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Lecture Transcripts

Development of a Scalable and Safe Procedure for the Production of (3*R*)-3-(2,3-Dihydro-1-benzofuran-5-yl)-1,2,3,4-tetrahydro-9*H*-pyrrolo[3,4-*b*]-quinolin-9-one, an Intermediate in the Synthesis of PDE-V Inhibitors RWJ387273 (R301249) and RWJ444772 (R290629)

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Abstract:

A scalable and safe process for the oxidative rearrangement of β-carboline to quinolone derivatives, intermediates in the synthesis of PDE-V inhibitors RWJ387273 (R301249) and RWJ444772 (R290629), has been developed.

Introduction

R301249 (RWJ387273) and R290629 (RWJ444772), depicted in Figure 1, are two PDE-V inhibitors active in the treatment of erectile disfunction.[1] An important issue in the treatment of erectile disfunciton with PDE-V inhibitors is the selectivity versus other enzymes of the phosphodiesterase family. Selectivity versus other enzymes can cause adverse cardiovascular side effects as well as visual disturbances by PDE-1 and PDE-6 inhibition. R301249 and R290629 are potent compounds with a greater selectivity for PDE-5 versus other PDE isozymes.

Results and Discussion

Medicinal chemistry routes for both compounds are shown in Schemes 1 and 2. The β-carboline derivative **6** was synthesized starting from 2,3-dihydrobenzofurane which, after bromination and formylation by a Grignard reaction with dimethylformamide, gives the aldehyde **3**. Condensation with tryptamine then leads to the imine **4** which is closed under Pictet−Sprengler conditions to the racemic β-carboline **5**. Resolution of **5** was performed either by diastereomeric salt formation with acetyl-D-leucine or by chiral chromatography.

The aim of this publication is to focus on the most crucial step of the synthesis namely the oxidative rearrangement of the indole derivatives to the quinolone derivatives. To synthesize R301249 this oxidative rearrangement was performed on the arylated indole derivative **7** yielding directly the final compound, whereas for R290629 the oxidative rearrangement was performed on the benzyl-protected compound **8**. The resulting quinolone **9** was then deprotected and subsequently arylated. As the final selection of the candidate still had to be made during the course of the investigation for a scalable method, it was decided a common penultimate would be pursued which in the final step could then be arylated to the desired API. This resulted in the approach as depicted in Scheme 3. In this approach, the oxidative rearrangement is performed on a protected β-carboline. Among the protective groups benzyl, *tert*-butoxycarbonyl, and benzyloxycarbonyl were considered.

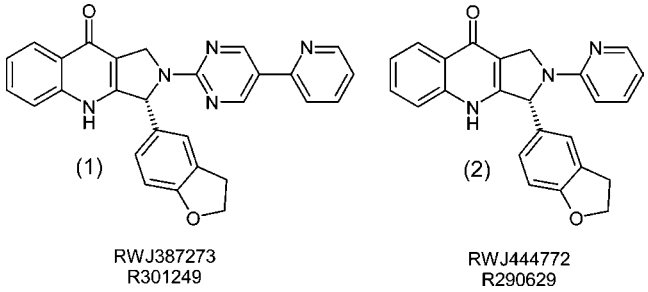

Figure 1. **Structures of PDE-V inhibitors R301249 and R290629.**

Compounds of the R290629 and R301249 type were identified by medicinal chemistry as minor byproducts during the N-alkylation of the corresponding indoles as a result of a Winterfeldt[2] oxidation due to the presence of small amounts of oxygen.[3] Winterfeldt oxidation of 1,2,3,4-tetrahydro-β-carbolines is well-known.[4] With acyl-β-carbolines, however, Winterfeldt oxidation failed to give the desired quinolones,[5]

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Scheme 1. **Synthesis of the β-carboline derivative T2513**

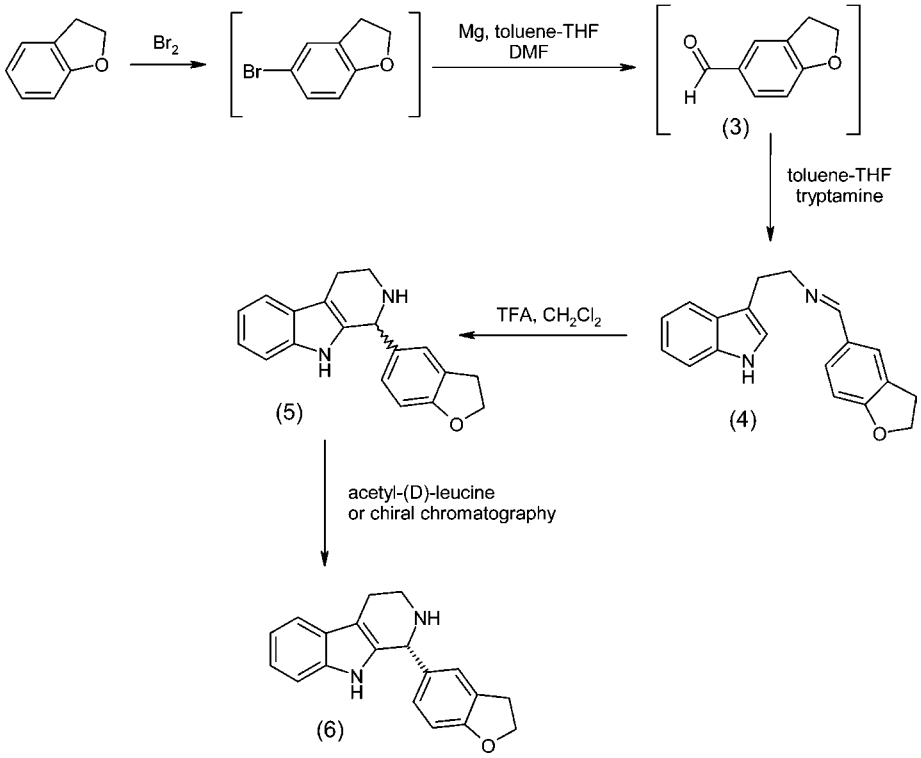

Table 1. **Initiation temperature of the decomposition of KO_2−solvent mixtures with and without ET_4NBr**

	without Et_4NBr (°C)	with Et_4NBr (°C)
dimethylformamide	80	75
acetonitrile	90	70
dimethylacetamide	85	80
dimethylimidazolidinone	120	100

and a more general applicable method to oxidize 1,2,3,4-tetrahydro-β-carbolines was needed.

Oxidative cleavage of the 2,3 bond of indoles with KO_2 in the presence of a phase transfer catalyst is well described in the literature.[6] So it was decided to also test this reagent on the *N*-benzyl-substituted β-carboline **11**. With 8 equiv of KO_2 and 8 equiv of Et_4NBr in DMF at 55 °C, quinolone **14** was obtained in low yield (20−25%). In a typical experiment a slurry of KO_2 and Et_4NBr in DMF was heated to 55 °C, and a solution of **11** in DMF was added over 20 min after which the reaction mixture was stirred for another 3 h.

Earlier safety investigations on the reaction mixture however had shown a thermal instability at relatively low temperatures. In an ARC-experiment on the reaction mixture with **11**, an exothermic decomposition starting at 39 °C with increased decomposition and pressure buildup at 60 °C was observed.[7]

An RC1 experiment on the desired reaction revealed a 75% heat accumulation after all **11** was added. The reaction generates a moderate heat flow over about 3 h, and in the worst case the temperature would rise 92 °C resulting in an MTSR[8] of 147 °C. This means that in case of a cooling failure the decomposition reaction will be triggered. As the boiling point of the solvent DMF is higher than the MTSR, evaporative cooling cannot serve as a safety barrier.

To reduce the risk involved with this reaction other solvents were screened. As shown in Table 1, the initiation temperature for the decomposition of KO_2−solvent mixtures with or without Et_4NBr is considerably higher in DMI as compared to DMF, CH_3CN, and DMA. Although the severity of the decomposition remained the same, the probability for the decomposition reaction to occur was lowered. To decrease the severity of a possible decomposition, further process development on the reaction in DMI was performed. The excess of KO_2 was reduced from 8 to 6 equiv, the amount of Et_4NBr was reduced from 8 to 1 equiv, and the reaction was performed more diluted, i.e., 7 L/mol instead of 2.3 L/mol and at 50 °C. As a result of this, the reaction time became longer, and it now took 24 h for complete conversion.

Additional RC1 and Phi-tec experiments on the adapted reaction conditions were performed. The RC1 experiment revealed that the reaction enthalpy was about 500 kJ/mol, but as the reaction is slow the specific heat release is only 1.5 W/L and can easily be controlled by cooling in a production plant. However, as shown in Figure 2 there is about 90% of thermal accumulation, so this is in fact a batch process and batch processes are not easy to control.

The graph of the Phi-tec run, as depicted in Figure 3, shows that the reaction or exothermic decomposition starts

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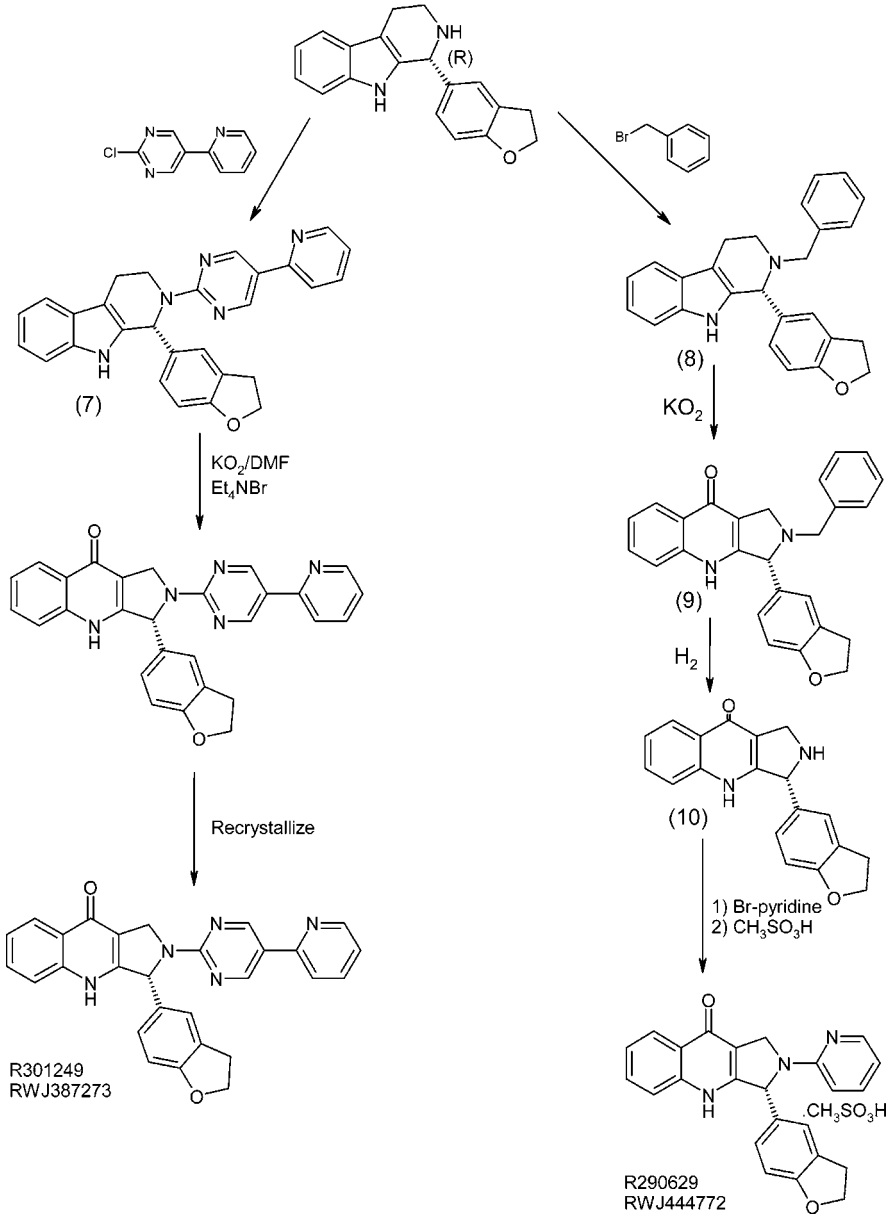
(8) MTSR: maximum temperature of the synthetic reaction. In our case 55 °C + 92 °C (adiabatic temperature rise) = 147 °C. The MTSR is dependent on the amount of unreacted reactants at the moment of the cooling failure.

Scheme 2. **Medicinal chemistry route to R301249 and R290629**

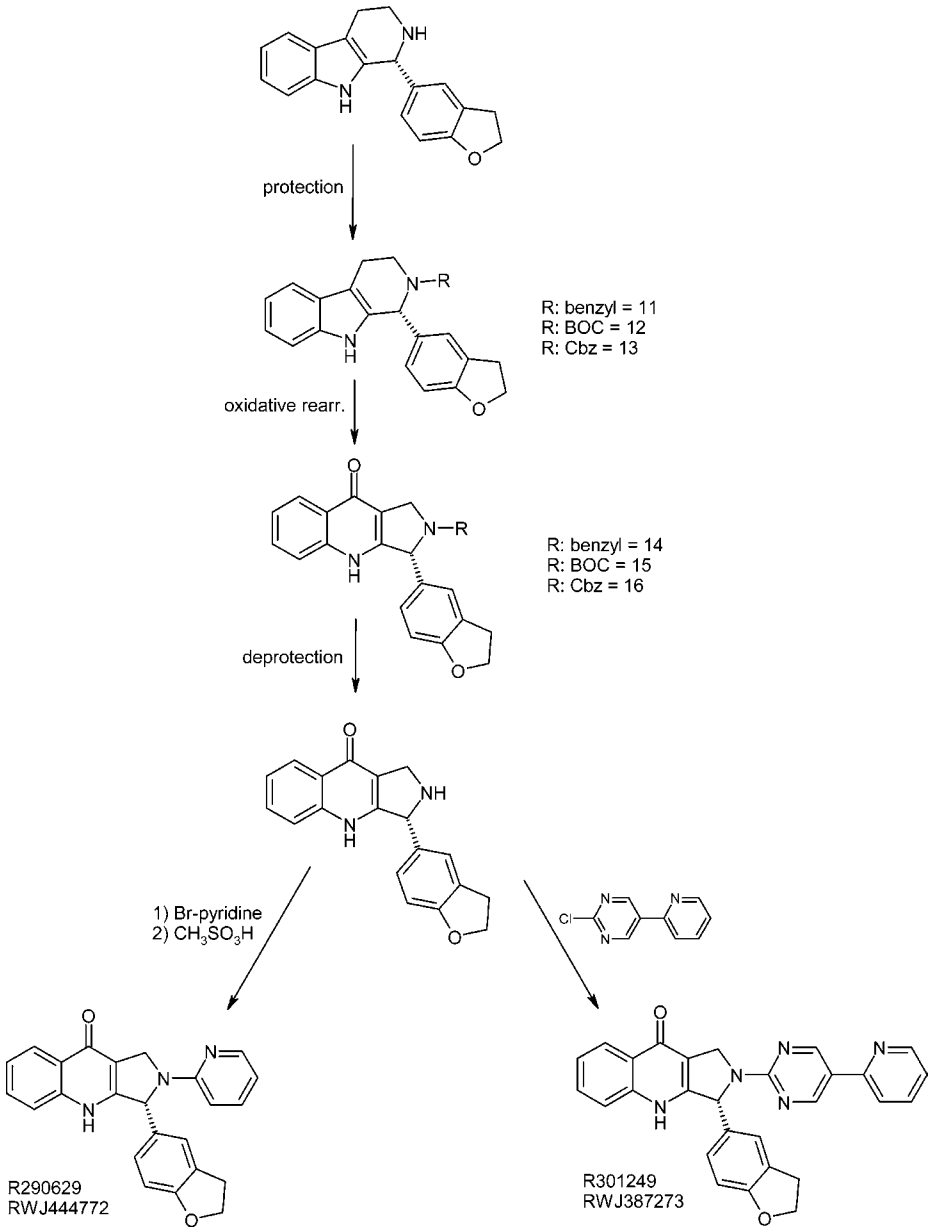


at 52 °C with a total, Phi corrected, adiabatic temperature rise of 192 °C. Already at 70 °C the self-heat rate is 0.56 °C/ min with a maximum of 102 °C/min at 150 °C. The conclusion of this adiabatic experiment was that the reaction temperature should not exceed 70 °C, the temperature at which the control on the reaction can be lost and a runaway cannot be avoided. Besides these safety aspects, the isolated yield of quinolone **15** was only 18−20%. Thus, it was decided to abandon the KO_2 approach and to look for safer oxidizing agents.

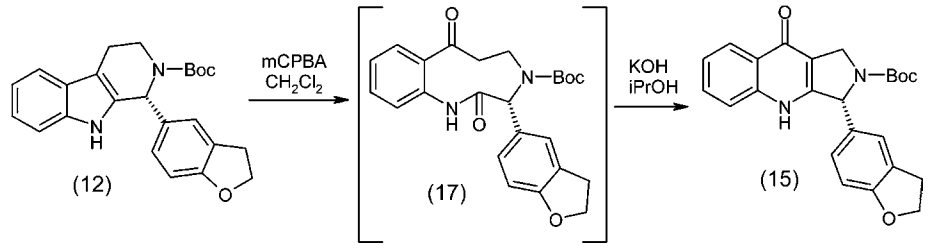
Oxidation of **11** with *m*-CPBA mainly resulted in the *N*-oxide of the starting material. To avoid this, the nonbasic BOC and Cbz derivatives **12** and **13** were considered. Typically, the *m*-CPBA oxidation was performed by dosing 3 equiv of a 0.166 molar solution of *m*-CPBA in dichloromethane to a 0.166 molar solution of **12** or **13** in dichloromethane at 20 °C over a 1 h period.

The graph of an RC1 experiment of the *m*-CPBA oxidation of the BOC-derivative **12** is depicted in Figure 4. From this experiment we may conclude that the reaction with *m*-CPBA is dose controlled with respect to the dosing end point and the immediate heat release will be dependent on the dosing time so that this reaction can be performed safely on a pilot plant scale. Moreover, the reflux of dichloromethane will serve as a safety barrier before the MTSR is reached**.** After workup, the residue of the reaction contained 20−30% of the keto-lactam **17** (Scheme 4) which on treatment with KOH was quantitatively converted to quinolone **15**. Attempts to isolate the keto-lactam **17** or quinolone **15** by crystallization failed, and a chromatographic purification was required to obtain **15** with an acceptable purity. This drawback was solved by using the benzyloxycarbonyl as a protecting group. Thus performing the *m*-CPBA oxidation on the Cbz-protected β-carboline **13** allowed us to isolate the keto-lactam **20** by crystallization from ethyl acetate. However due to the poor selectivity of *m*-CPBA, formation of byproducts was substantial resulting in a keto-lactam yield of only ±20%.

Scheme 3. **Approach to common penultimate**



Scheme 4. **Keto-lactam formation after mcpba-oxidation of T2542**



So it was decided a more selective oxidizing agent should be looked for.

Oxidation of 2,3-substituted indoles has been reported by Hino et al.,[9] and one of the formed intermediates was the hydroxy-imine **18** as shown in Scheme 5. Hino showed that this intermediate could be converted to the keto-lactam **19** in good yields by further oxidation with *m*-CPBA. Epoxidation of the indole could be done with dimethyldioxirane (DMD) as this is known to be a good epoxidizing agent. It can be formed in situ from acetone and oxone at controlled pH.[10]

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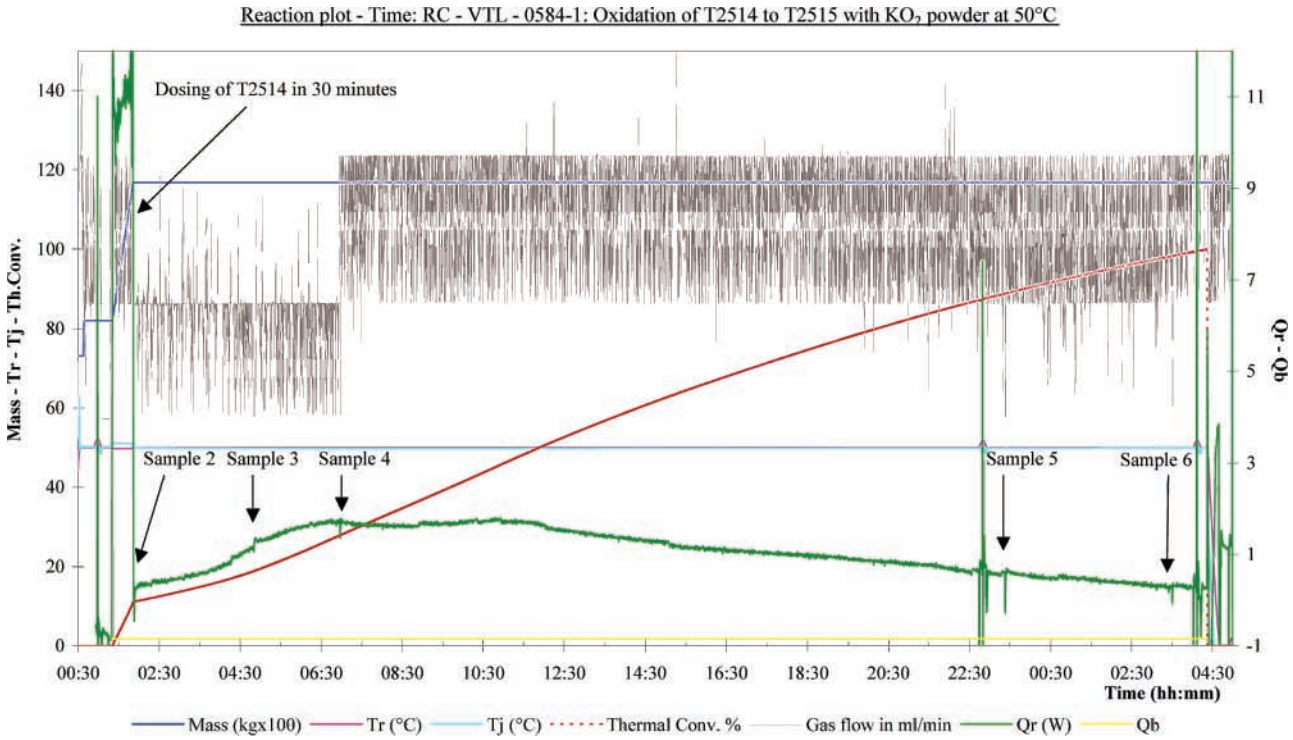


Figure 2. **Graph of RC_1-experiment of KO_2 oxidation of T2514 in DMI.**

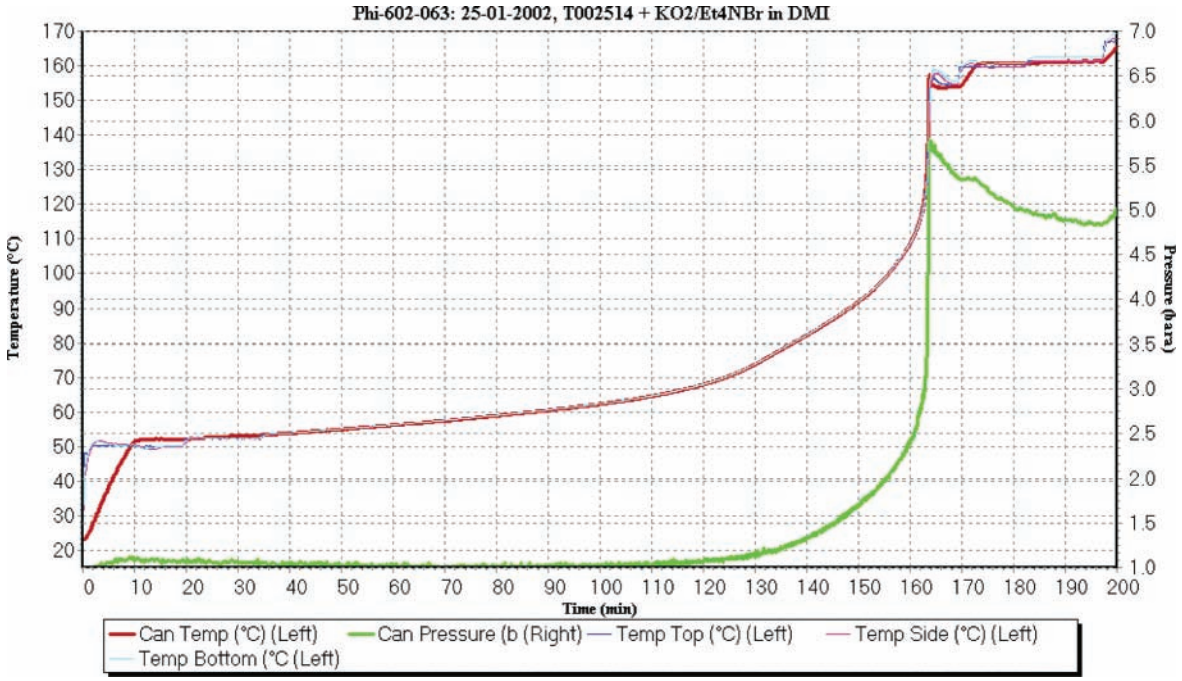


Figure 3. **Phi-tec run on mixture of T2514, KO_2, and ET_4NBr in DMI.**

A Phi-Tec experiment on in situ generated DMD solutions in water/ethyl acetate/acetone, $NaHCO_3$ showed that these solutions were thermally stable up to 70 °C. So a stepwise oxidative rearrangement was developed in which a solution of **13** in ethyl acetate/acetone was first reacted with oxone followed by *m*-CPBA oxidation to the keto-lactam **20**. Starting from β-carboline **6**, the keto-lactam **20** was isolated by crystallization from ethyl acetate with an overall yield of 36% on a 46 mol scale (Scheme 6). Though the yield of this reaction was nearly doubled it still seemed that the *m*-CPBA sequence was responsible for the still relatively low yield. After the DMD-oxidation step the reaction mixture contained up to 60−70% (HPLC area percent) of the hydroxy-imine **22**. Also in this type of oxidation most of the impurities started to form upon addition of *m*-CPBA. The most important impurity was the hydroxy-ketone **23** (identification in reaction mixture by LC−MS). This impurity, formed for 25 mol %, could possibly be formed by attack of *m*-CPBA on the enamine rather than on the imine as shown in Scheme 7.

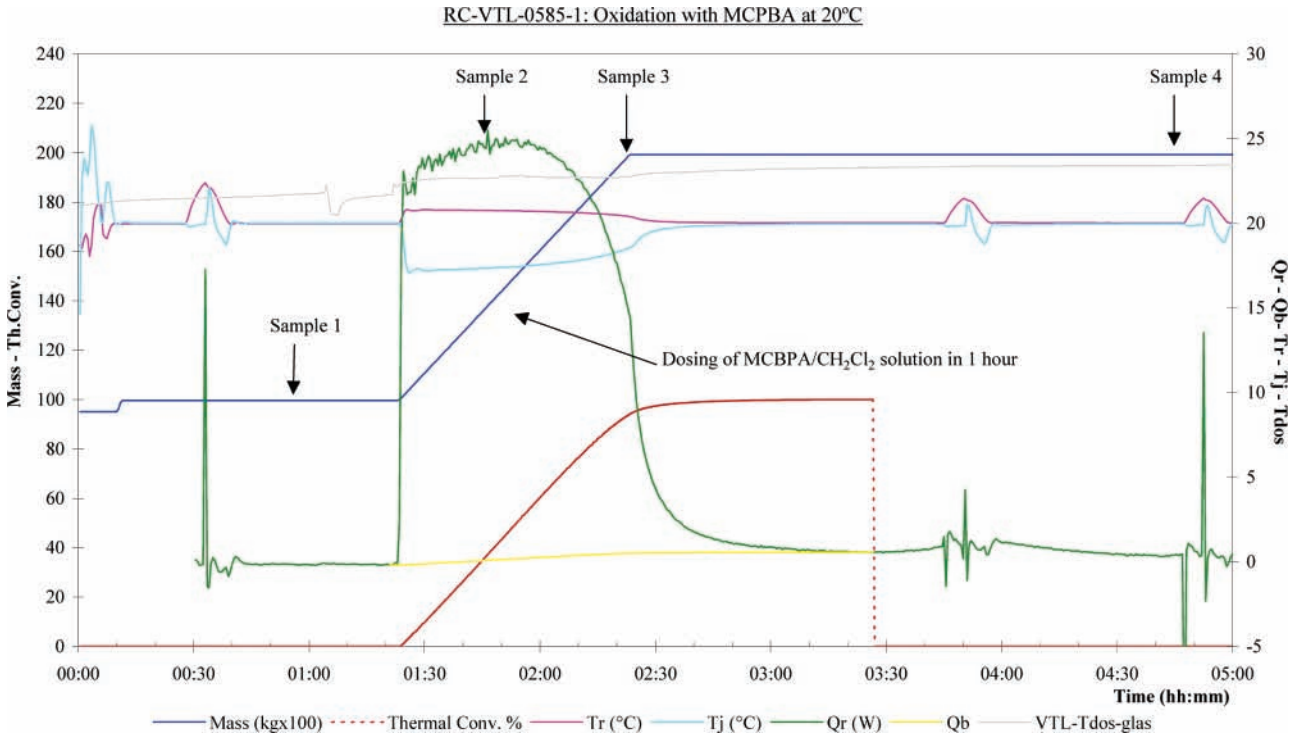
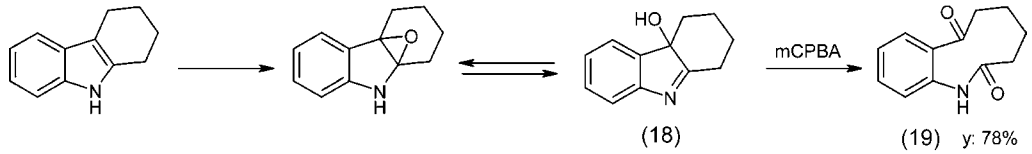
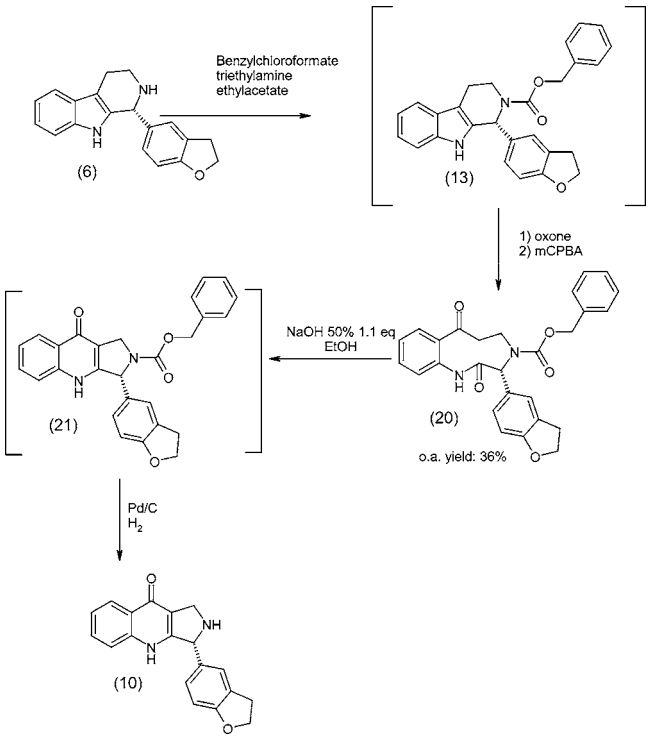


Figure 4. **Graph of RC_1-experiment of mcpba-oxidation of T2542 in CH_2Cl_2.**

Scheme 5. **Oxidation of 2,3-substituted indoles as reported by Hino et al.**



Scheme 6. **Reaction scheme as applied in pilot plant**



Using this stepwise oxidation approach, six pilot plant batches were performed successfully to give keto-lactam **20** which after ring closure to the quinolone **21** and subsequent deprotection provided us with a sufficient penultimate for delivery of the targeted amounts of APIs.

Conclusion

In conclusion, we have developed a process for the oxidative rearrangement of *β*-carboline derivatives to quinolone derivatives that has been successfully applied on a 40 to 50 mol scale. As compared to the original $KO_2^{\bullet}$ oxidation, the yield has been doubled, and even more important is that the process can be performed safely.

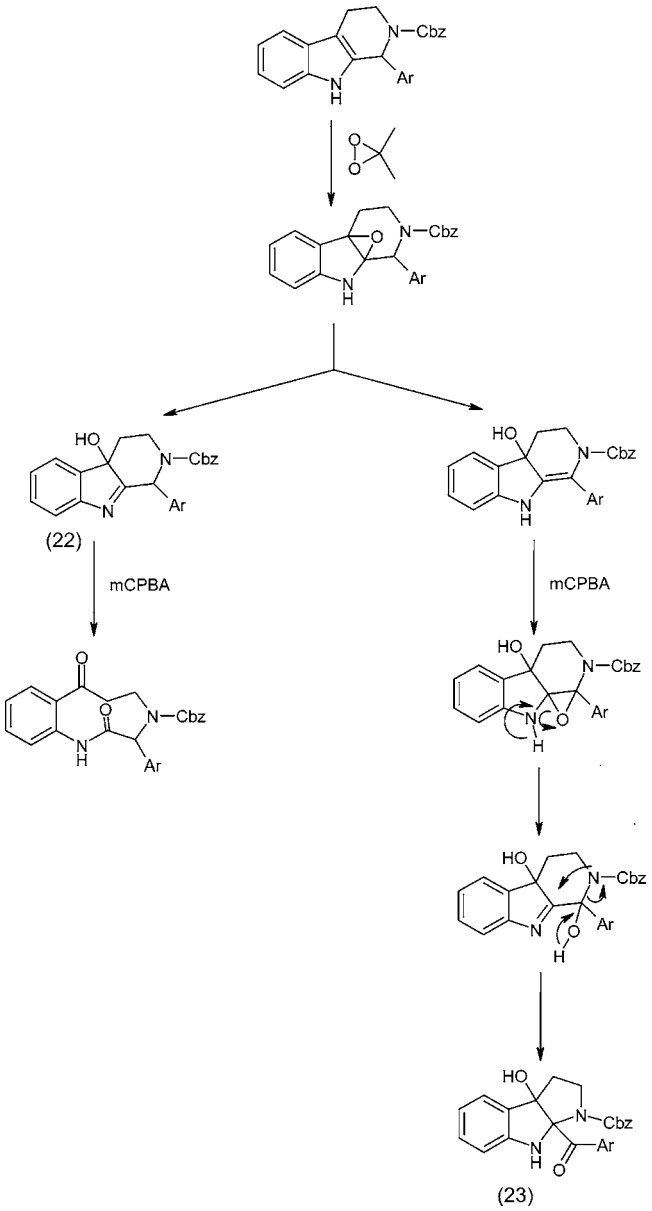
Experimental Section

General. Starting materials, reagents, and solvents were obtained from commercial suppliers and were used without any further purification.

^{1}H NMR spectra were recorded at 400 MHz on a Bruker Avance-400 instrument.

Benzyl (3*R*)-3-(2,3-Dihydro-1-benzofuran-6-yl)-2,7-dioxo-1,2,3,5,6,7-hexahydro-4*H*-1,4-benzodiazonine-4-carboxylate (20). A 250 mL vessel was charged successively with 1-(*R*)-1-(2,3-dihydrobenzofuran-5-yl)-2,3,4,9-tetrahydro-1*H*-*β*-carboline (**6**) (5.22 g, 0.018 mol), ethyl acetate (150 mL), and triethylamine (2.1 g, 0.0208 mol). The mixture was heated to 40−45 °C. Then the heating was stopped, and benzylchloroformate (3.55 g, 0.0208 mol) was added dropwise. The addition was slightly exothermic, and the temperature rose from 42 to 51 °C. The mixture was stirred for

Scheme 7. **Possible pathway for the formation of the hydroxy-ketone impurity**



another 2 h at 51 to 42 °C. Water (18 mL) was added, and the layers were separated while keeping the temperature at 35−40 °C. To the organic layer acetone (107 mL) was added, and the mixture was cooled to 20−25 °C. Subsequently, water (36 mL) and $NaHCO_3$ (4.82 g, 0.057 mol) were added, and the mixture was further cooled to 0−5 °C. A solution of oxone (15.5 g, 0.025 mol) in water (60 mL) was added by means of a dosing pump over a 2 h period at 0−5 °C. After the addition was complete, the mixture was stirred for another 2 h at 0−5 °C. Subsequently a solution of *m*-chloroperbenzoic acid 71% (5.34 g, 0.217 mol) in dichloromethane (62 mL) was added in 15 min at 0−5 °C. The mixture was stirred for another 1.5 h at 0−5 °C and then washed successively with water (76 mL) and with a solution of $NaHCO_3$ (6 g) in water (76 mL). After checking for peroxides, the organic layer was evaporated to nearly dryness, and the resulting oily residue was crystallized from ethyl acetate (40 mL). After stirring for 18 h at 10−25 °C the precipitate was filtered, washed with ethyl acetate (2 mL), and dried in vacuo at 50 °C for 20 h yielding 3 g (36.5%) of the title compound.

^{1}H NMR (400 MHz, DMSO-d_6) showed a mixture of rotamers: δ ppm [2.75−2.90] (m, 2H); [3.08−0.019] (m, 3H); [4.45−4.53] (o, 3H); [5.01−5.24] (4 × d (o), 2H); 5.93, 5.96 (2 × s, 1H); [6.67−6.72] (2 × d (o), 1H); [6.84−6.90] (2 × d (o)n 1H); 7.01, 7.03 (2 × s, 1H); [7.19−7.67] (o.m. 9H); 10.84, 10.86 (2 × s, 1H)

Probably other rotamers visible: [3.38−4.28] (m); [4.60−4.77] (2 × d); 5.54, 5.61 (2 × s); 9.68, 9.73 (2 × s). o: overlapping.

(3*R*)-3-2,3-Dihydro-1-benzofuran-5-yl)-1,2,3,4-tetrahydro-9*H*-pyrrolo[3,4-*b*]quinolin-9-one (10). A 1 L flask was charged successively with keto-lactam **20** (45.6 g, 0.1 mol) and ethanol (400 mL). To the resulting suspension was added a NaOH 50% aqueous solution (5.8 mL, 0.11 mol), and the mixture was stirred for 1 h at 20−25 °C. Subsequently concentrated HCl (9.9 mL, 0.11 mol) was added dropwise, and after stirring for another 30 min the precipitated salts were filtered and washed with ethanol (100 mL). The combined filtrates were transferred into a hydrogenation vessel, and concentrated HCl (9 mL, 0.1 mol) was added. The solution was flushed with nitrogen, and palladium on charcoal (5%−50% aqueous, 5 g) was added and subsequently hydrogenated at 25−30 °C. When deprotection was complete the mixture was filtered. NH_4OH (10 mL, 0.13 mol) was added to filtrate, followed by a dropwise addition of water (550 mL). The solution was then seeded with quinolone **(10)** (0.1 g). When crystallization had started, another portion of water (550 mL) was added dropwise in 1 h. The mixture was stirred for another 18 h after which the precipitate was filtered and washed with water (50 mL). After drying at 50 °C for 18 h, 22.7 g (75%) of the title compound was obtained.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.13 (t, J = 8.69 Hz, 2 H), 4.02 (dd, J = 12.97, 1.38 Hz, 1 H), 4.18 (dd, J = 12.97, 2.90 Hz, 1 H), 4.50 (t, J = 9.06 Hz, 2 H), 5.37 (dd, J = 2.77, 1.76 Hz, 1 H), 6.73 (d, J = 8.31 Hz, 1 H), 7.07 (dd, J = 8.31, 1.76 Hz, 1 H), 7.17 (d, J = 1.26 Hz, 1 H), 7.26−7.31 (m, J = 8.06, 5.79, 2.01 Hz, 1 H), 7.53−7.57 (m, 1 H), 7.56−7.60 (m, 1 H), 8.11−8.15 (m, 1 H), 11.58 (s, 1 H).

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