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Communications to the Editor

First Scale-Up to Production Scale of a Ring Closing Metathesis Reaction Forming a 15-Membered Macrocycle as a Precursor of an Active Pharmaceutical Ingredient

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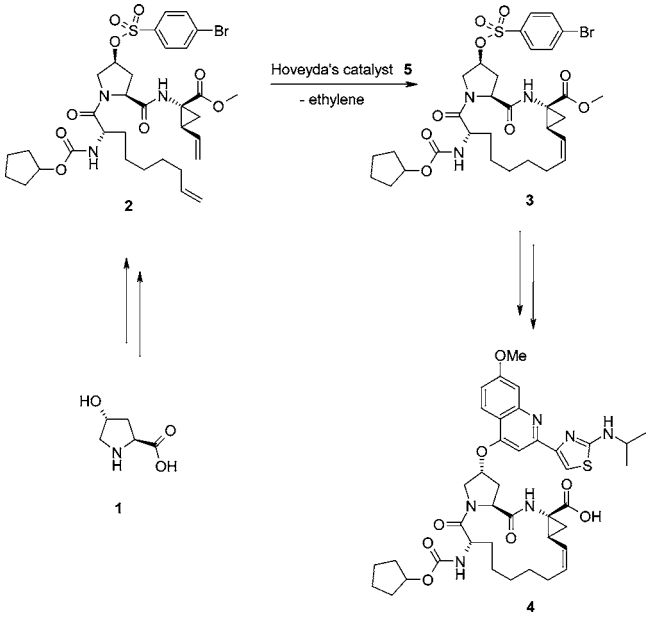
Abstract:

BILN 2061 ZW (4) is a new chemical entity which shows promising results against the Hepatitis C virus. The major issue in the synthetic route represents the scale-up of a ring closing metathesis reaction to form a 15-membered macrocycle. The parameters chosen for the macrocyclization are discussed, and the experience during large scale synthesis, trouble shooting, and possible improvements for future campaigns are described.

During the past few years, the ring closing metathesis reaction (RCM) has become an increasingly important synthetic method in the synthesis of highly functionalized organic compounds; e.g., for the synthesis of macrocyclic systems, this reaction represents a powerful tool.[1] On the other hand, a macrocyclization using an RCM suffers some serious disadvantages with regard to a scale-up of the reaction to production scale. The reaction is usually performed in highly diluted solutions[1] which causes tremendous volume time requirements (VTR), resulting in high manufacturing costs. The consumption of large amounts of solvent has an impact too on the raw material costs but also represents an environmental issue. In consequence the RCM in production scale is an appropriate reaction for the synthesis of products which are somewhat insensitive towards manufacturing costs. Herein we report, for the first time to our knowledge, the scale-up of an RCM forming a macrocyclic system to production scale.

The antiviral drug BILN 2061 ZW was developed as a Hepatitis C virus (HCV) NS3 protease inhibitor.[2] The active

Scheme 1



pharmaceutical ingredient **4** is synthesized in several steps from *L*-hydroxyproline (**1**) (Scheme 1).[3] The key step of the synthetic route represents the conversion of the diene **2** to the 15-membered macrocycle **3** by a RCM reaction. The parameters for the RCM process to be applied in a large scale synthesis, determined before the first production campaign in laboratory scale experiments, are described as follows.[4]

Most RCM reactions described in the literature are performed using dichloromethane as solvent. For the formation of the macrocyclic compound **3**, reaction times in dichloromethane are unacceptably high (>12 h) due to the restricted temperature range caused by the low boiling point

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(4) full experimental details for the whole synthetic route will be published soon: Yee, N. K.; Houpis, I. N.; Haddad, N.; Frutos, R. P.; Gallou, F.; Wang, X.-J.; Wei, X.; Simpson, R. D.; Feng; X.; Fuchs, V.; Xu, Y.; Tan, J.; Zhang, Li., Xu, J.; Smith-Keenan, L. L.; Vitous, J. Ridges, M. D.; Spinelli, E. M.; Johnson, M.; Samstag, W.; Donsbach, K.; Nicola, T.; Winter, E.; Brandenburg, J.; Farina, V. Manuscript in preparation.

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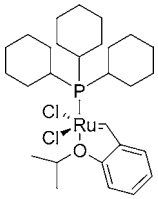
Scheme 2



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of the solvent. Instead of this environmentally unfriendly solvent, we chose toluene which can be used up to 110 °C and which allows an easier extractive workup of the reaction mixture. The reaction temperature was set to 80 °C. Higher temperatures were shown not to be acceptable for quality, safety, and economical reasons: At temperatures higher than 90 °C a considerable exothermic decomposition of both the diene **2** and the macrocycle **3** is observed which leads to dramatic losses of yield and quality. As mentioned above the macrocyclization requires highly diluted solutions to avoid intermolecular cross metathesis as a competing reaction. These requirements are opposed to the intention to optimize the throughput of the process. In our case, the dilution of 118 mL of toluene for 1 g of diene **2** was chosen as a compromise. The diene precursor **2** was introduced as a 30−50% solution in toluene. Before use, the solvent is degassed using nitrogen until the concentration of oxygen is below 1 mg/l. The degassing is continued during the whole reaction time to get complete conversion by removing the formed ethylene from the solution.

The Ru-based first generation Hoveyda's catalyst (**5**)[5] (Scheme 2) was chosen as an appropriate precatalyst. As a solid it is an air-stable catalyst which is easy to handle even in kilogram amounts without strict oxygen exclusion. Using this precatalyst the RCM yields exclusively the desired *Z*-isomer of the macrocyclic intermediate **3**. The *E*-isomer has never been detected in any significant amount. The catalyst loading is 3 mol % relative to the diene **2**. Due to the reaction temperature of 80 °C, it is favorable to add the catalyst **5** to the degassed diene solution in three equal portions as a solid over a period of 2 h because the catalyst (e.g., the active species) is not stable for the total reaction time.[6] So, the combination of the high reaction temperature with the addition of the catalyst in several portions reduces the overall required amount of the expensive catalyst **5**.

Applying the parameters described above, the reaction is complete within 3−4 h (<3% of diene **2** left, monitored by HPLC). The focus of the subsequent workup was to develop an extractive purification of the crude reaction mixture and the isolation of the product as a storable solid. After several aqueous extractions (water, HCl, $NaHCO_3$) and a charcoal treatment of the organic layer at 50 °C, the toluene is almost completely distilled off yielding a concentrated solution. The product **3** is isolated as an amorphous solid by precipitation from methyl cyclohexane. We never succeeded in purifying the product by crystallization, and therefore approximately 10% of impurities deriving from intermolecular cross metathesis reactions are included which can be easily removed during the subsequent synthetic steps. A typical yield by HPLC assay is 83%, the purity is approximately 90% (HPLC area), and the Ru content is between 500 and 1000 ppm.

Table 1. **Multipurpose equipment used for the RCM process**

procedure	apparatus	vol (L)
RCM reaction	glass lined stirred tank reactor	3000
aqueous work up	glass lined stirred tank reactor	6000
distillation and charcoal treatment	glass lined stirred tank reactor	2000
precipitation	glass lined stirred tank reactor	3000
isolation	stainless steel centrifuge	
drying	glass lined tumble dryer or stainless steel mixing dryer	

We had to produce approximately 400 kg of the macrocyclic intermediate **3** in two cGMP campaigns. Due to the restricted reactor volumes available in our pilot plant, we were forced to transfer the procedure directly to production scale in a full cGMP environment to reach the timelines set by the internal project plan. Standard multipurpose equipment (stirred tank reactors, centrifuges, dryers) was used for the process as shown in Table 1.

After the first successful batches, the process was streamlined to reduce the volume time requirement: Two reactions were performed in parallel in two 3000 L vessels, and the workup and isolation were combined (see Figure 1). In one attempt, the product of two sets of two parallel reactions (four reactions in total) was isolated in one precipitation. The realization of the different procedures of the process (reaction, workup, distillation, precipitation) in a cascade of different vessels allows the interlocking of several batches and therefore saves time. Furthermore, a cleaning of the reaction vessels between two runs is not necessary.

The degassing of the large amounts of toluene and diene solution was done by an apparatus developed in-house which allows an efficient use of nitrogen to remove oxygen. During the reaction a stream of 1000 L of nitrogen per h was passed through the reaction mixture by a tube. In most cases, the reaction time to get complete conversion was higher than anticipated from laboratory experiments: in general 4−9 h of reaction time were needed. In some cases, a supplementary

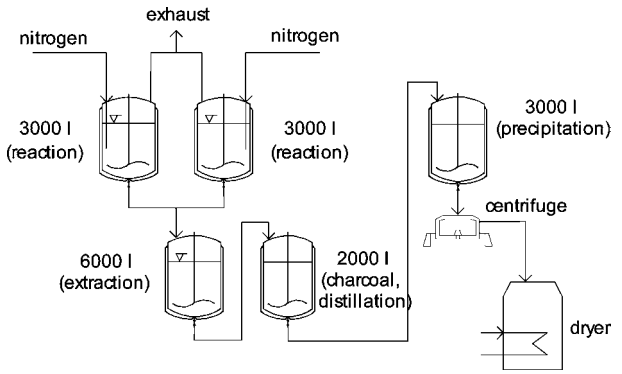

Figure 1. **Flowchart of the RCM process showing the flow of product from the reaction vessel to the dryer.**

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(6) Hughes, R. C.; Dvorak, C. A.; Meyers, A. I. *J. Org. Chem.* **2001**, *66*, 5545.

amount of 0.5 mol % of Hoveyda's catalyst **5** was added. Obviously the removal of ethylene was not as efficient as that in the lab experiments. Moreover different qualities of the diene precursor **2** and catalyst **5** showed to have a larger impact onto the reaction rate than they did in the laboratory scale. The standard batch size for the reaction was 20.2 kg of diene **2**, of which two or four reactions were combined for workup and isolation as described above. The workup, the average yield of the process (83%), and the quality of the product (HPLC purity, Ru content) were similar to the results obtained on the laboratory scale. Attempts to reuse toluene distilled from the reaction mixtures after aqueous workup showed similar results to the batches using virgin toluene. This interesting aspect will help to reduce the enormous amounts of solvent in future campaigns.

During the first production campaign a serious issue arose. The first two batches showed a totally different behavior during the reaction compared to the laboratory experiments. Besides the expected product **3**, 10−15% of an isomer was formed, the reaction time was higher (8 to > 12 h), and up to 5.3 mol % of catalyst were needed to get complete conversion. The structure of the isomer was not unambiguously elucidated, but NMR and MS experiments revealed that the isomerization occurred on the cyclopropane moiety. We checked all raw materials by use-testing and found out that an impurity in the toluene seemed to be the reason for the isomerization and the inhibition of the catalysis. Structural elucidation of aqueous extracts of the toluene revealed that traces of morpholine (<20 ppm) in the technical grade toluene seemed to cause the unusual behavior of the RCM reaction. The undesired impact of morpholine onto the reaction was proven in laboratory experiments by spiking reaction solutions with morpholine. Due to the large amounts of solvent compared to the catalyst, even such a small concentration of a nucleophile is able to seriously disturb the catalytic reaction: 20 ppm of morpholine in approximately 2500 L of toluene represents an almost equimolar amount compared to the catalyst. Therefore, we had to establish a procedure to clean up toluene and to remove completely morpholine and eventually other unknown basic nucleophiles. For all subsequent batches, we extracted toluene with aqueous HCl and water and dried the solvent by azeotropic distillation before use. All subsequent large scale RCM reactions using the precleaned toluene as solvent were successful. Therefore it was not necessary to monitor the morpholine impurity in both the virgin and the extracted solvent.

In summary we have produced almost 400 kg of the macrocyclic intermediate **3** by applying the ring closing metathesis reaction. The feasibility and usefulness of this challenging reaction for the production of pharmaceutical compounds was thereby proven. Although the first two production campaigns were successful, there is some need for improvements. Therefore, the development of the process is ongoing. Increasing the concentration during macrocyclization by more than 20% resulting in a gain of throughput seems to be possible without loss of yield and quality. Furthermore, it is planned to use a thin film evaporator to distil off the large amounts of toluene in one of the future campaigns because distillation proved to be the time-consuming bottleneck of the process. A new process for the removal of Ru from intermediate **3** was developed in the laboratory[7] because getting the heavy metal content below 10 ppm was shown to be an issue for the final drug substance **4**. Furthermore, new more reactive catalysts such as Grela's catalyst[8] are being investigated with the aim to shorten the reaction times and to reduce the catalyst loading.[9]

We hope that our contribution helps to establish the RCM as a more powerful synthetic method in large scale production of complex molecules. The aim of our ongoing research for improvements of the process is to further develop the RCM so that it will become a standard reaction in large-scale synthesis. We are confident that, soon, it will be even possible to use the RCM for market supply of pharmaceutical compounds on a multiton scale.

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(7) Patent pending.
(8) Grela, K. S.; Harutyunyan, S.; Michrowska, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4038.
(9) Using only 0.7 mol % of Grela's catalyst, the reaction is complete within 30 min under similar reaction conditions (dilution, temperature) as described in this paper.