Three-step assembly of 4-aminotetrahydropyran-2-ones from isoxazoline-2-oxides†

A. S. Naumova,ab A. A. Mikhaylov,∗a Yu. A. Khomutova,a R. A. Novikov,a D. E. Arkhipov,c A. A. Koryukovc and S. L. Ioffe∗a

Tetrahydropyran-2-ones with a 4-amino function connected to a tertiary carbon atom – a widely naturally occurring fragment – are constructed by a three step protocol from easily available isoxazoline 2-oxides. In the first stage, the carbon skeleton of the target product is formed upon a C,C-coupling of a silyl ketene acetal with a nitronate function, under silyl triflate catalysis. The key step of the assembly consists of the oxidative cleavage of an endocyclic N–O bond of intermediate cyclic nitroso acetals with mCPBA, accompanied with lactone ring closure, and gives rise to β-nitro-δ-lactones in 63–85% yields. The latter are reduced with amalgamated aluminium, to furnish the target scaffold.

A common retrosynthetic analysis for the β-amino acid moiety in lactones 1 employs a Mannich-type disconnection with the γ-imino alcohol cations A as key precursors for the generation of amines 1 (Scheme 1). However, this type of reaction is not generally applied, due to the complexity of the Mannich reaction with ketimines, although the approach could provide the fast and simple assembly of the target molecule 1.

Our recent results in the area of five-membered cyclic nitronates chemistry suggest that the easily available five-membered nitronates 2 (isoxazoline 2-oxides) can serve as useful synthetic equivalents for ketiminium cations A (Scheme 1) in the reaction with a silyl ketene acetal, but this approach requires an additional step for the reduction of both of the N–O bonds and the cyclization of the resulting products.

Introduction

The 4-aminosubstituted six-membered lactone scaffold (marked as structure 1 in Fig. 1), derived from β-amino acids, occurs in different classes of natural products, like stephadiamine,1 kopsihainin D2 and the tetrodotoxin (TTX) family (Fig. 1), exhibiting various biological activities. In particular, TTX and its congeners constitute the key components of the puffer fish fugu poison and due to their complex structure are considered as classical objects for total synthesis. However, few syntheses of these compounds have succeeded.7–10 Difficulties usually arise from the construction of the stereogenic quaternary carbon center connected with an amine (further guanidine) function. For this purpose, non-trivial or indirect methods such as Beckmann7b and Overman† rearrangements, asymmetric transferring Strecker synthesis or chiral Rh-catalyzed C–H nitrene insertion have to be employed. Therefore, the development of simple, direct methods for the construction of lactones 1 is an urgent task.

In this manuscript a convenient strategy for the synthesis of the scaffold 1 is suggested, which is based on a detailed investigation of the transformations of cyclic nitronates.11

† Electronic supplementary information (ESI) available: Copies of 1H, 13C and two-dimensional NMR spectra for all novel compounds, CCDC 959160 and 959161. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ra47309k

Fig. 1 Selected natural products containing β-alkyl-β-amino-δ-valerolactone moiety 1.
Thus, the suggested strategy starts with the coupling of nitronates 2 with silyl ketene acetal. This transformation, like other Mukaiyama–Mannich reactions, requires a Lewis acid catalyst – tert-butylidemethylsilyl triflate (TBSOTf), in particular – for the production of nitroso acetal 3 (Scheme 2) in a rather highly diastereoselective fashion. The products 3 contain the complete carbon skeleton of the target amines 1 and for their transformation into lactones 1, only the transformations of the functional groups is required. However, the direct reduction of compounds 3 into amines 1 with both N–O bonds cleavage and lactone ring closure, within one step protocol turned out to be ineffective. A more convenient approach seems to employ two steps (Scheme 2): (1) lactone cycle formation via oxidation of isoxazolidines 3 into nitro compounds 4; (2) selective nitro group reduction in lactones 4. This modified scheme is supported with our recent research on the six-membered analogues of nitroso acetal 3 which are effectively oxidized with mCPBA into the corresponding nitro compounds with the retention of the relative configuration of all the stereocenters.

A nitro group connected to a tertiary carbon in lactones 4 can be a priori regarded as a latent amine function, due its inertness to common reagents. Therefore, in this manuscript, the main accent was on the preparation of the nitroso acetal 3 (step 2 → 3) and their oxidation to nitro lactones 4.

**Results and discussion**

Starting from the available nitronates 2 (ref. 11), a representative series of functionalized nitroso acetal 3a–h was obtained via silyl ketene acetal addition, according to a well-known protocol, or its modified version (Table 1, see the Experimental section for details). Only three of these: compounds trans-3a, 3g (inseparable mixture of isomers trans/cis 5.5:1) and trans-3d (containing 8% of the cis-isomer) have been obtained previously. The synthesis of the derivatives trans-3b and cis-3b proceeded in a rather similar way, although for 3e the trans-selectivity was apparently decreased in comparison with the analogous 3d.

To the best of our knowledge, no 4-substituted nitronates 2 were introduced in this type of reaction beforehand. These compounds were found to exhibit nearly a 100% trans-selectivity in coupling with the silyl ketene acetal, but required prolonged reaction times. The synthesis of the 4-phenyl-substituted trans-3c was completed in only 24 h with 0.2 equivalents of TBSOTf. The synthesis of the even more bulky bicyclic trans-3f required a full equivalent of the promoter within 8 h exposure at −78 °C. The trans-position of the substituent at C-4 and the introduced ketene acetal residue was proved by NOE NMR experiments (see Fig. 3).

The electrophilic activity of the nitronate 2h, containing a halomethyl group at C-3, might appear in two different fashions – nucleophile addition at the C=N bond, or its halogenation. Fortunately, the nitronate 2h (R = Br) reacted with the silyl
ketene acetal in a usual fashion, to give the respective nitroso acetal 3b (trans/cis = 8 : 1).

For the elaboration of the second stage of the suggested protocol (Scheme 2, 3 → 4) the oxidation was optimized on the model nitroso acetal 3a. When the conditions, previously reported for 6-membered cyclic analogues of 3,15 were applied to 3a (Scheme 3), protocol (i), the target nitro lactone 4a was obtained in only a 55% yield, along with the nitrous acid elimination product 5a (8%) and a mixture of unidentified linear by-products. The best result (Scheme 3), conditions (ii), achieved with sole mCPBA utilization and prolongation of the reaction time up to 3 days, accomplished the lactone ring-closure step. With the latter process in hand, this increased the isolated yield of the nitro lactone 4a to 85%.

The optimized oxidation conditions were applied to the whole nitroso acetal 3 series. The individual diastereomers of the 5- or 4-aryl substituted nitroso acetals trans-3a–c and cis-3b were smoothly oxidized to give the desired lactones 4a–c and 4b' in moderate to high yields with the retention of configuration of all the stereocenters (Table 2, entries 1–4). The R'CH₂-substituted at C-3 nitroso acetals 3f–h (R' = Ph, Br, entries 7–9), that were usually used as diastereomeric mixtures, also gave the target nitro lactones 4f–h, but a longer reaction time was required. When the nitroso acetals 3d,e, with the electron-withdrawing CO₂Me group at C-5 were employed (entries 5–6), only the formation of acyclic γ-nitro alcohols 6d,e – the proposed precursors of lactones 4 – was observed, reasonably due to the lower nucleophilicity of the alcohol function in these substrates. Even more acidic conditions (Amberlyst-15®), did not manage to achieve the cyclization of 6d and 6e into the corresponding lactones, 4d and 4e.

The configurations of compounds 4b and 4h were supported by X-ray diffraction analysis (Fig. 2). The stereochemistry of the other nitro lactones 4 was assigned by the similarity of their coupling constants with those of 4b and 4h in the 1H NMR spectra. The nitro group formation in all of the compounds 4 was proven by 14N NMR.

The last step of the lactones 1 preparation – selective reduction of the nitro group – despite many precedents in the literature for tertiary nitro compounds17,19 – turned out to be rather capricious. The standard hydrogenation conditions, like Pd/C in MeOH performed on 4a gave only the acyclic product 7 in almost a quantitative yield as the result of the hydrogenolysis of the CH(Ph)–OC(O) fragment (Scheme 4). The other screened reagents (NaBH₄/NiCl₂,20 Fe/AcOH,19 Fe/NH₄Cl19 and even H₂/Ni₂O₃17,19) gave mainly the “HNO₃” elimination product 5a, along with by-products, of unknown structures. [A more convenient protocol for the synthesis of enones 5 from lactones 4 was developed with the utilization t-BuOK in THF. It furnished compounds 5a and 5e with 94% and 95% yields, within 15–30 minutes, respectively (Scheme 4)].

In these circumstances, we managed to reduce the nitro group with the rarely used amalgamated aluminium.21 The most complicated intermediates – nitro compounds 4a and 4b with the benzyl carboxylate function – gave the protected derivatives Boc-1a and Boc-1b of target amines in 52 and 57% yields, respectively (Scheme 4). For the extremely sterically hindered lactone 4e, a slightly modified procedure was applied, when the reduction and protection were divided into two technical steps. By this methodology and the utilization of a catalytic amount of DMAP for the Boc₂O activation, the desired product Boc-1c was obtained in a 79% yield.

Fig. 2 Molecular structures of 4b and 4h presented in thermal ellipsoids at 50% probability. Hydrogen atoms are omitted for clarity.

Fig. 3 Key NOE correlations for trans-3c and trans-3f.

Scheme 3 Optimization of nitroso acetal 3 oxidation.
Conclusions

In summary, we have demonstrated that the target \(\beta\)-amino-\(\delta\)-lactones 1, or more precisely, their N-Boc derivatives, can be obtained from the five-membered cyclic nitronates 2, according to the suggested three-step protocol. The novelty of the approach consists of the combination of three transformations (\(C,C\)-coupling, oxidation and selective reduction of the NO\(_2\) group). This procedure was applied to the synthesis of scaffolds 1 for the first time. In our opinion, there are no obstacles for the accomplishment of this strategy in an asymmetric manner.

Experimental section

General remarks

Reactions with TBSOTf were performed in oven-dried (150 °C) glassware under an argon atmosphere. The NMR spectra were recorded on a Bruker AM-300 (\(^1H\): 300.13 MHz, \(^{13}C\): 75.47 MHz, \(^{14}N\): 21.69 MHz, \(^{29}Si\): 59.63 MHz) and Bruker AMX-400 (\(^1H\): 400.1 MHz, \(^{13}C\): 100.6 MHz) and referenced to a residual solvent peak. The chemical shifts are reported in ppm (\(\delta\)); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). The ratios of the stereoisomers were derived from the relative integral intensities of the characteristic signals in the \(^1H\) NMR spectra. Coupling constants, \(J\), are reported in Hertz. Key NOESY correlations are shown with arrows (Fig. 2). The IR spectra were recorded on a Bruker VEKTOR-22 in the range 400–4000 cm\(^{-1}\) (resolution 2 cm\(^{-1}\)) as a thin layer. The melting points were determined on Kofer melting point apparatus and are uncorrected. The elemental analyses were performed by the Analytical Laboratory of the N. D. Zelinsky Institute of Organic Chemistry. The HR mass spectra were recorded on a Bruker MicroTOFF spectrometer with electrospray ionization (ES-I).

The X-ray diffraction measurements were carried out using SMART 1000 CCD and Smart APEX II diffractometers at 100 K.

Table 2 Oxidation of nitro acetals 3 series

| # | Nitro acetal 3 (substituents) | Reaction time, days | Product, yield, % (trans/cis dr\(^a\)) |
|---|---|---|---|
| 1 | trans-3a (R = 5-Ph, R' = H) | 3 | 4a, 85 |
| 2 | trans-3b (R = 5-(4-BrC\(_6\)H\(_4\)), R' = H) | 3 | 4b, 79 |
| 3 | cis-3b (R = 5-(4-BrC\(_6\)H\(_4\)), R' = H) | 3 | 4b', 63 |
| 4 | trans-3c (R = 4-Ph, R' = H) | 2 | 4c, 76 |
| 5 | 3d, trans/cis, 11/1 (R = 5-CO\(_2\)Me, R' = H) | 1 | 6d/6d', 95 (15 : 1) |
| 6 | 3c, trans/cis, 5.2/1 (R = 5-CO\(_2\)Me and 5-Me, R' = H) | 1 | 6e/6e', 92 (6.3 : 1) |
| 7 | 3f, trans/cis, 8/1 (R = cis-4,5-(CH\(_2\))\(_3\), R' = Ph) | 7 | 4f, 64 |
| 8 | 3g, trans/cis, 5.5/1 (R = 5-Ph, R' = Ph) | 5 | 4g/4g', 79 (6.5 : 1) |
| 9 | 3h, trans/cis, 8/1 (R = 5-Ph, R' = Br) | 5 | 4h, 85 (>20 : 1) |

\(^a\) Determined by \(^1H\) NMR spectra.

Scheme 4 Reduction and accompanying reactions of nitro lactones 4a–c.

Conclusions

In summary, we have demonstrated that the target \(\beta\)-amino-\(\delta\)-lactones 1, or more precisely, their N-Boc derivatives, can be obtained from the five-membered cyclic nitronates 2, according to the suggested three-step protocol. The novelty of the approach consists of the combination of three transformations (\(C,C\)-coupling, oxidation and selective reduction of the NO\(_2\) group). This procedure was applied to the synthesis of scaffolds 1 for the first time. In our opinion, there are no obstacles for the accomplishment of this strategy in an asymmetric manner.
The frames were integrated and corrected for absorption by the APEX 2 program package [APEX2 Software Package, Bruker AXS Inc., 5465, East Cheryl Parkway, Madison, WI 53177, 2005]. The details of crystallographic data and experimental conditions are given in Table S11 in the ESI.† The structures were solved by a direct method and refined by the full-matrix least-squares technique against F2 in the anisotropic–isotropic approximation. The hydrogen atoms were located from the difference Fourier maps and refined in a rigid body model. All the calculations were performed using the APEX 2 program package [APEX2 Software Package, Bruker AXS Inc., 5465, East Cheryl Parkway, Madison, WI 53177, 2005].

The analytical thin-layer chromatography was performed on silica gel plates, with the QF-254 indicator. The visualization of the TLC plates was accomplished with a UV light and/or anisaldehyde/H2SO4. The preparative liquid chromatography was performed on columns with “Merck”-silica (Kieselgel 60, 230–400 mesh). All the solvents for the chromatography and extractions were of technical grade and distilled prior to use. The following solvents and reagents were distilled from the indicated drying agents: CH2Cl2, CHCl3, Et3N (CaH2), MeOH (Mg), THF, dioxane (LiAlH4).

### Synthesis of nitroso acetics 3 (first step, see Scheme 3)

**Nitroso acetics trans-3b and cis-3b.** TBSOT (150 μL, 173 mg, 0.65 mmol) was added at −78 °C to a stirred solution of 5-(4-bromophenyl)-3-methyl-isoxazole-2-oxide 2b (837 mg, 3.27 mmol), 1-(tert-butyl(dimethyl)silyloxy)-3-methylisoxazolidin-3-yl)acetate 0.65 mmol) was added at.

The following solvents and reagents were distilled from the given in Table SI1 in the ESI.

Details of crystallographic data and experimental conditions are.

The precision of the NMR measurements was refined by the full-matrix least-squares calculation. The chemical shifts are given in Table SI1 in the ESI.

The residual water was removed by lyophilization. The residue was subjected to column chromatography (eluents EA–hexane 1:40 → 1:20 → 1:10) to give the separation of all diastereomers, trans-3b (852 mg, 59%) and cis-3c (237 mg, 16%) each as a slowly crystallizing colorless oil (dr 3.5 : 1).

### Methyl **rel-(2R,3S,5R)-5-(4-bromophenyl)-(2-tert-butylidimethylsilyloxy)-3-methylisoxazol-3-yl)acetate cis-2b.** Mp = 46 °C (pentine), TLC: Rf = 0.51 (hexane–EtOAc, 3/1); 1H NMR (300.13 MHz, 323 K, CDCl3); δ = 0.17 and 0.19 [2s, 6H, Si(CH3)3], 0.91 [s, 9H, t-Bu], 1.34 [3s, 3H, Me], 2.52 [t, J = 12.0 Hz, 1H, CH2CH3], 2.59–2.68 [m, 2H, CH2CH3 and CH2H4(CO2Me)], 2.90 [d, J = 14.9 Hz, 1H, CH2H4(CO2Me)], 3.70 [s, 3H, CO2Me], 5.25 [dd, J = 7.8 Hz, 1H, CH], 7.36 [d, J = 8.3 Hz, 2H, CH3-Ar] and 7.44 [d, J = 8.3 Hz, 2H, CH3-Ar] ppm; 13C NMR (75.47 MHz, 299 K, CDCl3); δ = −4.9 and −4.6 [Si(CH3)3], 17.8 [C(CH3)3], 21.9 [CH3], 26.0 [C(CH3)3], 41.5 [CH2CO2Me], 43.7 [CH3], 51.4 [OCH3], 74.6 [CNO2], 84.6 [CH], 121.4 [C(F3)], 129.1 and 131.1 [CH-F3 and CH=CH-F3], 135.5 [CBr], 171.3 [CO = O] ppm; 29Si NMR (300 K, CDCl3); δ = 25.4 ppm.

C19H23NO4BrSi (444.44): calcd C, 51.35; H, 6.80; N, 3.15; found C, 51.66; H, 7.05; N, 3.38%.

### Methyl **rel-(2S,3R,5R)-2-(tert-butylidimethylsiloxy)-3-methyl-4-phenoxyisoxazol-3-yl)acetate trans-3c.** Obtained by the same procedure as 3b. The reaction was performed on 2.0 mmol scale with 24 h exposure. Yield 681 mg (93%); dr > 20:1; mp = 26 °C (pentine); TLC: Rf = 0.49 (hexane–EtOAc, 5:1); 1H NMR (400.1 MHz, 305 K, CDCl3); δ = 0.15 and 0.23 [2s, 6H, Si(CH3)3], 0.95 [s, 9H, t-Bu], 1.09 [s, 9H, Me], 2.56 [d, J = 14.9 Hz, 1H, CH2H4(CO2Me)], 2.77 [d, J = 14.9 Hz, 1H, CH2H4(CO2Me)], 4.07 [dd, J = 9.9, J = 7.9 Hz, 1H, CH], 4.26 [t, J = 7.9 Hz, 2H, CH2F], 4.59 [dd, J = 9.9, J = 7.9 Hz, 1H, CH2F], 7.27–7.35 [m, 5H, Ph] ppm; 13C NMR (100.6 MHz, 305 K, CDCl3); δ = −5.1 and −4.7 [Si(CH3)3], 18.1 [C(CH3)3], 20.4 [CH3], 26.0 [C(CH3)3], 40.3 [CH2CO2Me], 51.2 [OCH3], 52.1 [CH], 73.0 [OCH3], 76.6 [CN], 127.3 [CH3-F3], 128.4 and 129.3 [CH3-F3], 136.7 [C-F3], 170.7 [CO = O] ppm; 29Si NMR (300 K, CDCl3); δ = 26.1 ppm. C19H23NO4Si (365.45): calcd C, 62.43; H, 8.55; N, 3.83; found C, 62.53; H, 8.38; N, 3.84%.

### Methyl **(2S,3R,5R)-3-methoxy-carbonyl-3,5-dimethylisoxazol-5-carboxylate 3e.** Obtained by the same procedure as 3b on a 2.0 mmol scale. Yield 691 mg (96%), dr 5.2 : 1 (inseparable mixture), colorless oil; TLC: Rf = 0.66 (hexane–EtOAc, 1:1); 1H NMR (400.1 MHz, 305 K, CDCl3); rel-2S,3R,5R-isomer, trans-3e (major): δ = 0.11 and 0.20 [2s, 6H, Si(CH3)3], 0.89 [s, 9H, t-Bu], 1.13 [s, 3H, NCCH3], 1.69 [s, 3H, OCCH3], 2.50 [d, J = 14.7 Hz, 1H, CH2H4], 2.51 [d, J = 12.8 Hz, 1H, CH2H4(CO2Me)], 2.82 [d, J = 14.7 Hz, 1H, CH2H4(CO2Me)], 2.85 [dd, J = 12.8 Hz, 1H, CH2H4(CO2Me)], 3.66 [3s, 3H, CO2CH3], 3.73 [3s, 3H, CH2CO2CH3]; rel-2R,3S,5R-isomer, cis-3e (minor): δ = 0.08 and 0.17 [2s, 6H, Si(CH3)3], 0.84 [s, 9H, t-Bu], 1.27 [3s, 3H, NCCH3], 1.53 [3s, 3H, OCCH3], 2.50 [d, J = 14.7 Hz, 1H, CH2H4], 2.51 [d, J = 12.8 Hz, 1H, CH2H4(CO2Me)], 2.82 [d, J = 14.7 Hz, 1H, CH2H4(CO2Me)], 2.85 [dd, J = 12.8 Hz, 1H, CH2H4(CO2Me)], 3.66 [3s, 3H, CO2CH3], 3.68 [3s, 3H, CO2CH3] ppm; 13C NMR (100.6 MHz, 305 K, CDCl3); rel-2S,3R,5R-isomer, trans-3e (major): δ = −5.0 and −4.4 [Si(CH3)3], 17.8 [C(CH3)3], 22.8 [NCCH3], 26.8 [C(CH3)3], 28.5 [OCCH3], 42.1 [CH2CO2Me], 46.5 [CH3], 51.7 [CH2CO2CH3], 52.6 [CO2CH3], 74.4 [N-C], 88.6 [N-O–C], 171.4 [CH2CO2Me], 174.0 [CO2Me]; rel-2R,3S,5R-isomer, cis-3e (minor): δ = −4.9 and −4.4 [Si(CH3)3], 17.9 [C(CH3)3], 24.3 [NCCH3], 25.2 [C(CH3)3], 25.8 [OCCH3], 42.3 [CH2CO2Me], 44.1
Nitro lactone 4 formation (second step, see Scheme 3)

General procedure. The nitroso acetel 3 (1.0 mmol) and mCPBA (70%, 271 mg, 1.10 mmol) as a solution in CH₂Cl₂ (3.0 mL) were kept, with occasional shaking, at room temperature for 1–7 days (a green or blue color of reaction mixture after mCPBA addition was observed in several cases, due to the intermediacy of nitroso compounds). The reaction mixture was poured into a mixture of EtOAc (15 mL)/NaHCO₃ (12 mL, saturated aqueous solution). The aqueous layer was back-extracted with EtOAc (2 × 5 mL). The combined organic phase was washed with H₂O (10 mL), brine (10 mL) and dried over Na₂SO₄. The residue was evaporated in vacuo. The yield was found as colorless crystals.

rel-(4R,6R)-4-Methyl-4-nitrotetrahydro-2H-pyran-2-one 4a. Yield 199 mg (85%), mp = 92–95 °C (EtO₂), TLC: Rₜ = 0.43 (hexane–EtOAc, 1/1). IR (thin layer from CCl₄): 1573 (br vs., νC=O), 1547 (vs., νC=O), 1354 (s, νCNO₂), 1260 and 1286 (C₉H₇Ph and mp), 137.2 [C (CH₃)], 167.6 [OC (C₆H₅)]; ¹⁴N NMR (299 K, CDCl₃): δ = 16 (r₁/r₂ = 1/3) ppm; ¹³C NMR (299 K, CDCl₃): δ = 17.7 [C (CH₃)], 172.0 [OC = O] ppm; ²⁹Si NMR (300 K, CDCl₃): δ = 25.1 ppm; HRMS (ES-I) cored for C₁₂H₁₂BrNO₄S (314.13): calcd C, 45.88; H, 3.25; found C, 45.92; H, 3.27; N, 4.46; found C, 45.62; H, 3.27; N, 4.42%.

rel-(4R,6R)-4-Methyl-4-nitrotetrahydro-2H-pyran-2-one 4b. Yield 249 mg (79%), mp = 162–165 °C (EtO₂), TLC: Rₜ = 0.33 (hexane–EtOAc, 1/1). ¹H NMR (299.13 MHz, 312 K, CDCl₃): δ = 10.55 [s, 3H, CH₃], 5.37 [d, δ = 17.2 Hz, 1H, CH₂CH₃], 5.35 [d, δ = 17.2 Hz, 1H, CH₂CH₃], 5.28 [dd, δ = 10.5, 3.5 Hz, 1H, CH], 7.25 [d, δ = 8.0 Hz, 2H, CH₂], 7.56 [d, δ = 8.0 Hz, 2H, CH₂], 4.91 ppm; ¹³C NMR (297.47 MHz, 312 K, CDCl₃): δ = 25.7 [C (CH₃)], 40.1 [CH₂], 41.6 [CH₂], 76.5 [CH], 83.9 [CNO₂], 123.2 [CBr], 127.5 [C₆], 132.2 and 136.3 [C₆], 166.0 [OC = O] ppm; ²⁹Si NMR (312 K, CDCl₃): δ = 44.1 [C (CH₃)], 129.3 [C₆H₇Ph], 137.2 [C (CH₃)], 167.6 [OC = O] ppm; ¹³C NMR (300.13 MHz, 312 K, CDCl₃): δ = 0.36 [s, 3H, CH₃], 2.08 [d, δ = 14.5, 17.7 Hz, 1H, CH₂CH₃], 2.18 [dd, δ = 14.5, 17.7 Hz, 1H, CH₂CH₃], 2.18 [dd, δ = 14.5, 17.7 Hz, 1H, CH₂CH₃], 2.18 [dd, δ = 14.5, 17.7 Hz, 1H, CH₂CH₃], 1.85 ppm; HRMS (ES-I) cored for C₁₂H₁₂BrNO₄S (314.13): calcd C, 45.88; H, 3.25; found C, 45.92; H, 3.27; N, 4.46; found C, 45.62; H, 3.27; N, 4.42%.
4.78 [t, J = 3J = 11.7 Hz, 1H, CH3H2], 7.04 [d, J = 7.7 Hz, 2H, CH3Ph], 7.30–7.42 [m, 3H, CH3Ph and CH3-Ph] ppm; 13C NMR (100.6 MHz, 305 K, CDCl3); δ = 24.4 [CH3], 40.9 [CH3C=O], 48.4 [CH], 68.5 [OCH2], 87.7 [CNO2], 125.8 and 129.2 [CH3Ph and CH3Ph], 129.4 [CH3Ph], 132.4 [C1Ph], 166.7 [OC=O] ppm; 14N NMR (28.9 MHz, 299 K, CDCl3); δ = 7 (ν1 = 100 Hz) ppm; C12H13NO3 (235.24) calculated: C, 69.09; H, 5.57; N, 9.59; found C, 69.09; H, 5.56; N, 9.62.

**Dimethyl rel-(2R,4R)-2-hydroxy-4-methyl-6-nitroanisoloxacarboxylic acid** 6d.

Yield 237 mg (95%), oil, TLC: Rf = 0.30 (hexane-ETOAc, 1/1); 1H NMR (300.13 MHz, 299 K, CDCl3); δ = 1.75 [s, 3H, CH3], 2.43 [dd, J = 14.7, J = 10.4 Hz, 2H, CH2CH3], 2.58 [dd, J = 14.7, J = 2.6 Hz, 1H, CH3CH2], 3.09–3.24 [m, 3H, CH2CH2 and OH], 3.67 [s, 3H, COMe], 3.79 [s, 3H, COMe], 4.27 [dd, J = 10.4, J = 2.4 Hz, 1H, CH ppm; 13C NMR (75.47 MHz, 299 K, CDCl3); δ = 24.1 [CH3], 41.7 and 41.8 [CH2], 52.0 and 53.1 [OCH2], 67.3 [CH3], 87.1 [CNO2], 169.7 and 174.3 [OC=O] ppm; 14N NMR (299 K, CDCl3); δ = 14 (ν1 = 200 Hz) ppm; HRMS (ES-I) calculated for C11H13NO4Na [M + Na]+ 324.1050; found 334.1050.

**rel-(4R,4aS,7aR)-4-Benzyl-4-nitrohexahydrocyclopenta[b]pyran-2(3H)-one 4f.** Yield 178 mg (64%), mp = 105–107 °C (hexane-ETOAc, 1/1); TLC: Rf = 0.66 (hexane-ETOAc, 1/1); 1H NMR (300.13 MHz, 301 K, CDCl3); δ = 1.52 [dd, J = 17.7, J = 12.3, J = 7.4 Hz, 1H, CH3H2], 1.73–1.97 [m, 3H, CH2(2)], 5.7 [H, CH2(2)], 5.2 [H, CH2(2)], 2.03–2.16 [m, 2H, CH3(3)], 2.94 [dt, J = 9.1, J = 5.7 Hz, 1H, CH2(3)], 2.98 [s, 2H, CH2Ph], 3.10 [d, J = 14.3 Hz, 1H, CH2H2CO], 3.10 [d, J = 14.3 Hz, 1H, CH2H2CO], 5.00 [dd, J = 7.3, J = 4.9 Hz, 1H, OCH], 7.03 [dd, J = 6.5, J = 2.9 Hz, 2H, CH2Ph], 7.29–7.37 [m, 3H, CH2Ph, CH2Ph] ppm; 13C NMR (75.47 MHz, 301 K, CDCl3); δ = 22.2 [CH2-2], 26.2 [CH2-1], 32.7 [CH2Ph], 34.3 [CH2-3], 44.9 [CH2CO], 45.6 [CH2], 82.3 [OCH], 90.0 [CNO2], 128.3 [CH2Ph], 129.1 and 130.1 [CH2Ph and CH2Ph], 132.2 [C1Ph], 167.3 [OC=O] ppm; 14N NMR (299 K, CDCl3); δ = 8 (ν = 220 Hz) ppm; HRMS (ES-I) calculated for C18H17NO5Na [M + Na]+ 328.1050; found 328.1050.

**4-Benzyl-4-nitro-6-phenyltetrahydro-2H-pyran-2-one 4g/4g'.** Yield 245 mg (79%), dr 6.5:1 (insoluble mixture), mp = 129–135 °C (EtOAc), TLC: Rf = 0.47 (hexane-ETOAc, 1/1); 1H NMR (300.13 MHz, CDCl3); rel-4R,6R-isomer 4g (major): δ = 2.65 [dd, J = 15.4, J = 11.7 Hz, 1H, CH3H2], 2.78 [dd, J = 15.4, J = 3.7 Hz, 1H, CH3H2], 3.07 [dd, J = 6.9 Hz, 1H, CH3H2], 3.26 [d, J = 16.9 Hz, 1H, CH3H2], 3.41 [d, J = 14.0 Hz, 1H, CH3H2], 5.12 [dd, J = 11.7, J = 3.7 Hz, 1H, CH], 7.11–7.19 [m, 2H, CH2Ph], 7.25–7.44 [m, 8H, Ph]; rel-4S,6R-isomer 4g' (minor): δ (selected signals) = 2.86 [d, J = 14.0 Hz, 1H, CH3H2], 3.50 [d, J = 14.0 Hz, 1H, CH3H2], 5.22 [dd, J = 12.5, J = 2.0 Hz, 1H, CH ppm; 13C NMR (75.47 MHz, CDCl3); rel-4R,6R-isomer 4g (major): δ = 37.6, 40.3, 44.8, [3 CH2], 77.0 [CH], 87.9 [CNO2], 125.8, 128.6, 129.0, 129.1, 129.2 and 129.9 [CH3Ph], 132.4 and 137.5 [C1Ph], 167.4 [OC=O]; rel-4S,6R-isomer 4g' (minor): δ = 37.1, 40.4 and 45.8 [3 CH2], 77.3 [CH], 87.9 [CNO2], 126.0, 127.3, 128.4, 128.9, 129.0 and 129.9 [CH3Ph], 132.0 and 138.1 [C1Ph], 166.7 [OC=O] ppm; 14N NMR (299 K, CDCl3); δ = 15 (ν1 = 200 Hz) ppm; HRMS (ES-I) calculated for C16H15NO3Na [M + Na]+ 334.1050; found 334.1050.

**Reduction of nitro lactones 4 into carbamates Boc-1 (third step, see Scheme 3).**

**General procedure.** Aluminum foil was cut into strips (8 pieces, 20 × 5 mm, 120 mg, 5.2 mmol, 20 eq.). The clean meal surface was washed with hexane and EtO. After that, it was poured into a 2% HgCl2 solution in water (10 mL) for 15 s, then washed with MeOH, and EtO without drying. After all these preliminary preparations the solution was added to nitro lactone 4a or b (0.26 mmol, 1.0 eq.) as a solution in THF/H2O (9/1, 5 mL) with water bath cooling (Caution! exothermic reaction and hydrogen evolution). The reaction mixture was stirred for 1 hour and Boc-O (40 mg, 0.18 mmol, 1.5 eq.) was added. After an additional 18 hours, the reaction mixture was poured into a EtOAc (15 mL)/H2O (10 mL) mixture. The water layer was back-extracted with EtOAc (2 × 3 mL). The combined organic layers were washed with H2O (7 mL), brine (10 mL) and dried over Na2SO4. The solvents were evaporated in vacuum. The residue was subjected to column chromatography (eluent EtOAc-hexane, 1/5 → 1/3 → 1/5), to give the protected amine Boc-1a or Boc-1b, respectively, as a colorless solid.

**tert-Butyl 4-[rel-(2R,4R)-4-methyl-6-oxo-2-phenyltetrahydro-2H-pyran-4-yl]carbamate Boc-1a.** Yield: 41.3 kg (52%); mp = 99–101 °C (CDCl3); TLC: Rf = 0.35 (hexane-ETOAc, 1/1); 1H NMR (400 MHz, 305 K, CDCl3); δ = 1.14 [s, 9H, (CH3)3], 1.54 [s, 3H, CH3], 2.21 [dd, J = 15.6, J = 3.4 Hz, 1H, CH3H2], 2.48 [t, J = 14.0 Hz, 1H, CH3H2], 2.72 [d, J = 16.9 Hz, 1H, CH3H2], 3.08...
mixture was filtered through Celite® and washed with MeOH (3 mL)/H2O (4 mL), brine (4 mL) and dried over Na2SO4. The residue was dissolved in CH2Cl2 (2.0 mL). The organic layer was separated and the residue was evaporated in vacuo. The residue was subjected to column chromatography (eluent EtOAc–hexane, 1/1) to give 30.1 mg (94%) of the enone 5a.

ref-(4S,5S)-4-Amino-4-methyl-5-phenyltetrahydro-2H-pyran-4-ylcarbamate Boc-1c. To furnish the protected amine, BocO (59 mg, 0.31 mmol) along with DMAP (2 mg, cat.) was added to the 1c solution and the reaction mixture was stirred for 2.5 hours. The solvents were evaporated in vacuo. The residue was subjected to preparative thin layer chromatography (eluent hexane–EtOAc, 1/1) chromatography to give 70 mg (79%) of pure Boc-1c as a colorless oil, crystallized from CH2Cl2–pentane mixture. Mp 106–107 °C (pentane–EtOAc, 2/1), TLC: Rf = 0.31 (hexane–EtOAc, 1/1); 1H NMR (400.1 MHz, 305 K, CDCl3): δ = 1.36 [s, 3H, CH3], 1.42 [s, 9H, t-Bu], 2.29 [d, J = 17.2 Hz, 1H, CH2H3], 2.80 [d, J = 17.2 Hz, 1H, CH2H3], 3.24 [t, J = 7.8 Hz, 3H, CH3], 4.48 [dd, J = 11.2, J = 7.8 Hz, 1H, CH2H3], 4.57 [dd, J = 11.2, J = 6.7 Hz, 1H, CH2H3], 6.52 [br s, 1H, NH], 7.23 [dd, J = 7.8, 1H, CH2H3], 7.8–7.34 [m, 3H, CH3-phen and CH2-phen] ppm. 13C NMR (100.6 MHz, 305 K, CDCl3): δ = 21.8 [CH3], 27.8 [t-Bu], 41.5 [CH2C = O], 50.8 [CH], 69.7 [OCH2], 69.7 [C–N], 82.7 [C–O], 128.2 [CH2-phen], 129.0 and 129.2 [CH2-phen and m-Ph] ppm. 13C (O=C=O) ppm; HRMS (ES-I) calcd for C17H16NO2Na [M + Na+] 328.1519; found 328.1523.

Other transformations of nitro lactone 4

3-Methyl-3-nitro-5-phenylpentanoic acid 7. A solution of nitro compound 4a (94 mg, 0.4 mmol) and suspended 5% Pd/C (15 mg) in MeOH (2.0 mL) was stirred in a H2 atmosphere (from a balloon) for 8 hours. After that, the catalyst was separated out on a filter paper, washed 5 times with MeOH (5 × 2 mL). The solvents were evaporated in vacuo. The residue was subjected to column chromatography (eluent MeOH–CHCl3, 1:25) to give 92 mg (97%) of the nitro acid 7 as colorless prisms; mp = 76–77 °C (hexane–EtOAc, 1:20), TLC: Rf = 0.38 (CHCl3/CH2Cl2, 25/1); 1H NMR (300.13 MHz, 299 K, CDCl3): δ = 1.81 [s, 3H, CH3], 2.19–2.37 [m, 2H, CH2], 2.63–2.69 [m, 2H, CH2], 2.94 [d, J = 16.9 Hz, 1H, CH2H3], 3.30 [d, J = 16.9 Hz, 1H, CH2H3], 6.00–7.10 [br s, 1H, COOH], 7.13–7.35 [m, 5H, Ph] ppm; 13C NMR (75.47 MHz, 299 K, CDCl3): δ = 22.9 [CH3], 30.2, 41.8 and 41.9 [3 CH2], 81.8 [CNO2], 126.5, 128.3 and 128.7 [CH2-phen], 139.7 [C-phen], 174.0 [COOH] ppm; C12H15NO4 (237.25): calcd C, 60.75; H, 5.90; N, 6.37; found C, 60.88; H, 5.92; N, 6.33.

4-Methyl-6-phenyl-5,6-dihydropyran-2-one 5a. 1BuOK (21 mg, 0.187 mmol) was added to a precooled to 0 °C solution of the nitro lactone 4a (40 mg, 0.170 mmol) in THF (1.0 mL). The reaction mixture was stirred for 15 min and poured into a EtO (5 mL)/H2O (4 mL) mixture. The water layer was back-extracted with EtO (2 × 2 mL). The combined organic layers were washed with H2O (4 mL), brine (4 mL) and dried over Na2SO4. The solvents were evaporated in vacuo. The residue was subjected to column chromatography (eluent EtOAc–hexane, 1/3) to give 30.1 mg (94%) of the enone 5a as a colorless solid; mp = 58–60 °C (EtO), TLC: Rf = 0.29 (hexane–EtOAc, 1/1); 1H NMR (300.13 MHz, 299 K, CDCl3): δ = 2.03 [s, 3H, CH3], 2.46 [dd, J = 17.9, J = 3.8 Hz, 1H, CH2H3], 2.65 [dd, J = 17.9, J = 12.1 Hz, 1H, CH2H3], 5.41 [dd, J = 12.1, J = 3.8 Hz, 1H, CH2H3], 5.92 [s, 1H, =CH], 7.27–7.55 [m, 5H, Ph] ppm; 13C NMR (75.47 MHz, 299 K, CDCl3): δ = 22.9 [CH3], 36.9 [CH2], 78.6 [OCH], 116.8 [–=CH], 126.1, 128.6 and 128.7 [CH2-phen], 138.7 [C-phen], 157.0 [=C], 164.9 [OC=O] ppm.

4-Methyl-5-phenyl-6,7-dihydropyran-2-one 5c. Obtained by the same procedure as 5a; yield 30.5 mg (95%), mp = 49–50 °C (EtO), TLC: Rf = 0.38 (hexane–EtOAc, 1/1); 1H NMR (400.1 MHz, 305 K, CDCl3): δ = 2.03 [s, 3H, CH3], 2.46 [dd, J = 17.9, J = 3.8 Hz, 1H, CH2H3], 2.65 [dd, J = 17.9, J = 12.1 Hz, 1H, CH2H3], 5.41 [dd, J = 12.1, J = 3.8 Hz, 1H, CH2H3], 5.92 [s, 1H, =CH], 7.27–7.55 [m, 5H, Ph] ppm; 13C NMR (75.47 MHz, 299 K, CDCl3): δ = 22.9 [CH3], 36.9 [CH2], 78.6 [OCH], 116.8 [=CH], 126.1, 128.6 and 128.7 [CH2-phen], 138.7 [C-phen], 157.0 [=C], 164.9 [OC=O] ppm.
[m, 3H, Ph] ppm; $^{13}$C NMR (100.3 MHz, 305 K, CDCl$_3$); $\delta = 21.7$ [CH$_3$], 45.1 [CH], 78.6 [OCH$_2$], 117.7 [=CH], 128.0 [CH$_2$-Ph], 128.1 and 129.1 [CH$_2$Ph], 137.1 [C$_6$Ph], 159.2 [=C], 164.2 [OC=O]; HRMS (ES-I) calcd for C$_{15}$H$_{12}$O$_2$ [M + Na]$^+$ 211.0730; found 211.0731.

X-Ray data

Single crystals, suitable for X-ray diffraction analysis, were obtained by the slow cooling and slow evaporation of CHCl$_3$ solutions of 4b, 4h, saturated at reflux.

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