Rearrangement of o-(pivaloylaminomethyl)benzaldehydes: an experimental and computational study

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Abstract
Treatment of alkoxy-substituted o-(pivaloylaminomethyl)benzaldehydes under acidic conditions resulted in the formation of the regioisomeric aldehydes and/or dimer-like products. Detailed NMR studies and single-crystal X-ray measurements supported the structure elucidation of the compounds. DFT calculations were also carried out to clarify the reaction mechanism, and to explain the observed product distributions and structural variances in the dimer-like products. Studies on the transformation of unsubstituted o-(pivaloylaminomethyl)benzaldehyde under similar conditions were presented as well.

Introduction
In a preliminary publication [1] we disclosed that methylene-dioxy-substituted o-(pivaloylaminomethyl)benzaldehyde (1a), when kept in dichloromethane (DCM) in the presence of a catalytic amount (0.13 equiv) of trifluoroacetic acid (TFA) for 72 h at room temperature, gave isomeric aldehyde 2a (48%) and the dimer-like racemic product 3a (11%). Both transformations were rationalized by the intermediacy of the isoindole 4a (Scheme 1).

The formation of aldehyde 2a can be explained by a protonation of the ring tautomer 1a, followed by an acid-catalyzed water elimination to afford intermediate isoindole 4a [2-6].
Then, the addition of water to the sterically less-hindered site of the latter compound followed by ring opening resulted in the rearranged aldehyde 2a [1].

As regards the formation of dimer-like product 3a, the tendency of pyrrole [7,8], indole [8], and isoindole [3,9,10] to dimerize and polymerize was observed long ago. A repeatedly mentioned example was the formation of type 5 dimers under various conditions. They were first isolated during the synthesis of 1-arylisoindoles 6 by hydrogenation of o-cyanobenzophenones 7 in the presence of Raney nickel (Ra-Ni), sometimes as the main product, depending on the activity of the catalyst [10] (Scheme 2).

The oxidative dimerization of 1-phenylisoindole (6a) to compound 5a took place under various conditions: when refluxing in benzene in the presence of air [5,11], during an attempted nitrosation (with sodium nitrite in acetic acid), and in Mannich reactions [12]. For the formation of dimers 5, various mechanisms were envisaged. Nevertheless, the formation of any dimer-like product structurally similar to 3a has not been observed so far.

In this report we describe our efforts to extend the reaction described in Scheme 1 to further o-(pivaloylaminomethyl)benzaldehydes and to support the results by density functional theory (DFT) calculations, single-crystal X-ray measurements and comprehensive NMR studies.

Results and Discussion
Acid-catalyzed transformations of compounds 1a–d
First we kept compounds 1a and 1b [2] in DCM in the presence of a catalytic amount (0.1 equiv) of TFA for 24 h at room temperature (Scheme 3) and the results are summarized in Table 1. In the case of aldehyde 1a, the yields obtained under these conditions were similar to those of the reaction mentioned
Scheme 3: Rearrangement of aminoaldehydes 1 to regioisomers 2 and formation of dimer-like products 3 and 8.

Table 1: Yields of rearranged aldehydes 2 and dimer-like products 3 and 8 in two different solvents.

<table>
<thead>
<tr>
<th>starting material</th>
<th>yield of products in DCM</th>
<th>yield of products in THF</th>
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<tr>
<td></td>
<td>2</td>
<td>yield (%)</td>
</tr>
<tr>
<td>1a</td>
<td>a</td>
<td>51</td>
</tr>
<tr>
<td>1b</td>
<td>b</td>
<td>6</td>
</tr>
<tr>
<td>1c</td>
<td>c</td>
<td>traces</td>
</tr>
<tr>
<td>1d</td>
<td>d</td>
<td>–</td>
</tr>
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</table>

above (Scheme 1). The treatment of derivative 1b, which possesses a methoxy group in the position para to the pivaloylaminomethyl moiety, resulted in the formation of significantly more of the dimer-like compound 3b as the major product and only a small amount of the aldehyde 2b. When the reactions were carried out under the same conditions in tetrahydrofuran (THF) instead of DCM, substantially less dimer-like product 3a or 3b was formed in favor of the rearranged aldehyde 2a or 2b.

When starting from aldehyde 1c [2], containing the methoxy function in the ortho position of the formyl moiety and meta to the pivaloylaminomethyl group, a practically full conversion of 1c was achieved in both solvents. However, only traces of an isomeric aldehyde (most likely 2c, based on analogy with 2a,b) could be detected by LC–MS besides several dimer-like products. The major one (8a, Scheme 3) could be isolated in a pure form (Table 1). In the case of the trimethoxy derivative 1d (prepared similarly to 1a–c, see Experimental), ca. 90% conversion was achieved in both solvents and the formation of the isomeric aldehyde 2d was not observed at all. As the only product, the dimer-like compound 8b could be isolated and characterized. The structure determination of products 3b and 8b was also supported by single-crystal X-ray measurements. These compounds were obtained as racemates and Figure 1 shows those enantiomers in which the chiral center of the isoindoline moiety possesses an R configuration. All attempts to grow appropriate single crystals from derivative 8a were unsuccessful.

It has to be emphasized that theoretically, the formation of four dimer-like regioisomers could be expected from aldehydes 1a–d, each of them as the mixture of two diastereomeric racemates. Although HPLC–MS measurements indeed indicated the presence of isomeric dimers in the crude product mixtures, only the major isomers 3a,b, and 8a,b could be isolated.
The main structural difference between the dimer-like products 3a,b and 8a,b concerns the position of the linkage of the ortho-formylated N-pivaloylaminobenzyl moiety to the isoindoline building block. In the former products 3a,b it is attached to the sterically less hindered, while in the latter compounds 8a,b to the more hindered site of the isoindoline part.

Proposed mechanism for the formation of rearranged aldehydes and dimer-like products

The formation of the rearranged aldehydes 2a,b can be explained by the protonation of ring tautomers 9 to 10 (Scheme 4), followed by a water elimination, and subsequent deprotonation of cations 11 to afford isoindoles 4 [3-5]. The protonation of the latter [6], followed by the attack of water at position 1 of cations 12, and subsequent deprotonation of intermediates 13, results in hydroxyisoindolines 11, which can finally tautomerize to aldehydes 2a,b. In the previous report, we have demonstrated the existence of an equilibrium in the course of the transformation of 1a to 2a by trapping isoindole intermediate 4a with N-phenylmaleimide as a dienophile in the acid-catalyzed reaction of both aldehydes 1a and 2a [1]. Moreover, as a reverse reaction, the formation of aldehyde 1a was observed in the transformation of aldehyde 2a under similar conditions [1]. However, this equilibrium is obviously influenced by the formation of the dimer-like products.

The formation of the dimer-like products 3a and 3b can be rationalized by the electrophilic attack of cations 12a,b at posi-

![Scheme 4: Proposed mechanism of the isomerization of aldehydes 1 via isoindoles 4.](image-url)
tion 3 of isoindoles 4a,b to give cations 15a,b (Scheme 5). The reaction of the latter with water, followed by deprotonation leads to dimer-like compounds 16a,b, being the ring tautomers of the isolated products 3a and 3b.

On the contrary, the formation of dimer-like products 8a and 8b can be explained by the electrophilic attack of cations 11c,d at position 1 (instead of position 3) of isoindoles 4c,d to afford cations 17a,b (Scheme 6), which transform to the dimer-like products 5a,b via their ring tautomers 18a,b.

The mechanism proposed for the formation of the intermediates 15a,b and 17a,b is supported by the fact that electrophilic substitution reactions of isoindole are well known in the literature [3,13-18] and these are analogous to that suggested for the dimerization of indole under acidic conditions (Scheme 7) [8]. Electrophilic attack of indole protonated at position 3 toward the position 3 of another indole molecule, followed by deprotonation affords dimer-like derivative 20. The fundamental difference of this transformation from that we observed in the case of isoindoles is that the attack of water at cation 19 and subsequent ring opening did not happen here.

**DFT calculations**

The proposed mechanism of the 1→2 rearrangement (Scheme 4) was investigated in detail by DFT level quantum chemical computations using the Gaussian 09 program package [19] (Figure 2). Optimization and frequency calculation have
been accomplished using the B3LYP/6-31+G (d,p) method [20-22], followed by single point energy calculation with the B3LYP/6-311++G (3df,3pd) method [23,24], considering the solvent effect of DCM with the IEFPCM implicit solvent model [25] in both cases. When inspecting the Gibbs-free energy diagram of the transformation of aldehydes 1a–c (Figure 2, Table 2 and Table 3), it is noteworthy that the main trends until the formation of isoindole intermediates 4a–c are very similar. However, there is a significant difference in the 4→12 transformations. While in the case of aldehydes 1a and 1b this step is exergonic, for aldehyde 1c it is highly endergonic. This finding explains why, contrary to the formation of aldehydes 2a and 2b, product 2c was practically not formed in the product mixture. Furthermore, it also explains the preference between the two regioisomeric cations 11 and 12 in the dimer-formation step. In the case of isoindoles 4a,b, cations 12a,b are more stable than cations 11a,b, and the routes 11→4→12 leading to 12a,b are exergonic. The simultaneous presence of isoindole 4a and cation 12a, or 4b and 12b, respectively, gives rise to the formation of dimer-like products 3a or 3b (Scheme 5). On the con-
Table 2: Relative Gibbs free energy values corresponding to the transformations.

<table>
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<tr>
<th>starting material</th>
<th>ΔG (kJ·mol⁻¹)</th>
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<tr>
<td></td>
<td>1→9</td>
</tr>
<tr>
<td>1a</td>
<td>−4.2</td>
</tr>
<tr>
<td>1b</td>
<td>−6.8</td>
</tr>
<tr>
<td>1c</td>
<td>−19.1</td>
</tr>
<tr>
<td>1d</td>
<td>−11.7</td>
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Table 3: Relative Gibbs free energy values corresponding to the transition states.

<table>
<thead>
<tr>
<th>starting material</th>
<th>ΔG# (kJ·mol⁻¹)</th>
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<tbody>
<tr>
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<td>1TS</td>
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<tr>
<td>1a</td>
<td>69.5</td>
</tr>
<tr>
<td>1b</td>
<td>61.5</td>
</tr>
<tr>
<td>1c</td>
<td>51.2</td>
</tr>
<tr>
<td>1d</td>
<td>62.3</td>
</tr>
</tbody>
</table>

A closer look on the transformation of trimethoxy derivative 1d reveals that dehydration is almost isoergic (ΔG = −1.6 kJ·mol⁻¹), but the formation of the isoindole intermediate (11d→4d) is endergonic (unlike in the case of the three other derivatives), with a larger activation free energy (ΔG#11TS = 40.2 kJ·mol⁻¹) than those of congeners a–c. Moreover, there are two further endergonic steps in this sequence (4d→12d, 14d→2d), which data altogether explain why product 2d was not detected at all and why cation 11d is preferred in the dimer formation, leading to product 8b.

Acid-catalyzed transformation of unsubstituted ortho-(pivaloylaminomethyl)benzaldehyde (1e)

In order to reduce the number of possible dimer-like products, we carried out the reaction with unsubstituted ortho-(pivaloylaminomethyl)benzaldehyde (1e). Since the positional change of the two functional groups cannot be observed in this case, we could focus on the formation of the dimer-like products.

According to the calculations it turned out that the acid catalyst (TFA in this case), as expected, had a crucial role in the protonation and deprotonation as well as in the dehydration and hydration elementary steps of the reaction sequence. Without catalyst, the 9a→11a→4a transformations required an energy investment of 150.7 and 163.3 kJ·mol⁻¹, instead of 54.4 kJ·mol⁻¹ and 33.7 kJ·mol⁻¹, calculated with TFA (Table 3).

In conclusion, the DFT calculations are consistent with the observation that the formation of the rearranged aldehydes 2a,b is more favorable than that of 2c,d, and explain the difference observed between the regiochemistry of dimers 3a,b and 8a,b.

Acid-catalyzed transformation of unsubstituted ortho-(pivaloylaminomethyl)benzaldehyde (1e)
Scheme 8: Reaction of o-(pivaloylaminomethyl)benzaldehyde (1e) to give dimer-like products 23a and 23b.

Figure 3: X-ray structures of compounds 23a (left) and 23b (right).

was carried out under the same conditions in THF instead of DCM. HPLC–MS analysis of the crude product mixture showed the presence of dimer-like product 23a (25%), the recovered starting material 1e (67%), and traces (ca. 1%) of the isomeric dimer-like product (23b). After work-up, 18% of compound 23a was obtained in addition to 51% of 1e.

As shown in the structures, the chiral center of the isoindoline moiety in the enantiomer of compound 23a shown in Figure 3 is R, while the other chiral center exhibits an S configuration, so its racemic form is hereinafter referred to as RS–SR. By the same logic, another designation for racemic 23b is RR–SS. The formation of intermediates 22a and 22b (Scheme 8), as the rate-determining step leading to major product 23a (RS–SR) and minor product 23b (RR–SS), respectively, was also investigated by DFT level quantum chemical calculations with the same parameters as in the case of the 1→2 rearrangement. The racemic RS and RR forms were taken into consideration, and the computations showed that the formation of the RS compound required an energy investment of $\Delta G^{\#}_{4e \rightarrow 22a} = 89.1 \text{ kJ/mol}$, while the reaction leading to the minor (RR) isomer had a larger activation barrier ($\Delta G^{\#}_{4e \rightarrow 22b} = 101.9 \text{ kJ/mol}$). Moreover, the formation of the latter intermediate was significantly more endergonic ($\Delta G^{\#}_{4e \rightarrow 22b} = 69.2 \text{ kJ/mol}$) than $\Delta G^{\#}_{4e \rightarrow 22a}$ (37.9 kJ/mol).

The structure elucidation of compounds 3a [1], 3b, 8a,b, and 23a,b was based on the molecular formula obtained from
In order to get a better insight into the stereochemistry of compounds 23a and 23b, we calculated their refined stereostructure by means of DFT geometry optimization in a DCM solution. As a result, one minimal energy conformer was identified for 23a and two for 23b (Figure 4). In the two preferred conformers of 23b (23b1 and 23b2), the plane of the ortho-formyl-substituted phenyl rings is twisted with 180° compared to each other. The Gibbs free energy difference between the two conformers is 4.1 kJ·mol⁻¹ suggesting the possibility of a rotation of the ortho-formylphenyl group. Notably, conformer 23b1 is the more stable one, corresponding to the structure determined by solid-phase X-ray measurements (Figure 3, right). It should be mentioned that a few signals in the NMR spectra of 23b, e.g., δHC−N (5.71 dd), δHC= (131.1), and δC= (142.5) showed a considerable line-broadening (coalescence), revealing a partially hindered rotation of the formylphenyl moiety, i.e., the occurrence of a conformational equilibrium to be taken into account. Even the δHC−N 13C NMR signal remained under the noise level, indicating that the interconversion of these conformers is slow in the NMR time-scale.

Although the NMR spectra have been measured in CDCl₃, we are convinced that the conformations observed in CDCl₃ are in good accordance with the ones computed considering the implicit solvent effect of DCM. Based on the structural similarity, the close dielectric constant (ε = 4.7 for CHCl₃ and 8.9

This compound, i.e., a diamagnetic shift of ca. 1.8 ppm occurred in this position. In order to explain this phenomenon, we should consider the anisotropic effect of the aromatic rings. Such steric arrangement is only possible in case of a RR–SS diastereomer (23b), with only one of the aromatic hydrogen atoms of the isoindoline moiety [H(7)] located in close proximity above the middle of the other aromatic ring. It can be concluded after all that the NMR data also made it possible to assign the SR–SR diastereomeric structure for compounds 3b, 8a,b, and 23a, and the RR–SS structure for congener 23b.

As regards the minor dimer-like product 23b, the high-resolution mass spectrum proposed exactly the same molecular formula as for 23a. The 1H and 13C spectra taken in CDCl₃ solution also exhibited several similar chemical shifts to those obtained for 23a, but some interesting differences were also detected. The δNH = 8.50 ppm chemical shift in 23b indicates a weaker hydrogen bond, compared to the value of 9.39 ppm obtained for 23a [27]. The detected 3J(H,H) coupling constant for the hydrogens attached to the two asymmetric centers is 10 Hz in this case, indicating a dihedral angle of ca. 180° in 23b. Moreover, an unexpected extremely upfield aromatic δH(7) value (5.71 ppm) was measured for the isoindoline moiety of this compound, i.e., a diamagnetic shift of ca. 1.8 ppm occurred in this position. In order to explain this phenomenon, we should consider the anisotropic effect of the aromatic rings. Such steric arrangement is only possible in case of a RR–SS diastereomer (23b), with only one of the aromatic hydrogen atoms of the isoindoline moiety [H(7)] located in close proximity above the middle of the other aromatic ring. It can be concluded after all that the NMR data also made it possible to assign the SR–SR diastereomeric structure for compounds 3b, 8a,b, and 23a, and the RR–SS structure for congener 23b.

**Figure 4:** Structures of the minimal energy conformer of stereoisomer 23a and those of two minimal energy conformers of 23b (23b₁ and 23b₂) in DCM solution, based on DFT calculations.
Conclusion

When alkoxy-substituted o-(pivaloylaminomethyl)benzaldehydes 1a,b were kept in solution (DCM or THF) in the presence of a catalytic amount of TFA at room temperature, the formation of regioisomeric aldehydes 2a,b and dimer-like products 3a,b was observed. After a similar treatment of related benzaldehydes 1c,d, only the dimer-like products 8a,b were isolated. The transformations occur via an isoindole intermediate 4. In order to reduce the number of expected products, the similar reaction of unsubstituted o-(pivaloylaminomethyl)benzaldehyde (1e) was also studied. DFT calculations supported the mechanism proposed for the transformations and explained the structural differences of the dimer-like products, as well as the observed product distributions.

Experimental

Compounds 1a,b,c [2], 2a, 3a [1] and 21 [26] are known in the literature, while compounds 1d,e, 2b, 3b, 8a,b and 23a,b are new. The synthetic procedures and characterizations are given either below (2a and 3a with new synthetic procedures, and 8a, 23a) or in Supporting Information File 1 (1d, 1e, 2b, 3b, 8b, 23b). All melting points were determined on a Büchi B-540 (Flawil, Switzerland) capillary melting point apparatus and are uncorrected. IR spectra were obtained on a Bruker ALPHA FT-IR spectrometer (Billerica, MA, USA) in KBr pellets. 1H NMR, 13C NMR, DeptQ, Dept-135, edHSQC, selective HSQC, HMBC, selective HMBC, NOESY, 1H,1H-COSY, one-dimensional selective NOE, and selective TOCSY spectra were recorded at 295 K on a Bruker Avance III HD 600 (Billerica, MA, USA; 600 and 150 MHz for 1H and 13C NMR spectra, respectively) spectrometer equipped with a Prodigy cryo-probehead. The pulse programs were taken from the Bruker software library (TopSpin 3.5) and full 1H and 13C assignments were achieved with widely accepted strategies [34,35]. 1H NMR assignments were accomplished using general knowledge of chemical shift dispersion with the aid of the 1H-1H coupling pattern (1H NMR spectra). CDCl3 was used as the solvent and tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and Hz, respectively. The lists of the NMR signals can be found in Supporting Information File 1. To facilitate the understanding of the 1H and 13C signal assignments, the structures of the compounds are also depicted on the spectra (Supporting Information File 1 pages S3–S43). High-resolution mass spectra were recorded on a Bruker O-TOF MAXIS Impact mass spectrometer (Billerica, MA, USA) coupled with a Dionex Ultimate 3000 RS HPLC (Sunnyvale, CA, USA) system with a diode array detector. HRMS spectra of the diastereomeric 23a and 23b compounds are shown on page S44 of Supporting Information File 1. Single-crystal X-ray diffraction (SC-XRD) measurements were carried out on a Rigaku R-Axis Spider diffractometer (Tokyo, Japan) with imaging plate area detector using graphite monochromatic Cu Kα radiation. SC-XRD structures were deposited at the Cambridge Crystallographic Data Centre under the following numbers: CCDC 1953421 (3a), 1953424 (3b), 1953422 (8b), 1953423 (23a) and 1958809 (23b). All reagents were purchased from commercial sources and used without further purification. The reactions were followed by analytical thin-layer chromatography on silica gel 60 F254 (Darmstadt, Germany) and on a Shimadzu LC-20 HPLC equipment coupled with an LCMS-2020 mass spectrometer (Kyoto, Japan). Purifications by flash chromatography were performed applying a Teledyne Isco Combiflash® RF system (Thousand Oaks, CA, USA) with RediSep® RF silica flash columns using a hexane–EtOAc solvent system. The preparative HPLC separation was carried out using a Merck LaPrep Sigma LP1200 pump and a Merck LaPrep P314 UV detector, under the conditions described below for compound 23b.

The DFT level computations at the B3LYP/6-31+G (d,p) level of theory were performed considering the solvent effect of DCM using the IEFPCM solvent model with the Gaussian 09 program package. The geometries of the molecules were optimized in all cases, and frequency calculations were also performed to assure that the structures are in a local minimum or in a saddle point. This was followed by single point measurements at the B3LYP/6-311++G (3df,3pd) level of theory that resulted in the energy values presented in Table S1 (Supporting Information File 1, page S45) and used for the figures of the paper. The conformations of the reported structures have been determined by conformational analysis. The solution-phase Gibbs free energies were obtained by frequency calculations as well. The G values obtained were given under standard conditions, the corrected total energies of the molecules were taken into account. Entropic and thermal corrections were evaluated for isolated molecules using standard rigid rotor harmonic oscillator approximations. That is, the Gibbs free energy was taken as the “sum of electronic and thermal free energies” printed in a Gaussian 09 vibrational frequency calculation. Standard state correction was taken into account. The transition states were optimized with the QST3 or the TS (berry) method. Transition states were identified by having one imaginary frequency in the
Hessian matrix, and IRC calculations were performed in order to prove that the transition states connect two corresponding minima.

**General procedure I for the synthesis of compounds 2a,b, 3a,b, 8a,b and 23a.** TFA (0.1 equiv) was added to a solution of 1a–e in DCM (20 mL). After stirring for 24 h at room temperature, an aqueous sodium carbonate solution (5%, 7 mL) and DCM (4 mL) were added. The aqueous layer was extracted with DCM (2 × 4 mL). The combined organic layer was dried over MgSO₄. The solvent was evaporated and the residue purified by flash chromatography (5–30% EtOAc in hexane). The corresponding fractions were collected, evaporated, and recrystallized from EtOAc/hexane to afford the title compounds as white solids.

**General procedure II for the synthesis of compounds 2a,b, 3a,b, 8a,b and 23a.** TFA (0.1 equiv) was added to a solution of 1a–e in THF (20 mL). After stirring for 24 h at room temperature, an aqueous sodium carbonate solution (5%, 7 mL) and DCM (4 mL) were added. The aqueous layer was extracted with DCM (2 × 4 mL). The combined organic layer was dried over MgSO₄. The solvent was evaporated and the residue purified by flash chromatography (5–30% EtOAc in hexane). The corresponding fractions were collected, evaporated, and recrystallized from EtOAc/hexane to afford the title compounds as white solids.

N\{[(5-Formyl-2H-1,3-benzo[dioxol-4-yl)methyl]-2,2-dimethylpropanamide (3a) [1], Method A: This compound was prepared according to general procedure I using 1a [2] (1.02 g, 3.88 mmol) and TFA (29 µL, 43 mg, 0.38 mmol). The title compound (42 mg, 4%) was isolated as a white solid. Analytical data are identical with those described in Method A.

N\{[(5-Formyl-2H-1,3-benzo[dioxol-4-yl)methyl]-2,2-dimethylpropanamide (3a) [1], Method A: This compound was prepared according to general procedure I using 1a [2] (1.00 g, 3.80 mmol) and TFA (29 µL, 46 mg, 0.41 mmol). The title compound (78 mg, 8%) was isolated as white solid. Mp 169–171 °C (EtOAc/hexane); IR (KBr): v>NH 3344, v>CH 3027, ν>C=O (amide) 1695, 1614, 1549, 1494, ν>C–C 1268, ν>C–O 1064 cm⁻¹; HRMS (m/z): [M + H]+ calcd for C₂₅H₂₈NO₅⁺ 481.2697; found: 481.2681; anal. calcd for C₂₅H₂₈NO₅ (480.61): N, 5.83; H, 7.55; C, 69.98%; found: N, 5.87; H, 7.36; C, 69.83%.

Method B: This compound was prepared according to general procedure I using 1a [2] (1.01 g, 4.06 mmol) and TFA (31 µL, 46 mg, 0.41 mmol). The title compound (78 mg, 8%) was isolated as white solid. Mp 169–171 °C (EtOAc/hexane); IR (KBr): v>NH 3344, v>CH 3027, ν>C=O (amide) 1663, ν>C–C (Ar) 1612, 1527, ν>C–O 1276, ν>C–O 1074 cm⁻¹; HRMS (m/z): [M+H]+ calced for C₂₅H₂₈NO₅⁺ 481.2697; found: 481.2681; anal. calcd for C₂₅H₂₈NO₅ (480.61): N, 5.83; H, 7.55; C, 69.98%; found: N, 5.87; H, 7.36; C, 69.83%.

1H and 13C spectra are shown on page S19 of Supporting Information File 1. Hydrogen–hydrogen connectivities were elucidated utilizing the 1H,1H-COSY experiment (page S20, Supporting Information File 1). The detected low J(H,H) coupling constant (ca. 1 Hz) revealed also in this case a dihedral angle of nearly 90° for the H–C–H moiety. One-dimensional sel-NOE experiments on signals 9.78, 6.88, 6.30, 5.91, 4.59, and 3.42 elucidated the characteristic steric proximities (pages S21 and S22 in Supporting Information File 1) and proved the SR–RS-type structure. The 13C signal assignment was supported with HSQC and HMBC spectra (pages S23 and S24 in Supporting Information File 1).

Method B: This compound was prepared according to general procedure I using 1e [2] (1.00 g, 4.02 mmol) and TFA (31 µL, 46 mg, 0.40 mmol). The title compound (71 mg, 7%) was isolated as white solid. Analytical data are identical with those described in Method A.

**N\{-[(6R,S)-7-(2,2-Dimethylpropanoyl)-2H,6H,7H,8H-1,3-dioxol-4-yl)ethyl]-2,2-dimethylpropanamide (3a) [1], Method A: This compound was prepared according to general proce-

According to general procedure I using 1e (1.01 g, 4.61 mmol) and trifluoroacetic acid (35 µL, 53 mg, 0.46 mmol). The title compound (584 mg, 58%) was isolated as white solid. Mp 156–158 °C (EtOAc/hexane); IR (KBr): νCH 3314, νCH 2965, νHC=O (amide) 1657, νC=O (amide) 1613, 1481 cm⁻¹; HRMS [M + H]⁺ calcd for C₂₉H₃₃N₂O₃ (420.55): N, 6.66; H, 7.67; C, 74.26%; found: N, 6.70; H, 7.42; C, 73.98%. The ¹H spectrum is shown on page S32 of Supporting Information File 1. The two-dimensional NOESY experiment (page S33 in Supporting Information File 1) revealed the characteristic steric proximities and proved the SR–RS-type structure. The ¹³C signal assignment (page S34 in Supporting Information File 1) was supported by edHSQC and HMBC measurements, together with their band selective versions (pages S35–S37 in Supporting Information File 1).

Method B: This compound was prepared according to general procedure II using 1e (1.03 g, 4.70 mmol) and TFA (36 µL, 53 mg, 0.46 mmol). The title compound (182 mg, 18%) was isolated as white solid. Analytical data are identical with those described in Method A.

Supporting Information

Detailed NMR studies (¹H NMR, ¹³C NMR, DeptQ, Dept-135, edHSQC, selective HSQC, HMBC, selective HMBC, NOESY, ¹H, ¹H-COSY, one-dimensional selective NOE, selective TOCSY spectra) of new compounds; HRMS spectra of compounds 3a, 3b, 8b, 23a, and 23b. (https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-136-S1.pdf)

Supporting Information File 2

Crystallographic information files for compounds 3a, 3b, 8b, 23a, and 23b. (https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-136-S2.zip)

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