1021, 901, 860, 739, 718, 701 cm^{-1}; MS (EI) *m*/*z* 234 (11), 218 (5), 174 (45), 160 (18), 145 (30), 129 (27), 107 (17), 105 (13), 91 (14), 84 (37), 77 (17), 70 (12), 57 (100), 56 (90); ^{1}H NMR (400 MHz): δ=0.92 (t, *J*=7.4 Hz, 3H), 1.41 (s, 9H), 1.61 (m, 2H), 2.12 (m, 1H), 3.57 (m, 1H), 3.80 (dd, *J*=8.7, 7.5 Hz, 1H), 4.19 (dd, *J*=8.7, 8.0 Hz, 1H), 4.59 (m, 1H), 4.66 (m, 1H), 7.25–7.40 (m, 5H); ^{13}C NMR (100 MHz) δ 12.3 (q), 24.9 (t), 28.3 (q), 48.3 (d), 63.6 (d), 72.3 (t), 79.6 (s), 85.3 (d), 125.8 (d), 127.6 (d), 128.4 (d), 140.3 (s), 155.1 (s).

4.9.7.2. 3(R)-(N-tert-Butoxycarbonylamino)-4(R*)-ethyl-2(R*)-phenyltetrahydrofuran (**26f**).* Colorless solid, yield 67 mg (33%). Mp 89 °C; R_f=0.40, hexane/EtOAc 5:1; IR (neat) 3352, 3067, 3033, 3013, 2955, 2932, 2875, 1685, 1532, 1455, 1391, 1299, 1240, 1167, 1040, 1017, 979, 756, 694 cm^{-1}; MS (ESI) *m*/*z* 314 ([M+Na$^+$], 100); MS (EI) *m*/*z* 234 (11), 218 (5), 174 (40), 161 (18), 145 (28), 129 (17), 107 (14), 105 (12), 91 (13), 84 (31), 77 (13), 70 (12), 57 (85), 56 (100); HRMS (EI) calcd for $C_{13}H_{16}NO_3$ ([M−^{t}Bu]$^+$) 234.1130, found: 234.1129; ^{1}H NMR (400 MHz) δ 0.95 (t, *J*=7.5 Hz, 3H), 1.29 (s, 9H), 1.45 (m, 1H), 1.69 (m, 1H), 2.08 (m, 1H), 3.57 (t, *J*=8.7 Hz, 1H), 4.15 (m, 2H), 4.31 (dd, *J*=8.7, 7.6 Hz, 1H), 5.05 (br d, *J*=4.9 Hz, 1H), 7.24–7.27 (m, 3H), 7.31–7.35 (m, 2H); ^{13}C NMR (100 MHz) δ 12.4 (q), 24.5 (t), 28.2 (q), 47.0 (d), 59.2 (d), 72.1 (t), 79.3 (s), 81.5 (d), 126.2 (d), 127.2 (d), 128.1 (d), 138.5 (s), 155.4 (s).

4.9.8. 3(R)-(N-tert-Butoxycarbonylamino)-4(R*)-(1(S*)-chloroethyl)-2(R*)-phenyltetrahydrofuran (**27f**).* Colorless solid, yield 55 mg (24%). Mp 122 °C; R_f=0.45, hexane/EtOAc 5:1; IR (neat) 3322, 2978, 2935, 2901, 1703, 1536, 1457, 1366, 1338, 1290, 1251, 1166, 1132, 1045, 1022, 907, 723 cm^{-1}; MS (EI) *m*/*z* 270/268 (4/13), 254/252 (2/6), 210/208 (6/18), 194 (10), 172 (35), 145 (40), 128 (17), 118 (27), 107 (14), 105 (16), 91 (11), 84 (63), 77 (18), 57 (100), 55 (13); Anal. Calcd for $C_{17}H_{24}ClNO_3$ (325.83): C 62.67 H 7.42 N 4.30. Found: C 62.77 H 7.69 N 4.20. ^{1}H NMR (300 MHz, C_6D_6) δ 1.25 (d, *J*=6.2 Hz, 3H), 1.26 (s, 9H), 1.92 (dq, *J*=8.7, 6.2 Hz, 1H), 3.55 (t, *J*=8.7 Hz, 1H), 3.74 (dq, *J*=8.7, 6.2 Hz, 1H), 3.99 (d, *J*=9.4 Hz, 1H), 4.12 (t, *J*=8.7 Hz, 1H), 4.27 (dt, *J*=9.4, 6.2 Hz, 1H), 4.79 (d, *J*=6.2 Hz, 1H), 7.04–7.09 (m, 1H), 7.13–7.19 (m, 2H), 7.27–7.29 (m, 2H); ^{13}C NMR (75 MHz, C_6D_6) δ 23.8 (q), 27.9 (q), 55.0 (d), 57.5 (d), 58.9 (d), 69.5 (t), 78.6 (s), 82.8 (d), 126.5 (d), 127.3 (d), 128.0 (d), 137.7 (s), 154.7 (s).

4.10. Reduction of 3a to 4(*R**)-(1-chloro-1-methylethyl)-2(*R**)-phenyldihydrofuran-3-one oxime (28a)

To a stirred solution of **3a** (141 mg, 0.52 mmol) in 7 mL EtOH was added 1.3 mL 10% HCl and zinc dust (120 mg, 1.82 mmol) at 30 °C. The mixture was stirred at the same temperature for 24 h. Another 1.3 mL 10% HCl and Zn dust (120 mg, 1.82 mmol) were added and stirring was continued for three days at 30 °C. The reaction mixture was diluted with 10 mL EtOAc, filtered, concentrated, diluted with 10 mL EtOAc, and washed with a saturated solution of $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the residue after evaporation was purified by column chromatography (hexane/EtOAc, gradient 10:1 to 2:1). Colorless solid, yield 49 mg (37%). Mp 80 °C; R_f=0.40, hexane/EtOAc 10:1; IR (neat) 3270, 3065, 3034, 2982, 2931, 2881, 1724, 1452, 1372, 1271, 1208, 1183, 1111, 1066, 1049, 999, 951, 931, 902, 757, 696 cm^{-1}; MS (EI) *m*/*z* 255/253 (M$^+$, 3/8), 238/236 (9/30), 107 (90), 105 (100), 94 (10), 82 (14), 79 (28), 77 (58), 67 (14), 51 (28); HRMS (EI) calcd for $C_{13}H_{16}{}^{35}ClNO_2$ 253.0869, found 253.0871; ^{1}H NMR (400 MHz) δ 1.72 (s, 3H), 1.82 (s, 3H), 3.40 (m, 1H), 4.21 (dd, *J*=9.5, 6.5 Hz, 1H), 4.30 (ddd, *J*=9.5, 7.7, 0.4 Hz, 1H), 5.71 (d, *J*=0.8 Hz, 1H), 7.11 (br s, 1H), 7.30–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 28.2 (q), 32.7 (q), 54.0 (d), 69.6 (t), 70.5 (s), 80.1 (d), 127.5 (d), 128.3 (d), 128.5 (d), 137.6 (s), 162.4 (s).

4.11. Hydrogenation of tetrahydrofurans 3a and 4a by palladium on charcoal

The palladium catalyst (10 mg, 10% Pd on activated charcoal) was placed into an autoclave and a solution of **3a** or **4a** (100 mg, 0.36 mmol) in 7 mL EtOH was added. The autoclave was flushed three times with hydrogen and charged with H_2 to 20 bar at 20 °C for the given time (see Scheme 10). Subsequently, Et_3N (0.10 mL, 0.72 mmol) and Boc_2O (168 mg, 0.77 mmol) were added. The reaction mixture was stirred overnight, filtered, concentrated in vacuum, and the crude products were purified by flash chromatography (hexane/EtOAc, gradient 10:1 to 2:1).

*4.11.1. N-tert-Butoxycarbonyl-2-(3-methylbutoxy)-2-phenylethylamine (**30a**).* Colorless oil, for yields and ratios, see Scheme 10 and Table 4. R_f=0.56, hexane/EtOAc 5:1; IR (neat) 3454, 3357, 3064, 3031, 2958, 2930, 2871, 1710, 1497, 1453, 1390, 1366, 1270, 1249, 1167, 1098, 1069, 981, 863, 755, 701 cm^{-1}; MS (EI) *m*/*z* 307 (M$^+$, 30), 177 (80), 107 (100), 79 (15), 77 (13), 71 (53), 57 (18), 55 (10), 43 (63); Anal. Calcd for $C_{18}H_{29}NO_3$ (307.43): C 70.32 H 9.51 N 4.56. Found: C 70.27 H 9.68 N 4.48. ^{1}H NMR (400 MHz) δ 0.85 (d, *J*=6.6 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 1.44 (s, 9H), 1.47 (m, 2H), 1.69 (non, *J*=6.6 Hz, 1H), 3.15 (dd, *J*=13.3, 4.5 Hz, 1H), 3.30 (dt, *J*=9.3, 6.6 Hz, 1H), 3.40 (dt, *J*=9.3, 6.6 Hz, 1H), 3.48 (m, 1H), 4.33 (dd, *J*=4.5, 3.0 Hz, 1H), 4.93 (br s, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (100 MHz) δ 22.5 (q), 22.7 (q), 25.0 (d), 28.4 (q), 38.7 (t), 47.1 (t), 67.5 (t), 81.0 (d), 85.2 (s), 126.6 (d), 127.8 (d), 128.5 (d), 140.0 (s), 155.9 (s).

4.12. Hydrogenation of tetrahydrofurans 3a,b, 4a, and 18a, 19a by Raney nickel (general procedure)

(a) Preparation of Raney nickel catalyst: Raney nickel alloy (230 mg) was treated with 360 mg NaOH dissolved in 3.5 mL H_2O at 80 °C under N_2 atmosphere for 30 min. The solvent was decanted and the solid washed to neutral pH with water and subsequently several times with dry EtOH without letting the catalyst become dry. (b) Reduction: freshly prepared wet Raney nickel catalyst was placed into an autoclave and a solution of **3**, **4**, **18a** or **19a** (0.29 mmol) in 5 mL EtOH was added. The autoclave was flushed three times with hydrogen and charged with H_2 to working pressure at the desired reaction temperature for the given time (see Table 4). The reaction mixture was cooled to room temperature and Et_3N (0.08 mL, 0.58 mmol) and Boc_2O (135 mg, 0.62 mmol) were added subsequently. The reaction mixture was stirred overnight, filtered, concentrated in vacuum and the crude products were purified by flash chromatography (hexane/EtOAc, gradient 10:1 to 2:1).

4.12.1. 3(R)-(N-tert-Butoxycarbonylamino)-2(R*)-methyl-4-phenylbutanol (**31b**).* Colorless solid, for yields and ratios, see Table 4. Mp 89 °C; R_f=0.25, hexane/EtOAc 2:1; IR (neat) 3447, 3363, 3065, 3031, 2984, 2930, 2884, 1679, 1520, 1445, 1390, 1313, 1275, 1251, 1170, 1041, 1008, 777, 754, 700 cm^{-1}; MS (ESI) *m*/*z* 302 ([M+Na$^+$], 100); MS (EI) *m*/*z* 206 (8), 188 (35), 132 (70), 120 (15), 102 (13), 91

(26), 88 (73), 57 (100), 44 (18); Anal. Calcd for $C_{16}H_{25}NO_3$ (279.37): C 68.79 H 9.02 N 5.01. Found: C 68.69 H 8.98 N 4.98. ^{1}H NMR (400 MHz) δ 1.14 (d, J=6.9 Hz, 3H), 1.36 (s, 9H), 1.55 (m, 1H), 1.78 (br s, 1H), 2.71 (dd, J=14.2, 8.1 Hz, 1H), 2.99 (dd, J=14.2, 5.1 Hz, 1H), 3.47 (m, 1H), 3.77–3.87 (m, 2H), 4.68 (br d, J=9.1 Hz, 1H), 7.19–7.32 (m, 5H); ^{13}C NMR (100 MHz) δ 15.4 (q), 28.6 (q), 38.7 (t), 39.2 (d), 53.6 (d), 64.9 (t), 79.9 (s), 126.7 (d), 128.8 (d), 129.5 (d), 138.4 (s), 157.1 (s).

*4.12.2. Methyl 3-(tert-butoxycarbonylamino)-4-isopropyltetrahydrofuran-2-carboxylates (**22j**,**23j**).* The following analyses were performed on the diastereomeric mixture before further separation. IR (neat) 3260, 3135, 3004, 2967, 2936, 2876, 1756, 1694, 1478, 1451, 1434, 1389, 1364, 1200, 1160, 1093, 1067, 995, 931, 917, 781, 716, 698 cm^{-1}; MS (EI) m/z 172 (18), 154 (16), 142 (19), 99 (45), 69 (13), 59 (22), 57 (100), 56 (95); Anal. Calcd for $C_{14}H_{25}NO_5$ (287.35): C 58.52 H 8.77 N 4.87. Found: C 58.47 H 8.81 N 4.88.

4.12.2.1. Methyl 3(S)-(tert-butoxycarbonylamino)-4(R*)-isopropyltetrahydrofuran-2(S*)-carboxylate (**22j**).* Colorless solid, yield 53 mg (64%). Mp 110 °C; R_f=0.40, hexane/EtOAc 5:1; ^{1}H NMR (400 MHz) δ 0.89 (d, J=6.6 Hz, 3H), 0.97 (d, J=6.6 Hz, 3H), 1.46 (s, 9H), 1.59 (m, 1H), 2.05 (m, 1H), 3.61 (br t, J=8.4 Hz, 1H), 3.77 (s, 3H), 4.28 (br t, J=8.4 Hz, 1H), 4.42 (m, 1H), 4.44 (s, 1H), 4.76 (br d, J=8.2 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.56 (q), 21.62 (q), 26.9 (d), 28.3 (q), 48.5 (d), 52.3 (q), 55.9 (d), 72.0 (t), 80.0 (s), 84.3 (d), 155.1 (s), 171.7 (s).

4.12.2.2. Methyl 3(S)-(tert-butoxycarbonylamino)-4(S*)-isopropyltetrahydrofuran-2(S*)-carboxylate (**23j**).* Colorless solid, yield 30 mg (36%). Mp 91 °C; R_f=0.37, hexane/EtOAc 5:1; ^{1}H NMR (500 MHz) δ 0.88 (d, J=6.7 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H), 1.44 (s, 9H), 1.70 (dsept, J=8.8, 6.7 Hz, 1H), 1.83 (m, 1H), 3.76 (s, 3H), 3.80 (br t, J=9.0 Hz, 1H), 4.11 (dd, J=9.0, 8.0 Hz, 1H), 4.17 (m, 2H), 4.69 (br s, 1H); ^{13}C NMR (126 MHz) δ 20.6 (q), 21.0 (q), 28.3 (q), 29.8 (d), 52.3 (q), 52.8 (d), 58.6 (d), 71.2 (t), 79.9 (s), 82.6 (d), 154.6 (s), 171.8 (s).

4.12.3. Methyl 3(S)-(tert-butoxycarbonylamino)-4(S*)-(1-chloro-1-methylethyl)-tetrahydrofuran-2(S*)-carboxylate (**29j**).* Colorless solid as a mixture with **23j**, yield 28 mg (30%). R_f=0.33, hexane/EtOAc 5:1; ^{1}H NMR (500 MHz) δ 1.44 (s, 9H), 1.55 (s, 3H), 1.63 (s, 3H), 2.53 (m, 1H), 3.77 (s, 3H), 4.05 (dd, J=9.3, 8.2 Hz, 1H), 4.19 (t, J=9.3 Hz, 1H), 4.30 (br d, J=5.5 Hz, 1H), 4.36 (m, 1H), 4.88 (br d, J=8.4 Hz, 1H); ^{13}C NMR (126 MHz) δ 28.3 (q), 30.2 (q), 31.5 (q), 52.4 (q), 57.4 (d) 58.0 (d), 66.9 (s), 70.2 (t), 79.9 (s), 82.7 (d), 154.6 (s), 170.9 (s).

*4.12.4. Methyl 3-(N-tert-butoxycarbonylamino)-2-(3-methylbutoxy) propionate (**30j**).* Colorless oil, yield 26 mg (31%) from **18a** and 13 mg (15%) from **19a**. R_f=0.44, hexane/EtOAc 5:1; IR (neat) 3374, 2956, 2933, 2872, 1746, 1715, 1509, 1458, 1391, 1366, 1248, 1203, 1162, 1126, 982, 863 cm^{-1}; MS (ESI) m/z 312 ([M+Na$^+$], 100); MS (EI) m/z 231 (18), 171 (10), 160 (16), 91 (12), 71 (23), 69 (29), 59 (25), 57 (48), 55 (22), 44 (100); Anal. Calcd for $C_{14}H_{27}NO_5$ (289.37): C 58.11 H 9.40 N 4.84. Found: C 58.59 H 9.39 N 4.93. ^{1}H NMR (400 MHz) δ 0.90 (d, J=6.7 Hz, 3H), 0.91 (d, J=6.7 Hz, 3H), 1.44 (s, 9H), 1.46–1.53 (m, 2H), 1.72 (non, J=6.7 Hz, 1H), 3.37 (m, 1H), 3.40 (dt, J=9.2, 6.8 Hz, 1H), 3.53 (m, 1H), 3.68 (m, 1H), 3.75 (s, 3H), 3.96 (br dd, J=5.6, 4.4 Hz, 1H), 4.91 (m, 1H); ^{13}C NMR (100 MHz) δ=22.5 (q), 24.9 (d), 28.3 (q), 38.3 (t), 42.6 (t), 52.0 (q), 69.5 (t), 77.8 (d), 79.7 (s), 155.8 (s), 171.5 (s).

*4.12.5. N-tert-Butoxycarbonyl-2-(3-methyl-2-butenyloxy)-2-phenylethylamine (**33a**).* Colorless oil, yield 16 mg (35%). R_f=0.47, hexane/EtOAc 5:1; IR (neat) 3557, 3063, 3029, 2975, 2931, 2871, 1700, 1500, 1454, 1391, 1366, 1250, 1168, 1097, 1067, 1027, 863, 755, 701 cm^{-1}; GC–MS (EI) m/z 231 (78), 108 (10), 107 (100), 105 (10), 79 (18), 77 (12), 71 (63), 59 (14), 57 (36); Anal. Calcd for $C_{18}H_{27}NO_3$ (305.41): C 70.79 H 8.91 N 4.59. Found: C 70.72 H 9.17 N 4.62. ^{1}H NMR (200 MHz) δ 1.44 (s, 9H), 1.56 (s, 3H), 1.75 (s, 3H), 3.20 (dd, J=8.7, 4.4 Hz, 1H), 3.39 (m, 1H), 3.80 (dd, J=11.3, 7.6 Hz, 1H), 3.91 (dd, J=11.3, 6.9 Hz, 1H), 4.40 (dd, J=8.7, 4.0 Hz, 1H), 4.96 (m, 1H), 5.36 (m, 1H), 7.26–7.37 (m, 5H); ^{13}C NMR (50 MHz) δ 18.0 (q), 25.8 (q), 28.4 (q), 47.0 (t), 65.3 (t), 79.2 (s), 80.1 (d), 120.8 (d), 126.7 (d), 127.9 (d), 128.5 (d), 137.5 (s), 139.8 (s), 155.7 (s).

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Supplementary data

Experimental procedures, analytical characterization, and configuration assignment of all new compounds. Copies of ^{1}H and ^{13}C NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.11.023.

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