α,γ-Dioxygenated amides via tandem Brook rearrangement/radical oxygenation reactions and their application to syntheses of γ-lactams

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Full Research Paper

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Keywords:
Brook rearrangement; cyclization; electron transfer; γ-lactams; tandem reactions

Abstract

Pyrrolidones are common heterocyclic fragments in various biologically active compounds. Here, a two-step radical-based approach to γ-lactams bearing three to four stereocenters starting from epoxides, N-allylic silylacetamides and TEMPO is reported. The sequence starts with a new tandem nucleophilic substitution/Brook rearrangement/single electron transfer-induced radical oxygenation furnishing orthogonally protected α,γ-dioxygenated N-allylamides with wide scope, mostly good yields, and partly good diastereo- and enantioselectivity for defined combinations of chiral epoxides and chiral amides. This represents a very rare example of an oxidative geminal C–C/O difunctionalization next to carbonyl groups. The resulting dioxygenated allylic amides are subsequently subjected to persistent radical effect-based 5-exo-trig radical cyclization reactions providing functionalized pyrrolidones in high yields as diastereomeric mixtures. They converge to 3,4-trans-γ-lactams by base-mediated equilibration, which can be easily further diversified. Stereochemical models for both reaction types were developed.

Introduction

Nitrogen-containing heterocycles are widely distributed in biologically active compounds [1-4]. Saturated nitrogen heterocycles such as pyrrolidines [5-9], piperidines, pyrrolizidines or indolizidines [10-16] are central fragments in various natural products, which are often synthesized from lactams by reduction. This makes them important building blocks in the total synthesis of alkaloids and their non-natural analogs [17-21]. However, the γ-lactam substructure itself is a central fragment of numerous bioactive alkaloids, such as pyrrocidine B (I) [22], fusaric C (II) [23], fusarisetin A (III) [24], pseurotin A (IV) [25], (−)-salinosporamide A (V) [26], parvistemoline (VI) [27], glochidine (VII) [28], and other alkaloids [29-34] (Figure 1).
Moreover, functionalized synthetic γ-lactams are important lead compounds, e.g., derivatives with antibacterial activity were discovered, what gains importance with respect to the increasing bacterial resistance toward traditional β-lactam antibiotics [35-39].

Various synthetic pathways can be applied for the construction of the γ-lactam scaffold [40-44]. The pyrrolidinone fragment is often synthesized by transition metal- [45-50] or Lewis acid-catalyzed cyclization reactions [51-54]. The Diels–Alder reaction can also be used for the preparation of functionalized γ-lactams in a single step [55]. Radical 5-exo or 5-endo cyclizations of substituted N-allyl or N-vinyl α-halo amides VIII [56-61] or X [62-66] using atom transfer and other chain reactions, as well as non-chain methods [67-73] have been used to approach diverse γ-lactam-containing skeletons of the general structure IX or XI, respectively (Scheme 1A).

Recently, we became interested in merging sigmatropic rearrangements with radical oxygenation reactions since profound changes in the connectivity patterns during both reaction modes will potentially significantly simplify the access to complex target molecules [74,75]. The principle is illustrated for a merger of nucleophilic opening of allylepotides 1 with silylacetamides 2/Brook rearrangement/radical oxygenation and radical carbocyclizations; C) proposed approach to functionalized γ-lactams 10 by Brook rearrangement/radical oxygenation and subsequent 5-exo cyclization reactions.

Based on this sequence various other reaction pathways can be envisaged. Among them we hypothesized that the nucleophilic ring opening of simple epoxides 7 by N-allylic 2-silylaceticamides would provide an intermediate alkoxide from which the
Brook rearrangement and subsequent oxygenation could proceed (Scheme 1C). This represents in the event a geminal C–C/C–O difunctionalization of amide 8 and results in the α,γ-dioxygenated N-allylic amides 9. Thermal radical cyclizations to lactams of type 10 based on the persistent radical effect (PRE) are unknown and may provide a simple access to 3,4-disubstituted γ-lactams.

We report here that tandem nucleophilic epoxide ring-opening/ Brook rearrangement/radical oxygenation reactions are indeed very effective for the synthesis of diverse N-allylic α-(aminoxy)amides 9 from various epoxides 7 and a range of N-allylic α-silylamides 8. α-(Aminoxy)amides 9 serve well for the synthesis of polysubstituted γ-lactams 10 with moderate dia-stereoselectivities. The stereochemistry of the initial cyclization with moderate dia-lactams γ the synthesis of polysubstituted 10-(Aminoxy)amides α 9.

Results
Tandem nucleophilic substitution/Brook rearrangement/radical α-oxygenation reactions

The N-allylic α-(trimethylsilyl)acetamides 8a–m were efficiently prepared by a two-step sequence. First, N-allyl acetamides 11a–m were synthesized by N-acetylation of the corre-sponding acyclic or cyclic allylic amines in very good yields (see Supporting Information File 1 for details). Their subsequent α-deprotonation by LDA followed by treatment with chlorotrimethylsilane at −78 °C [81] resulted in clean C-silylation of the corresponding enolate providing silylacetamides 8a–m in good to very good yields (Table 1, entries 1–13).

For the synthesis of the targeted orthogonally protected α-(aminoxy)-γ-(silyloxy)amides 9 α-silyacetamides 8a–k were deprotonated by s-BuLi and treated with commercially available racemic epoxides 7a–d.f (Table 2, entries 1–7 and 13–15) or with enantioselectively pure epoxides (S)-7b, (R)-7b, or (S)-7e (Table 2, entries 8–12) at 0 °C. The epoxide opening/Brook rearrangement steps were typically complete after an hour, except for cyclohexene oxide 7f for which the nucleophilic opening and Brook rearrangement steps took 24 h (Table 2, entry 13). Ferrocenium hexafluorophosphate (4) and TEMPO (3) were subsequently added to trigger the single electron oxidation of the formed amide enolates and radical oxygenation affording α-(aminoxy)amides 9a–n in good 51–77% isolated yields. Cyclic units in the allylic N-substituent (Table 2, entries 14 and 15) and the epoxide (Table 2, entry 13) are tolerated. Most dioxygenated amides 9b–h.m.n were isolated as inseparable 1:1.2:1 anti/syn mixtures of unassigned diastereomers (Table 2, entries 2–8, 14 and 15), thus the silyloxy group in γ-position did

![Table 1: Preparation of tertiary N-allylic α-(trimethylsilyl)amides 8a–m](image)

| entry | R³ | R² | R¹ | R⁴ | R⁵ | 8, % |
|-------|----|----|----|----|----|-----|
| 1     | a  | allyl | H  | H  | H  | H   | a, 76 |
| 2     | b  | CH₃ | H  | H  | H  | H   | b, 70 |
| 3     | c  | Bn  | CH₃ | H  | H  | H   | c, 75 |
| 4     | d  | Bn  | H  | CH₃ | CH₃ | H   | d, 72 |
| 5     | e  | (S)-PhCH₃ | H  | H  | H  | H   | e, 89 |
| 6     | f  | (S)-β-NapCH₃ | H  | H  | H  | H   | f, 95 |
| 7     | g  | (S)-PhCH₃ | H  | CH₃ | CH₃ | H   | g, 88 |
| 8     | h  | (S)-PhCH₃ | CH₃ | H  | H  | H   | h, 93 |
| 9     | i  | (S)-PhCH₃ | -(CH₂)₃ | H  | H  | i, 84 |
| 10    | j  | Bn  | -(CH₂)₃ | H  | H  | j, 82 |
| 11    | k  | Bn  | -(CH₂)₄ | H  | H  | k, 85 |
| 12    | l  | Bn  | H  | -(CH₂)₂ | - | l, 91 |
| 13    | m  | Bn  | H  | H  | -(R)-(CH₂)₂ | m, 76 |

General conditions: 11 (1 equiv), iPr₂NH (1.1 equiv), n-BuLi (1.1 equiv), TMSCl (1.05 equiv), −78 °C, 1 h; Nap = naphthyl.
not influence the face selectivity of radical coupling with TEMPO (3). However, since for all dioxygenated amides 9 the stereocenter at the alkoxylamine unit will be destroyed in the subsequent radical reaction, the low diastereoselectivity at that center is not of concern. In contrast, in the reactions of silyl-ami-

Table 2: Tandem nucleophilic ring opening/Brook rearrangement/radical oxygenation.

| entry | 8 | 7b | R1 | R2 | R3 | R4 | R5 | R6 | R7 | 9, % | anti/syn |
|-------|---|----|----|----|----|----|----|----|----|-----|--------|
| 1     | a | a  | allyl | H | H | H | H | CH3 | CH3 | a | 61 | –      |
| 2     | a | b  | allyl | H | H | H | H | CH3 | H   | b | 77 | 1:1:1  |
| 3     | a | c  | allyl | H | H | H | H | C2H9 | H   | c  | 71 | 1:1    |
| 4     | a | d  | allyl | H | H | H | H | Ph  | H   | d  | 56 | 1:1:1  |
| 5     | b | b  | CH3  | H | H | H | H | CH3 | H   | e  | 68 | 1:1:1  |
| 6     | c | b  | Bn   | CH3| H | H | H | CH3 | H   | f  | 51 | 1:1    |
| 7     | d | b  | Bn   | CH3| CH3| H | H | CH3 | H   | g  | 53 | 1:1    |
| 8     | a | (S)-e | allyl | H | H | H | H | H   | H   | h  | 65 | 1:1:1  |
| 9     | e | (S)-b | B   | H | H | H | H | CH3 | H   | i  | 64 | 3:1    |
| 10    | e | (R)-b | B   | H | H | H | H | CH3 | H   | i  | 63 | 3:1    |
| 11    | f | (S)-b | C   | H | H | H | H | CH3 | H   | j  | 62 | 3:1    |
| 12    | g | (S)-b | B   | H | CH3| CH3| H | CH3 | H   | k  | 61 | 3:1    |
| 13d   | f | a  | allyl | H | H | H | (CH2)4- | H   | I  | 63 | 7:1    |
| 14    | j | b  | Bn   | -(CH2)3- | H | H | CH3 | H   | m  | 61 | 1:2:1  |
| 15    | k | b  | Bn   | -(CH2)4- | H | H | CH3 | H   | n  | 62 | 1:1:1  |

N-Cyclopent-2-enyl and N-cyclohex-2-enylamines 8f,m provided the oxygenated products 9o,p in 68% and 63% yields, respectively, as 2:2:1:1 mixture of diastereomers (Scheme 2). Thus, the chiral cyclic amide substituent on the nitrogen atom influences the selectivity of the radical coupling with TEMPO to some extent, though less than the 1-arylethyl groups.

A good diastereoselectivity was also observed for the ring-opening/Brook rearrangement/oxygenation sequence with cyclohexene oxide 7f, which furnished the dioxygenated amide 9i with a 7:1 anti/syn diastereoselectivity for the radical coupling (Table 2, entry 13). When the reaction was quenched after completion of the Brook rearrangement, N-allyl-N-propyl-2-(2-((trimethylsilyl)oxy)cyclohexyl)acetamide was obtained as a single diastereomer because of the stereospecific epoxide ring-opening in 80% yield (not shown, see Supporting Information File 1 for details).

The configuration of the major anti-diastereomer of alkoxylamine 9j was determined by X-ray crystallography after desilylation and hydrochloride formation (see Supporting Information File 1 for details). The (R)-configuration at C2 as well as the (S)-configuration at both, C4 and the N-arylethyl group were established (Figure 2).

Somewhat surprisingly, amides 8h,i did not react with propylene oxide 7b neither at 0 °C nor at room temperature. In order to confirm enolate formation from 8h,i with s-BuLi, a
deuterium quenching experiment with D₂O was performed. Analysis by ¹H NMR spectroscopy revealed 87 and 91% deuterium incorporation, respectively, indicating that a deprotonation occurred, but the epoxide opening was hampered by the combination of a sterically more demanding branched amide substituent and the R² substituent at the internal carbon of the allylic unit.

Transformation of α-(aminoxy)amides 9 to lactams 12 by persistent radical effect-based cyclization reactions

The acyclic α-(aminoxy)amides 9a–k are suitable precursors for thermal radical cyclization reactions based on the persistent radical effect. Heating them to 150 °C in tert-butanol provided diverse 1,3,4-trisubstituted pyrrolidones (Table 3). For stability reasons the initially obtained silyl-protected lactams 10a–k were deprotected without isolation by TBACF in THF affording hydroxy lactams 12a–k in 66–93% yields. The thermal cyclization of α-(aminoxy)amide 9a provided two diastereomers of lactam 12a in a 2:1 trans/cis ratio (Table 3, entry 1). The N-allylic amides 9b–f provided lactams 12b–f as mixtures of four inseparable diastereomers in which those with trans orientation of the substituents at C3 and C4 of the formed 2-pyrrolidone ring predominated with moderate selectivity (Table 3, entries 2–7). The diastereomeric ratio is more or less independent of the nature of the amide substituent R¹ or the substituent R⁴. Amide 9f with a methyl group at the internal position of the alkene unit cyclized exclusively in the 5-exo-trig mode and provided the pyrrolidone 12f with a quaternary center at C4 in moderate yield and similar diastereoselectivity as for 12a–d (Table 3, entry 7); a product of potentially competing 6-endo cyclization was not detected. Amides 9g,k with trisubstituted alkene units furnished 4-isopropenylpyrrolidones 12g,k in very good yields as mixtures of inseparable diastereomers (Table 3, entries 7 and 11); no alkoxyamine-containing products were isolated. Lactam 12h with a defined hydroxy group configuration in the side chain at C3 of the lactam as well as pyrrolidones 12i–k bearing configurationally defined 1-arylethyl groups at the amide nitrogen and the hydroxy group in the C3 side chain were obtained as inseparable mixtures of four diastereomers (Table 3, entries 8–11). The two possible trans-diastereomers predominated with moderate selectivity. These results indicate negligible asymmetric inductions from the chiral centers, both at the exocyclic hydroxy substituent in the C3 side chain (Table 3, entry 8) and/or of the 1-arylethyl group during the radical cyclization under the reaction conditions (Table 3, entries 9–11). The size of the arylethyl substituent at the nitrogen atom also plays essentially no role for the diastereoselectivity of the cyclization (Table 3, entry 10 vs entry 9).

The minor cis-diastereomer of N-(1-β-naphthylethyl)pyrrolidone 12j crystallized after oxidation to ketone 13j and its configuration was unequivocally established by X-ray crystallography (Figure 3, vide infra). Similarly, the minor cis-diastereomer of hydroxy lactam 12k crystallized and its configuration was confirmed. The configuration of the other lactams was assigned by analogy, by base-mediated equilibration and oxidation experiments (vide infra).

The α-(aminoxy)-γ-(silyloxy)amides 9l–p with cyclic units are also suitable precursors for radical cyclization reactions (Scheme 3). 3-(2-Hydroxycyclohexyl)-2-pyrrolidone 12l was obtained by the thermal cyclization of α-(aminoxy)cyclohexylacetamide 9l as a mixture of two major trans isomers 12lA and
Table 3: Hydroxyalkyl-γ-lactams 12 by PRE-based radical 5-exo cyclizations\(^{a}\).

![Diagram showing the reaction of 9a–k to form 12a–f and 12h\(^{j},i,j\).]

| entry | 9  | R\(^{1}\) | R\(^{2}\) | R\(^{3}\) | R\(^{4}\) | R\(^{5}\) | 12, % | dr |
|-------|----|---------|---------|---------|---------|---------|-------|----|
| 1     | a  | allyl   | H       | H       | CH\(_{3}\) | CH\(_{3}\) | a, 91 | 2:1|
| 2     | b  | allyl   | H       | H       | CH\(_{3}\) | H     | b, 87 | 2.5:2.5:1:1|
| 3     | c  | allyl   | H       | H       | C\(_{4}\)H\(_{9}\) | H     | c, 86 | 2:2:1:1|
| 4     | d  | allyl   | H       | H       | Ph     | H     | d, 86 | 3:3:1:1|
| 5     | e  | CH\(_{3}\) | H       | H       | CH\(_{3}\) | H     | e, 82 | 2:2:1:1|
| 6     | f  | Bn      | CH\(_{3}\) | H       | CH\(_{3}\) | H     | f, 66 | 3:3:1:1|
| 7     | g  | Bn      | H       | CH\(_{3}\) | CH\(_{3}\) | H     | g, 93 | 2:2:1:1|
| 8     | h  | allyl   | H       | H       | \((S)-\text{CH}_2\text{OBn}\) | H     | h, 72 | 4:4:1:1\(^{b}\)|
| 9     | i  | (S)-PhCHCH\(_{3}\) | H       | H       | \((S)-\text{CH}_3\) | H     | i, 82 | 2:2:1:1|
| 10    | j  | (S)-β-NapCHCH\(_{3}\) | H       | H       | \((S)-\text{CH}_3\) | H     | j, 77 | 2:2:1:1|
| 11    | k  | (S)-PhCHCH\(_{3}\) | H       | \((S)-\text{CH}_3\) | \((S)-\text{CH}_3\) | H     | k, 92 | 2:2:1:1|

\(^{a}\)General conditions: 1) 9 (1 equiv), t-BuOH, 150 °C, 1 h; 2) TBAF (1.2 equiv), THF, 0 °C, 30 min; \(^{b}\)the enantiomeric product is shown for clarity and simplicity.

Figure 3: X-ray crystal structure of the minor cis-diastereomers of the keto lactam 13j (left) and the hydroxy lactam 12k (right). Displacement ellipsoids are drawn at the 30% probability level.
Scheme 3: Thermal radical cyclization reactions of amides 9I–p bearing cyclic units. Conditions: a) t-BuOH, 150 °C, 1 h; b) TBAF, THF, 0 °C. All = allyl.

12IB, which were accompanied by traces of a C3−C4 cis-diestereomer, was assigned by NOE experiments of 3-(2-oxocyclohexyl)lactams 13l prepared from 12l by Dess–Martin oxidation (vide infra). The thermal cyclization of compounds 9m, n with N-cycloalkenylmethyl substituents provided spirolactams 12m, n in good yields, but with overall low diastereoselectivity. In the cyclization of 9m lactams 12mA and 12mB with trans orientation at C4 and the newly introduced aminoxy group at C5 were the major diastereomers, which results in an overall 4.5:1 trans/cis cyclization diastereoselectivity. The radical coupling with TEMPO (3) proceeded with moderate 2:1 diastereoselectivity for both pairs of the cyclized diastereomers. In the case of azaspiro[4,5]decane 12n with a spirocyclohexyl substituent the cyclization diastereoselectivity was with 2.5:1 lower than that for 12m. However, the coupling diastereoselectivity with TEMPO (3) amounted to 4:1 for the trans diastereomers 12nA,B and exclusive for the cis isomer 12nC. The relative configuration of diastereomer 12nA was unequivocally established by X-ray crystallography of the hydrochloride adduct of the keto lactam 13nA (Scheme 3, insert). The relative configuration of the compounds 12m, n was determined by analogy, by ROESY investigations for the keto lactams 13m, n, and by isomerization experiments for 12n (vide infra). Amides 9o, p with cycloalkenyl substituents on the nitrogen were transformed to fused lactams 12o, p with good diastereoselectivity. Azabicyclo[3.3.0]octanone 12o prepared from amide 9o with a racemic cyclopent-2-enyl group on nitrogen was obtained as an inseparable mixture of four diastereomers 12oA and 12oB. In major 12oA the hydroxypropyl and tetramethylpiperidinylxoy groups reside on the convex face of the bicyclic system. Amide 9p with an enantiomerically enriched cyclohex-2-enyl substituent cyclized with exclusive diastereoselectivity and only two diastereomers 12pA differing in the orientation of the hydroxy group were obtained in high yield. The radical coupling with TEMPO also occurred exclusively at the convex face of the bicyclic system. The configurations of the fused lactams were assigned by chemical derivatization and NOE experiments (vide infra).

Functionalization reactions of lactams 12

Base-mediated isomerization reactions

Lactams 12 are mixtures of two, four, six or eight diastereomers (not shown). The relative configuration of pyrroldone 12l was assigned by NOE experiments of 3-(2-oxocyclohexyl)lactams 13l prepared from 12l by Dess−Martin oxidation (vide infra). The thermal cyclization of compounds 9m, n with N-cycloalkenylmethyl substituents provided spirolactams 12m, n in good yields, but with overall low diastereoselectivity. In the cyclization of 9m lactams 12mA and 12mB with trans orientation at C4 and the newly introduced aminoxy group at C5 were the major diastereomers, which results in an overall 4.5:1 trans/cis cyclization diastereoselectivity. The radical coupling with TEMPO (3) proceeded with moderate 2:1 diastereoselectivity for both pairs of the cyclized diastereomers. In the case of azaspiro[4,5]decane 12n with a spirocyclohexyl substituent the cyclization diastereoselectivity was with 2.5:1 lower than that for 12m. However, the coupling diastereoselectivity with TEMPO (3) amounted to 4:1 for the trans diastereomers 12nA,B and exclusive for the cis isomer 12nC. The relative configuration of diastereomer 12nA was unequivocally established by X-ray crystallography of the hydrochloride adduct of the keto lactam 13nA (Scheme 3, insert). The relative configuration of the compounds 12m, n was determined by analogy, by ROESY investigations for the keto lactams 13m, n, and by isomerization experiments for 12n (vide infra). Amides 9o, p with cycloalkenyl substituents on the nitrogen were transformed to fused lactams 12o, p with good diastereoselectivity. Azabicyclo[3.3.0]octanone 12o prepared from amide 9o with a racemic cyclopent-2-enyl group on nitrogen was obtained as an inseparable mixture of four diastereomers 12oA and 12oB. In major 12oA the hydroxypropyl and tetramethylpiperidinylxoy groups reside on the convex face of the bicyclic system. Amide 9p with an enantiomerically enriched cyclohex-2-enyl substituent cyclized with exclusive diastereoselectivity and only two diastereomers 12pA differing in the orientation of the hydroxy group were obtained in high yield. The radical coupling with TEMPO also occurred exclusively at the convex face of the bicyclic system. The configurations of the fused lactams were assigned by chemical derivatization and NOE experiments (vide infra).

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Table 4: Isomerization of lactams 12 using KOT-Bu in t-BuOH a.

| entry | 12 | R^1   | R^2 | R^3   | R^4   | trans-12 | dr  |
|-------|----|-------|-----|-------|-------|----------|-----|
| 1     | a  | allyl | H   | CH_3  | CH_3  | a        | 17:1|
| 2     | b  | allyl | H   | CH_3  | H     | b        | 12:12:1:1|
| 3     | c  | allyl | H   | C_4H_9| H     | c        | 16:16:1:1|
| 4     | d  | allyl | H   | Ph    | H     | d        | 13:13:1:1|
| 5     | e  | CH_3  | H   | CH_3  | H     | e        | 4:4:1:1  |
| 6 b   | f  | Bn    | CH_3| CH_3  | H     | f        | 3:3:3:1  |
| 7 b   | g  | Bn    | H   | CH_3  | H     | g        | 7:7:1:0  |
| 8 b   | h  | allyl | (S)-CH_2OBn| H | h | 17:17:1:1|
| 9 b   | i  | (S)-PhCHCH_3| H | (S)-CH_3| H | i | 1:1:0:0  |
| 10 b  | j  | (S)-β-NapCHCH_3| H | (S)-CH_3| H | j | 4:4:1:1  |
| 11 b  | k  | (S)-PhCHCH_3| H | (S)-CH_3| H | k | 1:1:0:0  |

a General conditions: 12 (1 equiv), KOT-Bu (0.5 equiv), t-BuOH, room temperature, 24 h; b reaction at 50 °C.

Attempts to influence the diastereomeric ratio of the cyclization products by irreversible stoichiometric deprotonation of the lactams 12d, f, i by LDA at −78 °C and subsequent protonation by methanol did not lead to substantial changes of the initial diastereomeric ratios. To confirm enolate formation, lactam 12f was deprotonated by LDA at −78 °C and quenched with D_2O, resulting in lactam 12f with 86% deuterium incorporation, but no change in the diastereomeric ratio.

Spirolactams 12m, n were also subjected to epimerization (Scheme 4). The change of the diastereomeric ratio A–D was not significant for 12m, whereas during equilibration of 12n the content of the cis isomers 12nC in the mixture decreased.
Oxidation of the side chain hydroxy group at C3
Hydroxy lactams 12 can be transformed to keto pyrrolidones 13 by a Dess–Martin oxidation (Table 5). For the isomerized ketones trans-12b–d this leads essentially to single keto lactams 13b–d (Table 5, entries 1, 3, and 4). The non-equilibrated ketones can also be used as exemplified for 12b providing an unchanged 2.5:1 trans/cis diastereomeric mixture (Table 5, entry 2, cf. Table 3, entry 2). The trans and cis orientation of the substituents at C3 and C4 of the pyrrolidine ring of 13b was confirmed by NOE experiments (see Supporting Information File 1 for details). The trans/cis mixture of 12f was similarly oxidized providing the pyrrolidine diastereomers 13f in good yield and unchanged ratio (Table 5, entries 6 and 7), thus confirming that they have opposite trans arrangement at C3 and C4 based on the fixed (S)-configuration of the 1-arylethyl substituents. One of the minor cis diastereomers of 13j crystallized and its configuration was unequivocally established by X-ray crystallography (Figure 3, vide supra).

Lactams 12l–o with cyclic subunits were also subjected to a Dess–Martin oxidation to confirm their relative configuration (Scheme 5). The diastereomeric mixture of lactam 12lA,B gave two trans-diastereomers of 13lA,B in an unchanged 1.2:1 ratio. Their opposite relative configuration at C3 and C4 was established by NOE experiments (see Supporting Information File 1). The rather complex diastereomeric mixture of spirolactams equil-12mA–D simplified on oxidation to partly separable mixtures of four and three diastereomers of keto lactams 13m, respectively. During purification of lactam 13m a major fraction was isolated in a 1.8:1 ratio, whereas the minor consisted of a 3:1 ratio, reflecting the initial 13mA:B:13mC:D ratio. The mixture of keto lactams 13nA–C was similarly separated to a 5:1 mixture of the lactams 13nA,B and the minor 13nC, respectively. This lends support to the C3–C4 trans arrangement for 13mA and 13mB as well as to the respective cis orientation in 13mC and 13mD. The oxidation of the hydroxy group in the bicyclic annulated racemic compound 12o reduced the number of diastereomers as expected to two, 13oA and 13oB, in a 4:1 ratio. The relative configurations of the major and the minor diastereomers were determined by NOE experiments (see Supporting Information File 1).

Further functionalization of lactams 12
Derivatizations of lactams 12 lead to valuable compound classes for further elaboration. The alkoxyamine functionality of lactam trans-12b was reductively cleaved by excess zinc in

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**Table 5:** Oxidation of hydroxy lactams trans-12 to keto lactams 13 by the Dess–Martin periodinan.

| entry | trans-12  | R¹  | R²  | R³  | 13  | dr  |
|-------|-----------|-----|-----|-----|-----|-----|
| 1     | b         | allyl | H   | CH₃ | b   | 88  | 1:0 |
| 2ᵇ     | b          | allyl | H   | CH₃ | b   | 86  | 2:5:1 |
| 3     | c         | allyl | H   | C₄H₉ | c  | 87  | 1:0 |
| 4     | d         | allyl | H   | Ph  | d   | 80  | 1:0 |
| 5     | f         | Bn   | CH₃ | CH₃ | f   | 90  | 3:1 |
| 6     | i         | (S)-PhCHCH₃ | H   | (S)-CH₃ | i   | 77  | 1:1:0:0 |
| 7     | j         | (S)-β-NapCHCH₃ | H   | (S)-CH₃ | j   | 81  | 4:4:1:1 |

ᵇGeneral conditions: trans-12 (1 equiv), DMP (1.3 equiv), t-BuOH (10 mol %), CH₂Cl₂, room temperature, 1 h;ᵇnon-isomerized 12b was used.
the presence of acetic acid at elevated temperature (Scheme 6); the dihydroxy lactam 14 was obtained in 82% yield. In the presence of LiAlH₄ pyrrolidone trans-12b was reduced to pyrrolidine 15 in 95% yield, whereas no reaction was observed with DIBAL-H, NaBH₄ or LiHBEts as the reducing agents; the starting material was typically recovered in 95% yield. However, the reduction of trans-12b by Red-Al in the presence of KOt-Bu was effective for the reduction of the lactam function to the hemiaminal followed by a nucleophilic exchange providing bicyclic hemiaminal 16 as 1:1 mixture of diastereomers in 83% yield. The stereochemical assignment of 16 is based on the relative configuration of the starting material. The N-allyl group in trans-12b can be also easily deprotected by a rhodium-catalyzed isomerization to the corresponding N-propenyl lactam followed by osmium tetroxide-catalyzed oxidative cleavage, providing lactam trans-17 in 62% yield. Additionally, the dia stereomeric mixture of lactam 12o was subjected to oxidative N–O bond cleavage by mCPBA furnishing bicyclo[3.3.0]octan- diones 18. The isolation of a mixture of four diastereomers as in the starting material indicates that radical coupling by TEMPO proceeds with exclusive diastereoselectivity (vide infra).

Discussion

The sequence nucleophilic epoxide opening/Brook rearrangement/single electron transfer-induced radical oxygenation proceeds efficiently with silylacetamides 8a–g,j,k giving α,γ-dioxygenated amides 9a–p in good yields (cf. Table 2). This transformation represents a rare geminal C–C/C–O functionalization of the starting silylacetamides 8. However, neither the silyloxy group in γ-position nor the size of the N-substituent influence the diastereoselectivity of radical coupling with TEMPO (3). In contrast, the chiral N-(1-phenylethyl)- and N-(1-naphthylethyl)-substituted amides 9i–k were obtained from (S)-propylene oxide (S)-7b with moderate 3:1 anti/syn-diastereoselectivity and from (R)-propylene oxide (R)-7b with good 8:1 anti/syn-diastereoselectivity. This makes the following oxygenation course most likely (Scheme 7). Silylacetamides 8e–g exist as approximately 4:1 rotamic mixtures of (Z/E)-isomers as determined by ¹H NMR spectroscopy at
room temperature and ROESY investigations (see Supporting Information File 1). This corresponds to the previously reported data for N-benzylacetamides [82]. It can be assumed that the amide enolates after the Brook rearrangement and the $\alpha$-amide radicals (4S,S)-19i–k and (4R,S)-19i, respectively, resulting after SET oxidation have a similarly preferred (Z)-orientation, since the environment around the amide does not change significantly during these elementary steps. A zig-zag conformation of the main chain places the bulky silyloxy and the methyl group of the 1-arylethyl unit in (4S,S)-19i–k, but the silyoxy group and the sterically more demanding phenyl ring of the 1-arylethyl group in (4R,S)-19i at the $\beta$-face shielding it in both radicals for the approach of TEMPO (3), but significantly more effectively in (4R,S)-19i (Scheme 7). The $\alpha$-face is in contrast much less crowded and allows smooth radical coupling providing a good 8:1 anti/syn-diastereoselectivity for (2S,4R)-9i, but only 3:1 for (2R,4S)-9i–k. Thus, the configurations of both, the epoxide 7 and the silylacetamide 8 are important in the nucleophilic ring opening/Brook rearrangement/radical oxygenation sequence for obtaining optimal anti-diastereoselectivity. Opposite absolute configurations in both components, 7 and 8, are displaying a synergistic effect for optimal stereocontrol in the radical oxygenation step with TEMPO (3).

A good diastereoselectivity of the oxygenation was also observed for the formation of 9i (cf. Table 2). Assuming a preferred conformation in radical 20, in which the interactions of the carbonyl group and the cyclohexane ring are minimized, the $\beta$-face at the radical center is significantly blocked by the silyloxy group hindering the approach of TEMPO (3), whereas the $\alpha$-face is free for radical coupling resulting in the formation of (2R*,4S*)-9i as the major product (Scheme 8).
The outcome of the thermal radical cyclizations of the dioxygenated amides 9 is dependent on the structure of the alkene unit, but the general trend is similar (Scheme 9). Amides with a terminal alkene unit furnished dioxygenated pyrrolidones 12a–f, h–j as products, amides 9g, k with trisubstituted alkene units exclusively lead to isopropenylpyrrolidones 12g, k. A similar reactivity was observed before in thermal radical cyclizations leading to cyclopentane derivatives [74, 75]. All γ-silyloxy amides 9a–k cyclize in the 5-exo mode via envelope transition states 21a–k in which both the amide resonance and the resonance of the radical with the carbonyl group are disturbed [83, 84]. Reactions via transition states trans-21a–k are energetically favored over the corresponding sterically more hindered
cis-oriented transition states cis-21a–k, however, the diastereoselectivity remains moderate under the thermal conditions. This is in line with the previously reported radical cyclization reactions to pyrrolidones [38, 85-88]. There is apparently no energy difference between the pairs of trans-21 or cis-21, thus the γ-silyloxy group exerts no influence. The cyclized radicals 22 couple subsequently with TEMPO providing lactams 12a–k after deprotection of the TMS groups. The cyclized tertiary alkoxyamines (R³ = Me) are known to be thermally labile [89-92] and consequently 4-isopropenyl-pyrrolidones 12g,k are isolated as the exclusive products. The cyclization of the 2-silyloxycyclohexyl-substituted amide 9l proceeds similarly providing almost equal amounts of two trans diastereomers 12l as single isomers because of the constrained conformation of radical 20, which allows a cyclization essentially only from the α-face (not shown, cf. Scheme 8).

Amides 9m,n with cyclopent-1-en-1-ylmethyl or cyclohex-1-en-1-ylmethyl substituents on nitrogen similarly cyclize via envelope transition states trans-21m,n and cis-21m,n with preferred trans orientation of the olefin unit and the silyloxy-bearing side chain (Scheme 10). Thus, similarly as for 12a–k, two cyclized diastereomeric radicals trans-22m,n and two radicals cis-22m,n result, which differ in their orientation with respect to the racemic silyloxy group (cf. Scheme 9). The situation in the azaspiro[4,4] and azaspiro[4,5] radicals 22m,n is, however, more complex since they are prochiral, and thus eight diastereomers result. The coupling of 22m,n with TEMPO (3) occurs predominately from the more accessible β-face of the cyclopentyl or cyclohexyl radicals, since the α-face is partially blocked by the oxygenated alkyl chain at C4. However, the diastereoselectivity is also dependent on the ring size of the spirocyclic radical and proved to be better for the cyclohexyl radicals 22n, where coupling with TEMPO proceeded with a 4:1 12nA/12nB selectivity and exclusive diastereoselectivity for 12nC (cf. Scheme 3).

Fused lactams 12o,p were obtained with good to excellent diastereoselectivity from N-cyclopent-2-enyl or N-cyclohex-2-enyl amides 9o,p (cf. Scheme 3). The 5-exo cyclization step of radicals 21o,p proceeds with good to exclusive trans diastereoselectivity forming the azabicyclo[3.3.0]octyl or azabicyclo[4.3.0]nonyl radicals 22o,p (Scheme 11). The subsequent coupling of 22o,p with TEMPO (3) occurs exclusively from the

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**Scheme 10:** The stereochemical course for the formation of products 12m,n by thermal radical cyclization of alkoxyamines 9m,n.
Accessible convex face of the bicyclic radicals providing the lactams 12o,p.

The diastereomeric mixtures resulting from the thermal radical cyclization converge easily to the corresponding trans isomers by base-mediated isomerization reactions, if C4 is not disubstituted.

Conclusion

We developed a two-step methodology for the synthesis of diverse γ-lactam scaffolds. A tandem reaction combining nucleophilic epoxide opening by N-allylic silylacetamides, Brook rearrangement, and radical oxygenation serves for the preparation of N-allylic α-(aminoxy)-γ-(silyloxy)amides 9, which represents an oxidative C–C/C–O difunctionalization at the α-position of the amides. With correct configuration combination of chiral epoxides 7 and chiral amides 8, 2,4-dioxygenated amides 9 can be obtained with good anti-diastereoselectivity and enantioselectivity. Dioxygenated amides 9 are convenient precursors for radical 5-exo cyclization reactions based on the persistent radical effect. The N,3,4-trisubstituted lactams 12 were obtained in good yields, but with moderate trans/cis diastereoselectivity. The use of N-cycloalkenyl amides enables access to fused and spirolactams. The diastereomeric mixtures resulting from thermal radical cyclization converge to trans-3,4-disubstituted lactams by basic epimerization in 3-position of the lactam under thermodynamic conditions. The pyrrolidones can be easily further diversified by oxidation and reduction reactions. Thus, this methodology is suitable for the synthesis of functionalized γ-lactams, which can be used as building blocks for the synthesis of natural products or biologically active compounds.

Experimental

Tandem nucleophilic epoxide opening/Brook rearrangement/α-oxygenation (general procedure)

In a similar manner as described in [74]: LiCl (252 mg, 6 mmol) was added to a round-bottomed flask containing a stirring bar, which was sealed with a septum, and dried under vacuum by a heat gun. Dry THF (8 mL) and amide 8 (1.0 mmol) were added under argon. The mixture was cooled to 0 °C in an ice/water bath, sec-butyllithium (1.4 M solution in cyclohexane, 0.8 mL, 1.1 mmol) was added dropwise by a syringe, and the mixture was stirred at 0 °C for 1 h. Then, the epoxide 7 (1.05 mmol) was added at once by syringe and the reaction mixture was stirred at 0 °C for 15 min. Then, the mixture was cooled to −78 °C, diluted with dry THF (8 mL), and TEMPO (3, 164 mg, 1.05 mmol) was added as a solid in a single portion. Ferrocenium hexafluorophosphate (4, 397 mg, 1.2 mmol) was added in small portions with vigorous stirring until a dark blue-green color of the reaction mixture persisted for 20 min. The reaction mixture was quenched by saturated NH₄Cl solution (5 drops), diluted with diethyl ether (10 mL), and filtered through a pad of silica gel, which was washed with a fresh portion of diethyl ether. The filtrate was evaporated, and the crude inhomogeneous mixture was purified by flash chromatography (gradient, hexanes/EtOAc 20:1 to 5:1) to give pure α-(aminoxy)amides 9.

Thermal radical cyclization of compounds 9 and further deprotection (general procedure)

The α-(aminoxy)amide 9 (0.65 mmol) was heated in t-BuOH (6 mL) in a microwave reactor at 150 °C for 1 h. The reaction mixture was diluted with diethyl ether (10 mL), and filtered through a pad of silica gel, which was washed with a fresh portion of diethyl ether. The filtrate was evaporated, and the crude residue was dissolved in THF (5 mL), the reaction mixture was cooled to 0 °C in an ice/water bath, tetrabutylammonium fluoride (1 M solution in THF, 0.96 mL, 0.96 mmol) was added and the mixture was stirred at this temperature for 30 min. The reac-
tion was quenched by saturated NH₄Cl solution, diluted with water (5 mL) and diethyl ether (5 mL), the organic layer separated, and the aqueous layer extracted with diethyl ether (2 × 5 mL). The combined organic extracts were dried over MgSO₄, filtered, and evaporated. The crude mixture was purified by column chromatography (gradient, hexanes/EtOAc 5:1 to 1:1) to give pure lactams 12 as diastereomeric mixtures.

**Equilibration of lactams 12**
*(general procedure)*

A solution of KOt-Bu (1 M in THF, 0.25 mL, 0.25 mmol) was added to a stirred solution of hydroxy lactam 12 (0.50 mmol) in t-BuOH (3 mL) at room temperature or 50 °C and the reaction mixture was stirred for 24 h. The reaction was quenched by the addition of saturated NH₄Cl solution, diluted with water (3 mL) and diethyl ether (5 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 5 mL). The combined organic extracts were dried over MgSO₄ and filtered. The filtrate was evaporated and the diastereomeric ratio was determined by ¹H NMR spectroscopy. The crude mixture was purified by flash chromatography (gradient, hexanes/EtOAc 10:1 to 1:1) to give lactam trans-12.

**Dess–Martin oxidation of hydroxylactams 12**
*(general procedure)*

A solution of hydroxy lactam 12 or trans-12 (0.7 mmol) in dichloromethane (4 mL) was added to a stirred solution of Dess–Martin periodinane (386 mg, 0.9 mmol) and t-BuOH (0.1 mL, 1.1 mmol) in dichloromethane (4 mL) at room temperature. After 30 min, saturated Na₂CO₃ solution (2 mL) was added. After 5 min of vigorous stirring, the mixture was diluted with dichloromethane (10 mL), the organic layer was separated, washed with brine, dried over MgSO₄, and the solvent was evaporated. The residue was purified by column chromatography (gradient, hexanes/EtOAc 10:1 to 1:1) to give keto lactam 13.

Supporting Information

**Supporting Information File 1**
Experimental details and spectral data. [https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-58-S1.pdf](https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-58-S1.pdf)

**Funding**
We thank the Grant Agency of the Czech Republic (16-18513S), the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic (RVO: 61388963) and the Gilead Sciences & IOCB Research Center for generous financial support. I.C. thanks the Ministry of Education, Youth and Sports of the Czech Republic (MSM0021620857) for financial support.

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**References**

1. Mal, D.; Shone, B.; Dinda, B. K. Pyrrole and Its Derivatives. In Heterocycles in Natural Product Synthesis: Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 187–220. doi:10.1002/9783527634880.ch6
2. Kiu, P.; Yi-Kauhaluoma, J. Pyridine and Its Derivatives. In Heterocycles in Natural Product Synthesis: Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 267–297. doi:10.1002/9783527634880.ch8
3. Martins, P.; Jesus, J.; Santos, S.; Raposo, L. R.; Roma-Rodrigues, C.; Baptista, P. V.; Fernandes, A. R. Molecules 2015, 20, 16852–16891. doi:10.3390/molecules20016852
4. Taylor, A. P.; Robinson, R. P.; Fabian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. Org. Biomol. Chem. 2016, 14, 6611–6637. doi:10.1039/c6ob00936k
5. Pyne, S. G.; Davis, A. S.; Gates, N. J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. Synlett 2004, 2670–2680. doi:10.1055/s-2004-834801
6. Milen, M.; Abranyi-Balogh, P.; Keglevich, G.Curr. Org. Synth. 2014, 11, 889–901. doi:10.2174/1570179411666140818210247
7. Felpin, F.-X.; Lébreton, J. Eur. J. Org. Chem. 2003, 3693–3712. doi:10.1002/ejoc.200300193
8. Li, J.; Ye, Y.; Zhang, Y. Org. Chem. Front. 2015, 2, 864–892. doi:10.1039/c7qo01077j
9. Shibano, M.; Tsukamoto, D.; Masuda, A.; Tanaka, Y.; Kusano, G. Chem. Pharm. Bull. 2001, 49, 1362–1365. doi:10.1248/cpb.49.1362
10. Bhat, C.; Tilve, S. G. RSC Adv. 2014, 4, 5405–5452. doi:10.1039/c3ra44193h
11. O’Hagan, D. Nat. Prod. Rep. 2000, 17, 435–446. doi:10.1039/c7qo0171d
12. Pinder, A. R. Nat. Prod. Rep. 1986, 3, 171–180. doi:10.1039/np8600300171
13. Moreira, R.; Pereira, D. M.; Valenlão, P.; Andrade, P. B. Int. J. Mol. Sci. 2018, 19, 1668. doi:10.3390/ijms19061668
14. Robertson, J.; Stevens, K. Nat. Prod. Rep. 2017, 34, 62–89. doi:10.1039/c5np00076a
15. Ratmanova, N. K.; Andreev, I. A.; Leoniev, A. V.; Monotova, D.; Novoselov, A. M.; Ivanova, O. A.; Trushkov, I. V. Tetrahedron 2020, 76, 131031. doi:10.1016/j.tet.2020.131031
16. Bronner, S. M.; Im, G.-Y. J.; Garg, N. K. Indoles and Indolizidines. In Heterocycles in Natural Product Synthesis: Majumdar, K. C.; Chattopadhyay, S. K., Eds.; Wiley-VCH: Weinheim, Germany, 2011; pp 221–265. doi:10.1002/9783527634880.ch7
17. Takao, K.-i.; Aoki, S.-y.; Tadano, K.-i. J. Synth. Org. Chem., Jpn. 2007, 65, 460–469. doi:10.5055/yukigoseikyokaishi.65.460
18. Lebedev, A. Chem. Heterocycl. Compd. (N. Y., NY, U. S.) 2007, 43, 673–684. doi:10.1055/s-10593-007-0110-1
19. Nagao, Y.; Matsunaga, H.; Kumagi, T.; Inoue, Y.; Miwa, Y.; Taga, T. J. Chem. Soc., Chem. Commun. 1992, 437–439. doi:10.1039/c9920000437
