Pyroglutamic Acid in Drug Synthesis, Part 1

A Method for the Synthesis of Enantiomerically Pure 4-Alkyl-4-arylpyroglutamic Acids☆

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Summary

Synthesis of the title compounds is described, starting from alkylation of the pyroglutaminol-acetal **4a**[1] at the α-lactam position C-6 with methyl iodide. Subsequent addition of 2-cyclohexen-1-one led to diastereoselective formation of the 1,2-aldol addition product **7b/7c**, which after dehydratization was aromatized with DDQ to yield the 6-methyl-6-phenyl derivative **7h**. Acetal cleavage and Jones oxidation yielded 4,4-disubstituted, enantiomerically pure pyroglutamic acid **3b**. X-ray analysis confirmed the assignment of the configuration of the newly created chiral centre.

Introduction

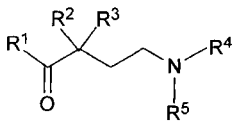
(*S*)-Pyroglutamic acid (**3a**) is a particularly promising compound of the "chiral pool", because – apart from its use as tool in drug synthesis – the compound itself is a rigidized relative of glutaric acid. From a theoretical point of view structural features of both the open chain compound 4-aminobutyric acid (γ-aminobutyric acid, GABA, **1a**) and the product of its – formally chemical – intramolecular ring closure (2-pyrrolidinone, **2a**) might be discovered in **3a**. They appear in a series of drugs, such as the open chain antiarrhythmic drug Disopyramide (**1b**) and the succinimide-type antiepileptics Ethosuximide (**2c**), Mesuximide (**2d**), and Phensuximide (**2e**)[2]. Owing to our interest in excitatory amino acid-[3,4] and GABA-[5]receptor oriented drug research, as well as our research interest in antiarrhythmic drugs[6], we decided to develop a stereoselective method for alkyl-aryl disubstitution of the α-position to the lactam carbonyl group of pyroglutamic acid (**3a**, Scheme 1), a structural element also of compounds **1b**, **1c**[7], and **2d** (Figure 1).

Results and Discussion

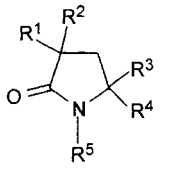
To avoid racemization of pyroglutamic acid in α-position to the carboxyl moiety during the reaction sequence, we decided to use a method for diastereoselective α-substitution of lactams based on the bicyclic *O,N*-acetal **4a** as presented by Thottathil[1]. Compound **4a** is obtained from (*S*)-pyroglutamic acid (**3a**) by reduction and diastereoselective acetal formation with benzaldehyde. The (3*R*)-configuration of the acetal carbon atom was assigned on basis of established data[8].

Bearing in mind that enhanced acidity of an α-arylated product in the second deprotonation step and reduced steric demand of a primary alkyl iodide in the sterically more hindered second alkylation would both confer a considerable advantage, we decided to carry out arylation[9,10] as the first and alkylation[11–13] as the second step.

Deprotonation of benzyl cyanides with sodium amide and consecutive arylation with electrophilic 2-chloropyridine is described as a method for the synthesis of **1b** and Pheniramin[2]. However, a series of attempts to use 2-halopyridines (chloro-, bromo-, and iodo-derivatives, respectively) to obtain **4e** and halobenzenes to obtain **4d** exhibiting a suitable substitution pattern for the arylation of deprotonated **4a** did not succeed. In these experiments the organic bases LDA and LICA (lithium-isopropyl-cyclohexylamide) were used for deprotonation of **4a**. Obviously, the tendency of the applied



1a R^1 = OH, R^2 = R^3 = R^4 = R^5 = H (4-aminobutyric acid, GABA)
1b R^1 = NH_2, R^2 = Ph, R^3 = 2-pyridyl, R^4 = R^5 = *i*Pr (Disopyramide)
1c R^1 = NH_2, R^2 = 2-Me-propyl, R^3 = 2-pyridyl, R^4 = R^5 = *i*Pr (no INN)



2a R^1 = R^2 = R^3 = R^4 = R^5 = H (pyrrolidin-2-one)
2b R^1 = R^2 = H, R^3 + R^4 = =O, R^5 = H (succinimide)
2c R^1 = Et, R^2 = Me, R^3 + R^4 = =O, R^5 = H (Ethosuximide)
2d R^1 = Ph, R^2 = Me, R^3 + R^4 = =O, R^5 = Me (Mesuximide)
2e R^1 = Ph, R^2 = H, R^3 + R^4 = =O, R^5 = Me (Phensuximide)

Figure 1

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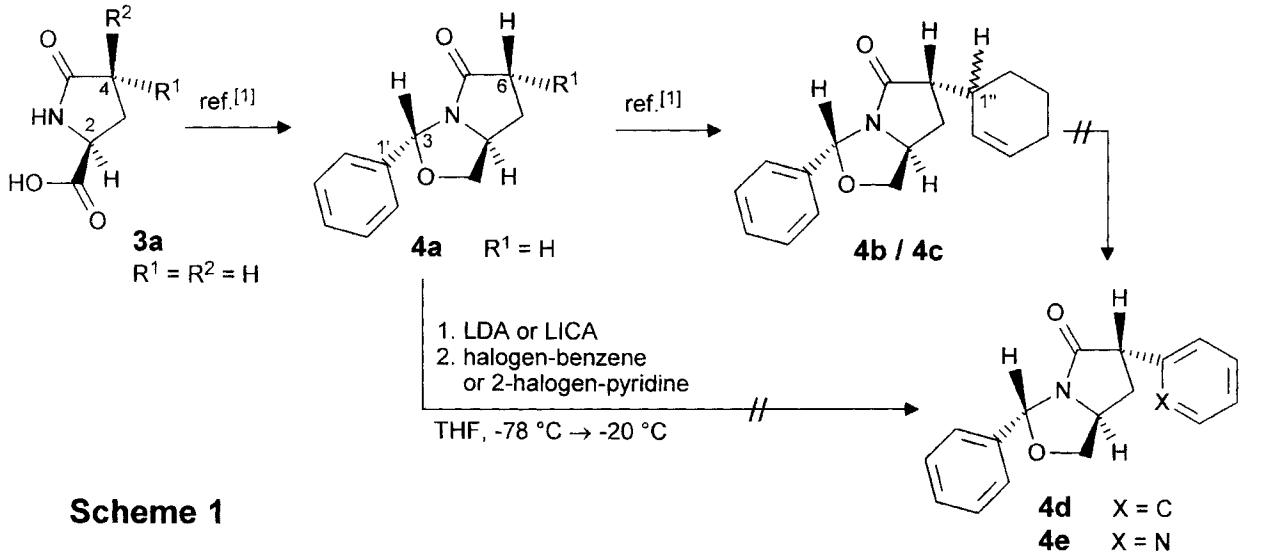
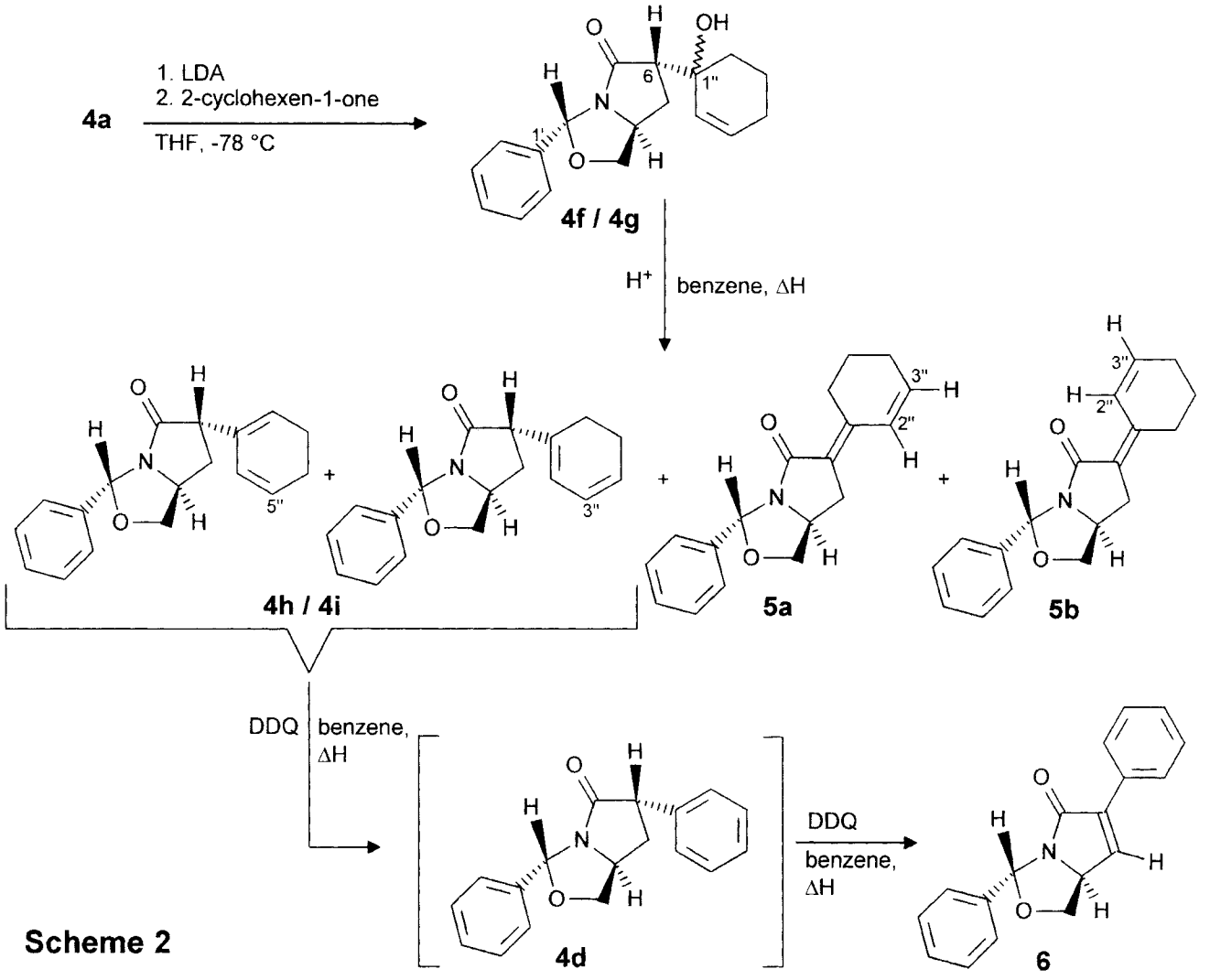


Scheme 1



Scheme 2

aromatic compounds to undergo nucleophilic aromatic substitution was too low in our case[14,15]. Also the use of catalytic reagents for arylation, such as the method described by Rathke[16] using iodine, failed to yield the desired products with either chloro- and bromobenzene or 2-chloro- and 2-bromopyridine, as did the method of Semmelhack[17] employing benzenechrometricarbonyl and an excess of iodine to phenylate ester enolates. No phenylated fraction could be isolated[18] in our experiments , but there was spectroscopic evidence for the formation of the diastereomeric 6-iodo-derivatives of **4a** [(6*R*), *exo*:(6*S*), *endo* ≈ 5:1, yield < 5%].

Thus an "alkylation-aromatization" approach was chosen, in which a cyclohexene derivative suited for subsequent aromatization was introduced in the first step. Thottathil had found that with **4a** alkylation at the lactam α-position C-6 proceeded stereoselectively to yield the (6*S*)-cyclohexenyl derivative with a de > 95% as a mixture of C-1″-diastereomers (**4b/4c**, Scheme 1). Our attempts at direct conversion of this cyclohexenyl ring using Pd/C at 300 °C[19] led only to decomposition. Attempts to aromatize **4b/4c** by radical allylic bromination of the cyclohexene double bond[20] followed by dehydrobromination and final catalytic dehydrogenation provided spectroscopic evidence for allyl-brominated and also dibrominated products in some of the fractions. The concept was abandoned, however, because of the complexity of the reaction mixture formed.

Instead, addition of 2-cyclohexen-1-one was attempted to yield in only one step a product of the same oxidation state as the allyl-brominated intermediate. Since it can undergo both 1,2-aldol addition and 1,4-Michael addition[21] kinetic reaction conditions were employed with 2-cyclohexen-1-one being added dropwise at –78 °C. Under these conditions the 1,2-addition product **4f/4g** was formed exclusively as a mixture of diastereomers (Scheme 2). According to the literature[1] we assumed that the addition had proceeded stereoselectively with respect to the α-position to the carbonyl group, yet non-selectively with respect to the second chiral center formed (carbinol C atom C-1″). Since this chiral centre was to be destroyed in the subsequent reaction step, the diastereomers were not separated.

To avoid acetal cleavage, dehydratization of the tertiary alcohol **4f/4g** was carried out by refluxing it in benzene with catalytic amounts of *p*-toluenesulfonic acid (pTSA)[22–25] and removing the reaction water by azeotropic distillation. Using column chromatography, two fractions (**4h/4i** and **5a/5b**) of isomeric compounds could be isolated from the reaction mixture, which had been formed in a ratio of 3:7. NMR analysis revealed that **4h** and **4i** were cyclohexadienyl-isomers, and that **5a** and **5b** were two isomers with exocyclic double-bonds. With respect to the isomeric ratio within the fractions, doubling of some of the signals in the ^{13}C NMR spectrum and of the acetal proton H-3 in the ^{1}H NMR spectrum allowed to establish a ratio of **4h/4i** = 10:1. Great differences in chemical shifts of the olefinic protons H-2″ and H-3″ made determination of the ratio of **5a**:**5b** ≈ 1:1 easy. Isomer **5a** could be assigned the *E*- and **5b** the *Z*-configuration. Isolation of **5a** as a side-product in other alkylations experiments[11] confirmed the interpretation of the NMR-spectra of the mixture of **5a/5b**.

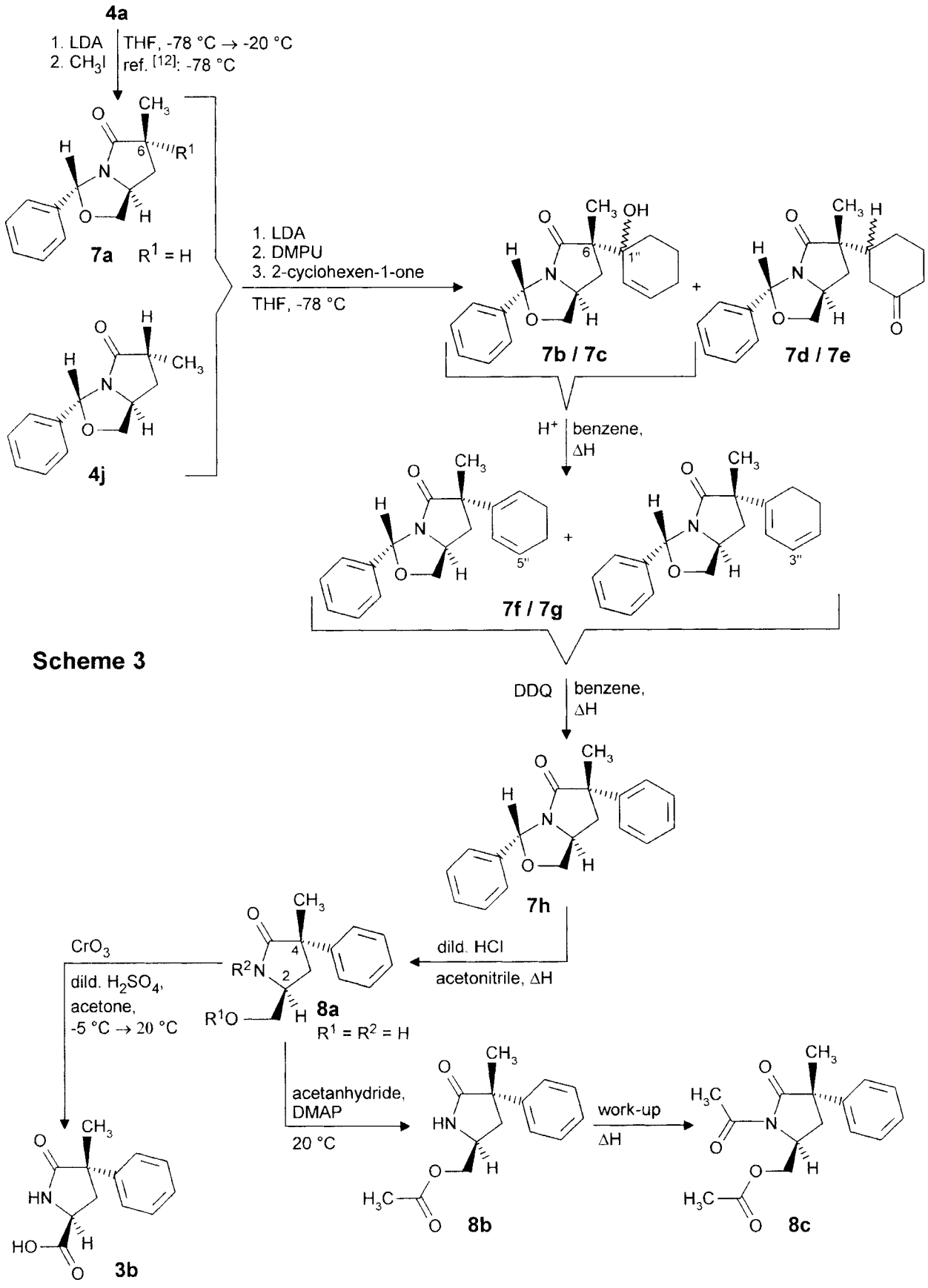
Attempts to influence the ratio **4h/4i** versus **5a/5b** in the dehydratization reaction and to direct the newly formed double bond into the cyclohexene-ring failed. In case of the dehydratization of **4f/4g** the thermodynamically favoured formation of the conjugated α,β,γ,δ-unsaturated carbonyl compounds **5a/5b** obviously prevails in the reaction[26].

Subsequent aromatization[27,28] of the mixture of the (6*S*)-cyclohexadienyl-intermediates **4h/4i** by oxidation with DDQ (2,3-dichloro-5,6-dicyanobenzoquinone)[29] did not stop at the stage of the α-phenyl-compound **4d**, but proceeded in a second rapidly occurring oxidation step to the arylated pyrroline-derivative **6**[30]. With equimolar use of DDQ the crude reaction mixture contained compound **6** and the unreacted educt mixture **4h/4i**. Upon addition of two mole equivalents of DDQ the educt was completely consumed and only **6** was isolated in poor yields (for troubles see aromatization of **7f/7g** to **7h**). In the ^{1}H NMR spectrum of **6** the characteristic signal of H-7a (ddd), which is – due to its new olefinic environment – markedly shifted downfield in comparison to saturated compounds, provided an excellent proof for the location of the double bond between C-6 and C-7. An alternative aromatization method using an excess of manganese dioxide failed completely[28].

Although compound **6** is a useful arylated pyroglutamic acid derivative, it was considered unsuited for further alkylation in position 6. Since the output of **6** in relation to **4f/4g** was less than 10%, hydrogenation of the double-bond C6-C7 to obtain **4d** well suited for further α-alkylations is no considerable synthetic alternative. However, taking into account that the planned reaction sequence, in principle, proceeded in the expected way and that both side reactions (preferred exocyclic dehydratization of the tertiary alcohol **4f/4g** and the impossibility of stopping dehydrogenation of **4h/4i** with DDQ at the stage of the α-phenyl-derivative **4d**) were caused by the presence of a hydrogen atom at C-6, we decided to switch the reaction sequence and to attempt alkylation before arylation. Replacement of the C-6 hydrogen atom by a methyl group would then exclude both side reactions in the arylation step.

Alkylation with the reactive "small" methyl iodide succeeded in high yields (Scheme 3). Independently of us[11,31], another working group briefly reported (without experimental details) the methylation of **4a**[12]. Indeed the preferred *endo*-orientation of the methyl group (ratio **7a**: **4j** = 3.5:1; ref.[12]: 5:1) was unexpected but is in line with stereoselectivities obtained by alkylation of analogous[32] or similar lactams derived from phenylglycinol[33]. As a shortcut we report that already the ethylation of **4a** leads preferably to the expected exo-product (*exo*:*endo* = 2:1)[11]. However, the fact that both diastereomers **7a** and **4j** form the same lithium enolate upon deprotonation in the second deprotonation step rendered the stereochemical course of the first reaction irrelevant with respect to the planned reaction sequence.

In the addition of 2-cyclohexen-1-one to the methylated diastereomers **7a** and **4j** the increased steric demand at the reacting carbanion C-6 caused by the presence of the methyl group required careful choice of reaction conditions. The reaction mixture was accurately kept at –78 °C and the 1,2-directing auxiliary 1,3-dimethyl-tetrahydro-2(*1H*)-pyrimidinone (DMPU)[34] was added. The tertiary alcohol **7b/7c** was isolated in 61% yield after chromatography. With-


4a
1. LDA
2. CH3I
THF, -78 °C → -20 °C
ref. [12]: -78 °C
7a R1 = H
4j
1. LDA
2. DMPU
3. 2-cyclohexen-1-one
THF, -78 °C
7b / 7c
7d / 7e
H+
benzene, ΔH
7f / 7g
DDQ
benzene, ΔH
7h
dild. HCl
acetonitrile, ΔH
8a
R1 = R2 = H
CrO3
dild. H2SO4,
acetone,
-5 °C → 20 °C
3b
acetanhydride,
DMAP
20 °C
8b
work-up
ΔH
8c

Scheme 3

out application of DMPU, the yield of **7b/7c** was about 10% lower. Despite of strict kinetic control the Michael-addition-product **7c/7d** was isolated too in 15% yield – in contrast to the case of the non-methylated educt. As had been previously observed with **4f/4g**, compound **7b/7c** was formed stereoselectively with respect to the α-position to the carbonyl group, but non-selectively with respect to the carbinol-C-atom C-1″.

Subsequent dehydratization was again achieved by refluxing **7b/7c** in benzene with catalytic pTSA and azeotropic removal of the reaction water. Because of the presence of the quaternary carbon atom C-6, exocyclic dehydratization could not occur in this case. Nevertheless, the ^{1}H NMR spectrum of the crude reaction mixture showed two methyl signals indicating formation of two compounds (ratio ≈ 1:1). This finding was supported by a ^{1}H NMR spectrum at elevated temperature (CCl_4, 90 °C), in which the two methyl singlets did not fuse. In fact, two fractions were obtained by CC, which could be assigned as the enriched 1,5- and 1,3-cyclohexadienyl isomers **7f** and **7g**.

Aromatization of the mixture **7f/7g** with DDQ to yield **7h** was attempted by refluxing it in benzene, so that both reactions (dehydratization and aromatization) could be carried out in a "one-pot synthesis". Work-up of the aromatization reaction proved to be rather tedious: Acetal cleavage occurred to some degree, and the voluminous residues during work-up absorbed parts of the product. The polar reddish quinones and hydroquinones were carefully removed (flash column chromatography). Both ^{1}H- and ^{13}C NMR spectra of **7h** confirmed that addition of 2-cyclohexen-1-one to C-6 had occurred stereoselectively from the outside of the "roof"-shaped bicyclic acetal yielding the (6*S*)-configuration.

Acetal cleavage of **7h** was easily achieved in acetonitrile and diluted hydrochloric acid yielding the pyroglutaminol derivative **8a** and benzaldehyde, which was carefully removed. Confirmation of the structure of **8a** was carried out using ^{1}H NMR spectroscopy. All protons could be assigned by help of acylation shifts observed with acetylation of **8a** to the *O*-acetyl-derivative **8b** and the *O,N*-diacetyl-derivative **8c**. In fact, in **8a-8c** the methylene protons of the hydroxymethyl-substituent exhibited shift differences of about 0.3 ppm in the ^{1}H NMR spectra.

Oxidation of the alcohol **8a** by Jones oxidation[1,35] yielded enantiomerically pure (*S-trans*)-4-methyl-4-phenyl-pyroglutamic acid **3b**. The structure of the compound was confirmed by ^{1}H NMR spectroscopy with NOE-experiments (in [D_6]DMSO) allowing assignment of the methylene protons at C-3 and by X-ray structure analysis.

We clearly emphasize that the sythesis of the key-compound **7h** is a rather lucky final result of great efforts towards α-aryl-derivatives of **4a**. Of course this method so far lacks of the obtainment of "*cis*"-aryl-compounds, and the alkyl- and the phenyl-group can not be exchanged via inversion of the reaction sequence. Furthermore, the fact that the aryl group is derived from 2-cyclohexen-1-one brings a restriction in the substitution of the phenyl group itself.

X-Ray Structure Analysis

Analysis of a single crystal of **3b** grown from methanol with the dimensions 0.15 × 0.30 × 0.45 mm on a Philips diffractometer PW 1100 (MoKα-radiation with a graphit-monochromator) yielded the following crystallographic data: orthorhombic cell with a = 30.60(1), b = 10.320(2), c = 7.082(2) Å and space goup $P2_12_12_1$. The density of about 1.3 g cm^{-1} was obtained from measurements in different liquids (ethyl acetate, water, chlorobenzene, dichlorobenzene) which leads to Z = 8 (D_x = 1.302) thus indicating the existence of two independent molecules in the unit cell. The intensities of 2040 unique reflections were measured with omega scans in the range of Θ = 2–24°, 1286 reflections with I 2σ (I). The solution of the structure by direct methods with MULTAN78[36] revealed the two expected molecules, which were refined by SHELX76 program[37]. A full matrix refinement with anisotropic temperature coefficients for the heavy atoms was calculated with the hydrogen atoms at geometrically fixed positions riding on the binding carbon atoms. In order to reduce the number of free parameters, the atoms of the phenyl and the methyl substituent were refined as rigid groups. Since the positions of the four heteroprotons could not be predicted by purely geometric criteria, they were refined as independent atoms. Reasonable hydrogen bonds could be calculated for all four heteroprotons. Final refinement with 156 parameters and all 2040 reflections yielded R = 0.088 and R_w = 0.054 $\{w = 1/[\sigma^2(f) + 0.0003 \times F^2]\}$.

As a main result the X-ray structure analysis confirmed the configuration assignment of the chiral centre at C-4 created in the reaction-sequence. The observed (*S*)-configuration is in keeping with a reaction course for the addition of 2-cyclohexen-1-one in which the rather bulky molecule is added stereoselectively from the outside of the "roof"-shaped bicyclic acetals **4f/4g**, **4j** and **7a**.

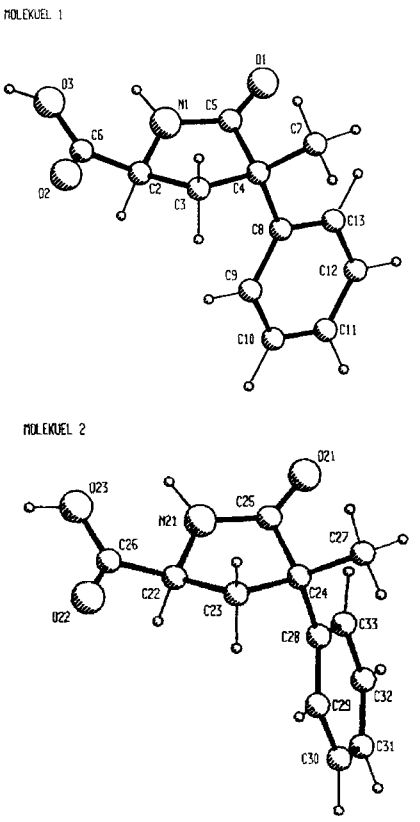


Figure 2

From Figure 2 it can also be seen that the two molecules are highly coincident with the exception of the orientation of the phenyl group. The angles of the plane of the phenyl group relative to the plane of pyrrolidin-2-one can be estimated by calculating torsional angles: e.g. C(3)–C(4)–C(8)–C(13) = +179.7° (molecule 1) and C(23)–C(24)–C(28)–C(33) = +145.1° (molecule 2). Corresponding values are found when comparing the torsional angles C(7)–C(4)–C(8)–C(9) in molecule 1 (+127.6°) with C(27)–C(24)–C(28)–C(29) in molecule 2 (+86.8°).

Further details and the complete data of this X-ray structure analysis are available from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen 2, upon statement of the deposition number CSD 59162, of the authors, and of the accepting journal. Figure 2 was plotted with PLUTO[38].

Experimental Part

General Remarks and Procedures

Mp: Kofler melting point apparatus (uncorrected).– Polarimetry: Perkin-Elmer 241.– IR (KBr): Perkin Elmer 298 Spectrophotometer.– NMR spectra were recorded on Bruker AC 80 and Bruker WM 250 using TMS as an internal standard. Compounds **7a** and **4j** were analyzed in detail on a Varian Unity plus 300 by means of COSY- and NOE-experiments. NMR data of these compounds were correlated to corresponding partial structures of related compounds. An asterisk (*) designates signals exchangeable with D_2O. α- and β-Descriptors to differentiate between methylene protons were assigned according to established rules, with α-protons in the bicyclic derivatives being located "*cis*" to the acetal-phenyl group and α-protons in the monocyclic compounds being located "*cis*" to the hydroxymethyl or carboxyl group at C-2.– Mass spectra: Varian MAT 111A. All elementary analyses were in agreement with the calculated values within 0.3%. Column chromatography: Silica gel (Merck) 0.04–0.063 mm. Solvent systems and R_f-values are indicated in the monographs below. TLC: Al sheets, 0.2 mm layer silica gel (type 60 F_{254}, Merck).

General Procedure for the Synthesis of a 5 mM LDA-Solution (ref.[11]): Under an argon-atmosphere a solution of 0.7 ml (5 mM) diisopropylamine (freshly distilled over KOH) in 10 ml of dry THF was cooled to –10 °C and 3.3 ml (5 mM) of a 1.5 M solution of *n*-butyllithium in hexane was added with vigorous stirring. 15 min later the flask was cooled to –78 °C.

Monographs

*[3R-[3α,6α(R*S*),7aα]]-6-(1-Hydroxycyclohex-2-enyl)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**4f/4g**)*

At –78 °C 4.06 g (20 mM) of compound **4a** (ref.[11]) in 25 ml of dry THF was added to a 20 mM LDA solution and stirring at –78 °C was continued for 30 min. Then 2.12 ml (22 mM) of freshly distilled 2-cyclohexen-1-one was added dropwise and strictly at –78 °C over a period of 30 min and stirring was continued at –78 °C until TLC indicated absence of educt (30 min). The reaction mixture was hydrolyzed cautiously with water (10 ml) and then poured onto 60 ml of crushed ice and water. The aqueous phase was saturated with sodium chloride and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (5 × 40 ml).

The combined organic phase was washed with water (1 × 40 ml) and brine (1 × 40 ml), dried over Na_2SO_4 and evaporated.

4f/4g: yield: 4.88 g (81%); mp 80–84 °C (*n*-propanol).– IR: ν = 3400 cm^{-1} (OH, weak signal), 1700 (C=O, amide).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.49–2.22 (m, 8H), 2.88 (m, 1H, 6-H), 3.38 (m, 1H, 1β-H), 3.28 (br. s) and 3.98 (br. s, together 1H, *, OH), 4.01 (m, 1H, 7a-H), 4.22 (m, 1H, 1α-H), 5.60 (m, 1H, olefinic H), 5.99 (m, 1H, olefinic H), 6.31 (s, 1H, 3-H), 7.35–7.50 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 18.15 + 18.31, 23.85, 24.13 + 25.13 (C-4″, C-5″, C-6″), 32.48 + 34.56 (C-7), 52.91 + 54.04 (C-6), 57.07 + 57.70 (C-7a), 70.66 (C-1″), 70.81 + 71.49 (C-1), 87.37 + 87.72 (C-3) 125.90 (C-2′, C-6′), 128.40 (C-3′, C-5′), 128.48 (C-4′), 128.90 + 129.53 (C-3″), 132.33 + 132.60 (C-2″), 138.94 (C-1′), 179.07 + 179.97 (C=O).– MS (70 eV); *m/z* (%) = 281 (12) [M^+ – H_2O], 203 (96) [M^+ – C_6H_9O].– Anal. ($C_{18}H_{21}NO_3$).

*[3R-(cis,6E)]-6-(Cyclohex-2-enylidene)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one and [3R-(cis,6Z)]-6-(Cyclohex-2-enylidene)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**5a/5b**) and [3R-(3α,6α,7aα)]-6-(Cyclohexa-1,5-dienyl)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one and [3R-(3α,6α,7aα)]-6-(Cyclohexa-1,3-dienyl)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**4h/4i**)*

A solution of 3.6 g (12 mM) of **4f/4g** in 120 ml of benzene was added slowly to a gently refluxing solution of 0.2 g pTSA in benzene in a Wheater-Soxhlet water separator containing molecular sieve (4Å). After 6 h of azeotropic removal of water, benzene was evaporated. CC (petroleum ether/ethyl acetate = 8/1) of the crude mixture (2.8 g) yielded two fractions:

5a/5b: R_f 0.52; yield: 1.6 g (48%), mp 94–96 °C (petroleum ether/ethyl acetate).– IR: ν = 1680 cm^{-1} (C=O), 1630 (α,β-unsat. carbonyl compound).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.80 (m, 4H, 2 H from both **5a** and **5b**), 2.25 (m, 6H, 2H from **5a** and 4H from **5b**), 2.65 (m, 2H, 1H from both **5a** and **5b**), 3.05 (m, 4H, 3H from **5a** and 1H from **5b**), 3.34 (t, *J* = 7.6 Hz, 2H, 1β-H in **5a** and **5b**), 4.00 (m, 2H, 7a-H in **5a** and **5b**), 4.24 (t, *J* = 7.6 Hz, 2H, 1α-H in **5a** and **5b**), 6.13 (m, 2H, 2″-H in **5a** and 3″-H in **5b**), 6.29 (m, 3″-H in **5a**), 6.36 (s, 2H, 3-H in **5a** and **5b**), 7.34 (6H, 3 aromatic H from both **5a** and **5b**), 7.48 (d, J_{ortho} = 6.0 Hz, 4H, 2′-H, 4′-H from both **5a** and **5b**), 7.84 (d, *J* = 10.0 Hz, 2″-H in **5b**).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.02 (**5a**), 22.15 (**5b**), 24.81 (**5a**), 25.52 (**5b**), 25.94 (**5a**), 26.92 (**5a**), 27.54 (**5b**), 28.64 (**5b**) (C-4″, C-5″, C-6″, C-7), 54.78 (C-7a), 71.68 (C-1″), 87.92 (C-3 in **5a**), 87.99 (C-3 in **5b**), 122.13 (C-1″ in **5a**), 122.20 (C-1″ in **5b**), 124.27 (C-3″ in **5b**), 125.99 (C-2′, C-6′), 126.55 (C-3″ in **5a**), 128.32 (C-3′, C-4′, C-5′), 135.44 (C-2″ in **5b**), 138.55 (C-2″ in **5a**), 139.64 (C-1′), 144.15 (C-6 in **5a**), 144.32 (C-6 in **5b**), 172.34 (C=O in **5b**), 173.26 (C=O in **5a**).– MS (70 eV); *m/z* (%) = 281 (100) [M^+], 175 (31) [M^+ – C_7H_5O] .– Anal. ($C_{18}H_{19}NO_2$).

4h/4i: R_f 0.32; yield: 0.72 g (21%), mp 87–89 °C (petroleum ether/ethyl acetate).– IR: ν = 1708 cm^{-1} (C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.17 (m, 6H, 3″-H, 4″-H, 7-H in **4h**; 5″-H, 6″-H, 7-H in **4i**), 3.37 (dd, *J* = 4.8, 9.0 Hz, 6-H), 3.48 (t, *J* = 7.7 Hz, 1H, 1β-H), 4.12 (m, 1H, 7a-H), 4.24 (dd, *J* = 6.8, 7.7 Hz, 1H, 1α-H), 5.72 (m, 1H, olefinic H), 5.90 (m, 2H, olefinic H), 6.36 (s, 1H, 3-H), 7.28–7.50 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.01, 22.25, 22.69, 24.36, (C-3″, C-4″ in **4h**; C-5″, C-6″ in **4i**), 28.69 + 28.93 (C-7), 50.89 + 52.50 (C-6), 57.38 + 57.46 (C-7a), 71.42 (C-1″), 87.29 (C-3), 120.75, 122.30, 124.12, 124.34, 125.39, 128.60 (C-2″, C-5″, C-6″ in **4h**; C-2″, C-3″, C-4″ in **4i**), 125.90 (C-2′, C-6′), 128.38 (C-3′, C-5′), 128.44 (C-4′), 133.10 (C-1″), 138.36 (C-1′), 178.22 (C=O).– MS (70 eV); *m/z* (%) = 281 (96) [M^+], 160 (26) [M^+ – C_8H_8O].– Anal. ($C_{18}H_{19}NO_2$).

*(3R-cis)-3,6-Diphenyl-3H,5H-1,7a-dihydropyrrolo[1,2-c]oxazol-5-one (**6**)*

To a refluxing solution of 0.56 g (2 mM) **4h/4i** in 30 ml was added a solution of 0.9 g (4 mM) 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 30 ml of benzene. The mixture was heated for further 10 min and cooled to room temp. The benzene phase was washed with a 10% sodium carbonate solution (3 × 15 ml). The combined aqueous fraction was extracted with ethyl acetate (2 × 20 ml). The combined organic phase was washed with brine (1 × 20 ml), dried over Na_2SO_4 and evaporated *in vacuo*. The reddish brown oily residue was submitted to CC (petroleum ether/ethyl acetate = 6/1); yield: 0.1 g, (20%), slightly yellow crystals, mp 97–99 °C (CH_2Cl_2/petroleum ether).– IR: ν = 1700 cm^{-1} (C=O), 1500 + 1450 (C=C in arom. rings), 750 + 700 (monosubst. arom. rings).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.48 (t, *J* = 8.3 Hz, 1H, 1β-H), 4.33 (dd, *J* = 6.7, 8.3 Hz, 1H, 1α-H), 4.61 (ddd, *J* = 2.0, 6.7, 8.3 Hz, 1H, 7a-H), 6.29 (s, 1H, 3-H), 7.32–7.44 (m, 6H, aromatic H), 7.58 (m, 2H, aromatic H), 7.88 (m, 2H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 62.31 (C-7a), 68.73 (C-1), 87.76 (C-3), 126.30, 127.20, 128.51, 128.59, 128.67, 129.19 (C-2′, C-3′, C-4′, C-5′, C-6′, C-2″, C-3″, C-4″, C-5″, C-6″), 130.76 (C-6), 138.80, 138.89 (C-1′, C-1″), 139.36 (C-7), 176.00 (C=O).– MS (70 eV); *m/z* (%) = 277 (1) [M^+], 247 (100) [M^+ – O=CH_2)].– Anal. ($C_{18}H_{15}NO_2$).

*[3R-(3α,6β,7aα)]-6-Methyl-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]-oxazol-5-one (**7a**) and [3R-(3α,6α,7aα)]-6-Methyl-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**4j**)*

At –78 °C 22.33 g (110 mM) of compound **4a** in 50 ml of dry THF was added to a 110 mM LDA solution. After 30 min of stirring at –78 °C 7.56 ml (121 mM) of methyl iodide was added slowly, the cooling bath was removed and temp. allowed to rise to –20 °C. When TLC indicated the absence of **4a** (30 min) the mixture was poured onto crushed ice and water (500 ml) and saturated with sodium chloride. The aqueous phase was extracted with ethyl acetate (4 × 150 ml). The combined organic fraction was washed with water (1 × 200 ml) and brine (1 × 200 ml) and evaporated. The ^{1}H NMR spectrum of the crude mixture revealed a ratio of the two methyl diastereomers **7a** and **4j** of 3.5:1. As a preparation for the use in the next step the oil was distilled [bp 105 C/0.05 Torr; yield **7a/4j**: 22.8 g (95%)]. For purpose of analysis a sample (1 g) of the crude mixture was submitted to CC (petroleum ether/ethyl acetate = 6/1).

7a: R_f 0.54; yield 0.62 g (62%), colourless oil, $[\alpha]_D^{20}$ = +198.75 (*c* = 1.042 in CH_2Cl_2).– IR: ν = 1710 cm^{-1} (C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.22 (d, *J* = 8.0 Hz, 3H, CH_3), 1.54 (dt, *J* = 8.0, 12.0 Hz, 1H, 7β-H), 2.61 (dt, *J* = 8.0, 12.0 Hz, 1H, 7α-H), 2.95 (m, 1H, 6-H), 3.51 (t, *J* = 8.0 Hz, 1H, 1β-H), 4.07 (quint, *J* = 8.0 Hz, 1H, 7a-H), 4.21 (t, *J* = 8.0 Hz, 1H, 1α-H), 6.33 (s, 1H, 3-H), 7.26–7.42 (m, 3H, 3′-H, 4′-H, 5′-H), 7.45 (m, 2H, 2′-H, 6′-H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 15.54 (CH_3), 34.73 (C-7), 39.93 (C-6), 56.57 (C-7a), 72.40 (C-1), 86.85 (C-3), 126.02 (C-2′, C-6′), 128.33 (C-3′, C-5′), 128.43 (C-4′), 138.89 (C-1′), 179.04 (C=O).– MS (70 eV); *m/z* (%) = 217 (31) [M$^+$], 216 (100) [M$^+$ – 1].– Anal. ($C_{13}H_{15}NO_2$).

4j: yield 0.16 g (16%), colourless oil, $[\alpha]_D^{20}$ = +158.43 (*c* = 0.902 in CH_2Cl_2).– IR: ν = 1710 cm^{-1} (C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.35 (d, *J* = 8.0 Hz, 3H, CH_3), 1.96 (dt, *J* = 10.0, 14.0 Hz, 1H, 7α-H), 2.19 (ddd, *J* = 4.0, 10.0, 14.0 Hz, 1H, 7β-H), 2.74 (m, 1H, 6-H), 3.41 (t, *J* = 8.0 Hz, 1H, 1β-H), 4.08 (m, 1H, 7a-H), 4.23 (t, *J* = 8.0 Hz, 1H, 1α-H), 6.31 (s, 1H, 3-H), 7.28-7.40 (m, 3H, 3′-H, 4′-H, 5′-H), 7.44 (m, 2H, 2′-H, 6′-H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 17.53 (CH_3), 29.86 (C-7), 39.18 (C-6), 56.78 (C-7a), 70.76 (C-1), 87.21 (C-3), 125.70 (C-2′, C-6′), 128.17 (C-3′, C-5′), 128.24 (C-4′), 138.95 (C-1′), 181.50 (C=O).– MS (70 eV); *m/z* (%) = 217 (39) [M$^+$], 216 (100) [M$^+$ – 1].– Anal. ($C_{13}H_{15}NO_2$).

*{3R-[3α,6α(R*S*),7aα]}-6-(1-Hydroxycyclohex-2-enyl)-6-methyl-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**7b/7c**) and {3R-[3α,6α(R*S*),7aα]}-6-methyl-6-(3-oxocyclohexyl)-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**7d/7e**)*

A solution of 22.8 g (105 mM) of the distilled mixture **7a/4j** in 50 ml of dry THF was added to 105 mM LDA solution at –78 C. After 30 min at –78 °C 50 ml of 1,3-dimethyltetrahydro-2(*1H*)-pyrimidinone (DMPU) was added and stirring continued for 45 min at –78 °C. Then 11.1 ml (115 mM) of freshly distilled 2-cyclohexen-1-one was added dropwise and strictly at –78 °C over a period of 2 h. Stirring at –78 °C was continued until TLC indicated educt absence (60 min). The reaction mixture was hydrolyzed cautiously with water (40 ml) and poured onto 400 ml of crushed ice and water. The aqueous phase was saturated with sodium chloride. After separation of the organic layer, the aqueous phase was extracted with ethyl acetate (5 × 150 ml). The combined organic phase was washed with water (2 × 100 ml) and brine (1 × 100 ml), dried over Na_2SO_4 and evaporated. The crude mixture (32.8 g) was submitted to CC (petroleum ether/ethyl acetate = 4/1).

7b/7c: R_f 0.56, yield: 20.2 g (61%); colourless oil. The ratio of the two 1″-diastereomeric alcohols was about 3:2.– IR: ν = 3480 cm^{-1} (OH), 1690 (C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.35 (s, 3H, CH_3), 1.45–2.17 (m, 7H, 4″-H, 5-″H, 6″-H, 7β-H), 2.33 + 2.51 (2 overlapping dd, *J* = 8.4, 14.0 Hz, 1H, 7α-H), 3.38 + 3.49 (2 overlapping t, *J* = 7.2 Hz, 1H, 1β-H), 3.99 (m, 1H, 7a-H), 4.26 (t, *J* = 7.2 Hz, 1H, 1α-H), 5.60 (m) + 6.00 (m, both signals together 2H, 2″-H, 3″-H), 6.28 (s) + 6.32 (s, ratio 2:3, together 1H, 3-H), 7.28–7.50 (m, 5H, aromatic H). OH (*, "baseline" signal 2.8–3.8 ppm).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 18.36 (C-5″), 21.33 + 21.75 (CH_3), 25.16 + 25.22 (C-4″), 31.11 + 31.75, 33.26 + 33.49 (C-7, C-6″), 54.60 + 55.71 (C-6), 55.90 + 56.20 (C-7a), 72.50 (C-1″), 72.28 + 72.77 (C-1), 87.24 + 87.51 (C-3), 125.93 (C-2′, C-6′), 128.44 (C-3′, C-5′), 128.49 (C-4′), 127.46 + 129.12 (C-3″), 133.15 + 133.81 (C-2″), 138.91 + 138.97 (C-1′), 180.60 + 181.47 (C=O).– MS (70 eV); *m/z* (%) = 295 (5) [M$^+$ – H_2O], 217 (100) [M$^+$ – C_6H_8O].– Anal. ($C_{19}H_{23}NO_3$).

7d/7e: R_f 0.33, yield: 4.9 g (15 %); mp 117–120 °C (petroleum ether/ethyl acetate). The ratio between the two 1″-diastereomeric ketones was about 3:1.– IR: ν = 1700 cm^{-1} (lactam-C=O, keto-C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.25 (s, 3H, CH_3), 1.35–1.80 (m, 3H, aliphatic H), 1.88–2.58 (m, 8H, aliphatic H), 3.40 + 3.50 (two overlapping t, *J* = 8.4 Hz, 1H, 1β-H), 4.01 (m, 1H, 7a-H), 4.26 (dd, *J* = 5.6, 8.4 Hz, 1H, 1α-H), 6.33 (s, 1H 3-H), 7.30-7.48 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 22.33 + 22.94 (CH_3), 24.82 + 24.96, 26.25 + 26.56 (C-5″, C-6″), 34.55 + 35.63 (C-7), 41.05, 43.02 + 43.39 (C-2″, C-4″) 45.31 (C-1″), 51.49 + 51.69 (C-6), 55.61 (C-7a), 72.70 (C-1), 87.33 (C-3), 125.89 (C-2′, C-6′), 128.46 (C-3′, C-5′), 128.53 (C-4′), 138.80 (C-1′), 180.30 (lactam-C=O), 210.33 (keto-C=O).– MS (70 eV); *m/z* (%) = 313 (3) [M$^+$], 285 (10) [M$^+$ – CO], 217 (74) [M$^+$ – C_6H_8O].– Anal. ($C_{19}H_{23}NO_3$).

*[3R-(3α,6α,7aα)]-6-(Cyclohexa-1,5-dienyl)-6-methyl-3-phenyl-3H,5H-tetra-hydropyrrolo[1,2-c]oxazol-5-one and [3R-(3α,6α,7aα)]-6-(Cyclohexa-1,3-dienyl)-6-methyl-3-phenyl-3H,5H-tetrahydropyrrolo[1,2-c]oxazol-5-one (**7f/7g**)*

A solution of 20.0 g (64 mM) **7b/7c** in 100 ml of benzene was added dropwise to a gently refluxing solution of 0.10 g pTSA in 200 ml of benzene in a Wheater-Soxhlet water extractor containing molecular sieve (4Å). After 15 h of azeotropic removal of the reaction water TLC indicated the complete consumption of **7b/7c**. For analytical purposes 10 ml of the benzene solution was taken from the reaction, evaporated to dryness and the oily residue (0.64 g) submitted to CC.

7f/7g: colourless oil; the ratio between the 1″,5″- and the 1″,3″-isomers was about 1:1.– IR: ν = 1710 cm^{-1} (C=O).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.35 (s, 3H, CH_3), 1.74 + 1.82 (two overlapping dd, *J* = 6.0, 12.8 Hz, 1H, 7β-H), 2.12 (m, 4H, 3″-H, 4″-H in **7f**; 5″-H, 6″-H in **7g**), 2.53 + 2.64 (two overlapping dd, *J* = 6.0, 12.8 Hz, 1H, 7α-H), 3.55 + 3.61 (two overlapping t, *J* = 6.8 Hz, 1H, 1β-H), 4.03 (m, 1H, 7a-H), 4.17 (t, *J* = 6.8 Hz, 1H, 1α-H), 5.74 (m, 1H, olefinic H), 5.96 (m, 3H, olefinic H), 6.36 (s, 1H, 3-H), 7.28–7.50 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 21.93 + 22.38, 23.10 + 23.33 (C-3″, C-4″ in **7f**; C-5″, C-6″ in **7g**), 22.77 + 23.46 (CH_3), 39.40 + 39.52 (C-7), 53.55 + 54.96 (C-6), 55.60 + 55.68 (C-7a), 71.93 (C-1), 86.95 (C-3), 118.42 + 119.63, 123.61 + 124.49, 125.46 (C-2″, C-5″, C-6″ in **7f**; C-2″, C-3″, C-4″ in **7g**), 126.03 (C-2′, C-6′), 128.40 (C-3′, C-4′, C-5′), 136.66, 138.64, 139.01 (C-1′, C-1″), 179.05 + 179.28 (C=O).– MS (70 eV); *m/z* (%) = 295 (100) [M$^+$].– Anal. ($C_{19}H_{21}NO_2$).

*[3R-(3α,6α,7aα)]-6-Methyl-3,6-diphenyl-3H,5H-tetrahydropyrrolo-[1,2-c]oxazol-5-one (**7h**)*

In a Wheater-Soxhlet water extractor containing molecular sieve (4Å) traces of water were removed from a solution of 14.5 g (64 mM) DDQ in 200 ml of benzene (10 h). In a "one-pot-synthesis" this solution was added to the reaction mixture of the dehydratization of **7b/7c** after 15 h of dehydratization (TLC control). After 10 min of further refluxing the reaction mixture was cooled to room temp. rapidly and washed with a 10% Na_2CO_3 solution (3 × 150 ml). The combined aqueous phase was extracted with ethyl acetate (4 × 100 ml). Finally the benzene- and the ethyl acetate-phases were combined, washed with brine (1 × 200 ml), dried over Na_2SO_4, and the solvents removed *in vacuo*. The residue was submitted to CC (petroleum ether/ethyl acetate = 5/1).

7h: yield: 11.1 g (59%), mp 80–81 °C (petroleum ether/ethyl acetate), $[\alpha]_D^{20}$ = +52.95 (*c* = 0.967 in CH_2Cl_2).– IR: ν = 1710 cm^{-1} (C=O), 1500 + 1450 (C=C in arom. rings), 750 + 735 (monosubst. arom. rings).– ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.56 (s, 3H, CH_3), 2.05 (dd, *J* = 8.0, 12.8 Hz, 1H, 7β-H), 2.90 (dd, *J* = 6.4, 12.8 Hz, 1H, 7α-H), 3.65 (dd, *J* = 6.4, 8.0 Hz, 1H, 1β-H), 3.97 (quint, *J* = 6.4 Hz, 1H, 7a-H), 4.18 (dd, *J* = 6.4, 8.0 Hz, 1H, 1α-H), 6.43 (s, 1H, 3-H), 7.21–7.47 (m, 10H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 26.49 (CH_3), 42.19 (C-7), 54.16 (C-6), 55.54 (C-7a), 71.76 (C-1), 86.98 (C-3), 125.50 (2 aromatic C), 126.02 (C-2′, C-6′), 126.96 (C-4″), 128.39 (C-3′, C-5′), 128.48 (C-4′), 128.74 (2 aromatic C), 138.42 (C-1′), 143.39 (C-1″), 179.31 (C=O).– MS (70 eV); *m/z* (%) = 293 (25) [M$^+$].– Anal. ($C_{19}H_{19}NO_2$).

(2S-trans)-4-Methyl-4-phenyl-5-oxo-2-pyrrolidinemethanol (**8a**)

11.1 g (38 mM) of **7h** were heated to reflux in a mixture of acetonitrile/2N HCl (2:1, 40 ml) for 30 min. Acetonitrile was evaporated under reduced pressure. The aqueous phase was extracted in a liquid-liquid extractor with CH_2Cl_2 for 6 h. After removal of CH_2Cl_2 the oily residue was submitted to CC (ethyl acetate).

8a: R_f 0.15, yield: 7.2 g (92%); slightly yellow oil; $[\alpha]_D^{20} = -22.53$ (c = 0.861 in CH_2Cl_2).– IR: ν = 3320 cm^{-1} (OH), 1690 (C=O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.53 (s, 3H, CH_3), 1.88 (dd, J = 9.2, 12.0 Hz, 1H, 3α-H), 1.97 (br. s, 1H, *, OH), 2.43 (dd, J = 6.8, 12.0 Hz, 1H, 3β-H), 3.44 (m, 1H, CH_2OH), 3.70 [m, 3H, CH_2OH, 2-H, NH (*)], 7.20–7.35 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 25.67 (CH_3), 39.71 (C-3), 49.08 (C-4), 53.36 (C-2), 65.81 (CH_2OH), 125.75 (2 aromatic C), 126.89 (C-4′), 128.65 (2 aromatic C), 143.28 (C-1′), 180.84 (C=O).– MS (70 eV); *m/z* (%) = 205 (18) [M^+], 174 (100) [$M^+ - CH_2OH$], 146 (52) [$M^+ - CH_2OH - CO$]. Anal. ($C_{12}H_{15}NO_2$).

(2S-trans)-4-Methyl-4-phenyl-5-oxo-2-pyrrolidinemethanol, Acetate (**8b**) *and (2S-trans)-1-Acetyl-4-methyl-4-phenyl-5-oxo-2-pyrrolidinemethanol, Acetate* (**8c**)

To a solution of 0.41 g (2 mM) **8a** in 25 ml of acetanhydride was added 0.03 g *N,N*-dimethylaminopyridine (DMAP). The mixture was stirred at room temp. (20 °C) for 30 min. TLC showed complete conversion to the *O*-acetyl product **8b**. Upon removal of acetic anhydride in a rotary evaporator applying a hot water bath (65 °C) parts of **8b** underwent *N*-acetylation to yield the *O,N*-diacetylated compound **8c**. The residue was dissolved in CH_2Cl_2 and the organic phase washed with 2N HCl, 10% Na_2CO_3 solution, and brine (1 × 5 ml each), dried over Na_2SO_4 and evaporated. CC yielded the separated compounds **8b** and **8c** (petroleum ether/ethyl acetate = 3/1; R_f **8c** > R_f **8b**).

8b: R_f 0.32, yield: 0.21 g (43%); colourless oil, $[\alpha]_D^{20} = -26.28$ (c = 0.837 in CH_2Cl_2).– IR: ν = 3400 cm^{-1} (NH), 1745 (acetyl-C=O), 1700 (lactam-C=O), 1230 (acetyl-C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.58 (s, 3H, CH_3), 1.92 (dd, J = 9.2, 12.8 Hz, 1H, 3α-H), 2.08 (s, 3H, $OOCCH_3$), 2.65 (dd, J = 6.3, 12.8, 1H, 3β-H), 3.79 (m, 1H, 2-H), 3.93 (dd, J = 8.0, 11.2 Hz, 1H, CH_2O), 4.26 (dd, J = 3.5, 11.2 Hz, 1H, CH_2O), 6.76 (br. s, 1H, *, NH), 7.18–7.45 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 20.41 ($OOCCH_3$), 25.61 (CH_3), 39.98 (C-3), 48.58 (C-4), 49.75 (C-2), 66.69 (CH_2OOCCH_3), 125.56 (2 aromatic C), 126.57 (C-4′), 128.35 (2 aromatic C), 143.09 (C-1′), 170.48 (acetyl-C=O), 180.15 (lactam-C=O).– MS (70 eV); *m/z* (%) = 247 (3) [M^+], 202 (55) [$M^+ - 1 - CO_2$], 187 (93) [$M^+ - H_3CCOOH$].– Anal. ($C_{14}H_{17}NO_3$).

8c: R_f 0.65, yield: 0.19 g (33%), colourless oil, $[\alpha]_D^{20} = -31.85$ (c = 0.774 in CH_2Cl_2).– IR: ν = 1743 cm^{-1} (acetyl-C=O), 1705 (lactam-C=O), 1260 (N-acetyl-C-O), 1230 (O-acetyl-C-O).– ^1H NMR ($CDCl_3$): δ (ppm) = 1.66 (s, 3H, CH_3), 2.10 (m, 4H, $OOCCH_3$, 3α-H), 2.53 (s, 3H, $NOCCH_3$), 2.72 (dd, J = 8.0, 13.0 Hz, 1H, 3β-H), 4.35 (m, 2H, CH_2O, 2-H), 4.54 (dd, J = 4.4, 10.8 Hz, 1H, CH_2O), 7.30–7.36 (m, 5H, aromatic H).– ^{13}C NMR ($CDCl_3$): δ (ppm) = 20.41 ($OOCCH_3$), 25.61 (CH_3), 25.90 ($NOCCH_3$), 35.69 (C-3), 49.39 (C-4), 52.42 (C-2), 63.63 (CH_2O), 125.31 (2 aromatic C), 127.26 (C-4′), 128.82 (2 aromatic C), 142.57 (C-1′), 170.33 (O-acetyl-C=O), 171.64 (N-acetyl-C=O), 178.46 (lactam-C=O).– MS (70 eV); *m/z* (%) = 289 (2) [M^+], 229 (28) [$M^+ - H_3CCOOH$].– Anal. ($C_{16}H_{19}NO_4$).

(2S-trans)-4-Methyl-4-phenyl-pyroglutamic acid = (2S-trans)-4-Methyl-4-phenyl-5-oxo-2-pyrrolidinecarboxylic acid (**3b**)

A solution of 6.97 g (34 mM) **8a** in 60 ml of acetone was added dropwise with vigorous stirring at –5 °C to a solution of Jones reagent (6.97 g CrO_3 dissolved in 8.4 ml of concd. H_2SO_4 and diluted with water to 25 ml) in 60 ml of acetone over a period of 3 h. The cooling bath was removed and the reaction mixture stirred at room temp. for further 3 h. 5 ml of 2-propanol was added to destroy the excess of Cr^{VI} (30 min). Then acetone was removed under reduced pressure. The thick oily residue was dissolved in a minimum of water, and the aqueous phase was extracted in a liquid-liquid-extractor with CH_2Cl_2 for 15 h. The organic phase was dried over Na_2SO_4 and evaporated.

3b: yield: 5.9 g (79%); mp 182–195 °C (methanol/water); $[\alpha]_D^{20} = -54.97$ (c = 1.05 in acetone).– IR: ν = 3300 cm^{-1} (NH), 2480 + 1940 (amino acid), 1725 (lactam-C=O), 1630 (carboxyl-C=O).– ^1H NMR (CD_3OD): δ (ppm) = 1.55 (s, 3H, CH_3), 2.30 (dd, J = 6.9, 13.0 Hz, 1H, 3α-H), 2.89 (dd, J = 8.1, 13.0 Hz, 1H, 3β-H), 4.20 (dd, J = 6.9, 8.1 Hz, 1H, 2-H), 7.36–7.50 (m, 5H, aromatic H). The NH-signal (br. s) was detected in a ^1H NMR measured in [D_6]DMSO (8.30 ppm).– ^{13}C NMR (CD_3OD): δ (ppm) = 25.29 (CH_3), 42.90 (C-3), 47.92 (C-4, overlaps with CD_3OD signal), 53.82 (C-2), 126.98 (2 aromatic C), 127.94 (C-4′), 129.61 (2 aromatic C), 144.59 (C-1′), 175.35 (carboxyl-C=O), 182.53 (lactam-C=O).– MS (70 eV); *m/z* (%) = 219 (23) [M^+], 174 (37) [$M^+ + 1 - CO_2$].– Anal. ($C_{12}H_{13}NO_3$).

References

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