Solution- and Solid-Phase Synthesis of Tetrahydroquinoline-Based Polycyclics Having α,β-Unsaturated γ-Lactam and δ-Lactone Functionalities

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Abstract: With the goal of the library generation using the tetrahydroquinoline-based derivative, a simple and practical enantioselective synthesis of the tetrahydroquinoline derivatives having α,β-unsaturated γ-lactam and δ-lactone functional groups was achieved. The phenolic hydroxy group in the α,β-unsaturated γ-lactam was utilized as an anchoring site for the solid-phase synthesis. The ring-closing metathesis approach yielded the desired tricyclic products on the solid phase.

Key words: lactams, lactones, fused-ring systems, heterocycles, asymmetric synthesis, solid-phase synthesis

We have launched a program that aims to develop a solid-phase, high-throughput synthesis of natural products, like tetrahydroquinoline-based polycyclics, having different ring skeletons.[1–4] The choice of the tetrahydroquinoline scaffold was made based on the fact that this is one of the commonly found building blocks in a wide variety of bioactive natural products.[5] In particular, we were involved in developing a practical enantioselective synthesis of the tetrahydroquinoline-based polycyclics containing α,β-unsaturated γ-lactam **1** and δ-lactone **2**. These two building blocks offer unique features. The presence of two orthogonal functional groups (i.e., hydroxy or amine, and the α,β-unsaturated carbonyl) in γ-lactam **1** (*O*-3 position) and δ-lactone **2** (*N*-1 position), respectively, could further be utilized in building complexity by diversification. The particular polycyclics we are discussing here are the tricyclics pyrrolo[1,2-*a*]quinoline (**4**) and pyrano[3,2-*b*]quinoline (**5**), presented in Figure 1.

pyrrolo[1,2-*a*]quinoline **4** pyrano[3,2-*b*]quinoline **5**

Figure 1 Tricyclic systems presenting in this article

The systems presented in Figure 1 are included in many bioactive, natural and pharmacological products. In this report, the solution- and solid-phase synthesis of our pyrroloquinoline and also the solution-phase synthesis of pyranoquinoline will be discussed. As illustrated in Schemes 1 and 2, tetrahydroquinoline-based tricyclics containing α,β-unsaturated γ-lactam **1** and δ-lactone **2** were prepared from our tetrahydroquinoline scaffold **3** which synthesis has already reported by our group.[6] Our approach for the preparing of pyrrolo[1,2-*a*]quinoline system is the ring-closing metathesis (RCM) reaction, the method which apparently never used for the construction of this tricyclic system. A similar method was used for the synthesis of pyrano[2,3-*b*]quinoline system. The solid-phase synthesis of pyrroloquinoline system will also be presented here.

We started our synthesis from **3** (Scheme 1).[6] Positions 1 and 2 in this tetrahydroquinoline had to be modified to accommodate two terminal olefins. Before this task, the secondary hydroxy group in **3** should be blocked to minimize the formation of the undesired side products. The benzoyl protection on **3** using coupling conditions resulted in a fully protected tetrahydroquinoline compound **6** with excellent yield (not shown). ^{1}H NMR showed a doublet at δ = 7.94 ppm (J = 7.3 Hz, 2 H) signaling two new aromatic protons close to the carbonyl. This carbonyl in the benzoyl group also showed a peak at δ = 166.1 ppm in ^{13}C NMR. Our next task was the preparation of one terminal olefin at position 2 of our tetrahydroquinoline system. Therefore, we needed to remove the TBS group first. The treatment of the fully protected compound **6** with tetra-*n*-butylammonium fluoride (TBAF) in acetic acid cleanly afforded compound **7** with a free primary alcohol moiety. The disappearance of TBS peaks in both ^{1}H NMR [δ = 0.82 (9 H) and –0.01 (6 H) ppm] and ^{13}C NMR [δ = 18.4 and –5.2 ppm] is the best indication for the successful deprotection reaction. The oxidation of this alcohol **7** with SO_3–pyridine system and a subsequent Wittig reaction gave compound **8** with the desired terminal olefin. Because of the low stability of the aldehyde intermediate, purification at the oxidation stage was not efficient. Therefore, it was decided to perform the next step (i.e., Wittig reaction) without the isolation and purification of the aldehyde. Although this step was successful, the yield was slightly lower than our expectations (55% for two steps). Mass spectra showed a peak at m/z = 468.4 [M + 1]. Moreover, the corresponding olefinic hydrogens and carbons appeared on ^{1}H NMR and ^{13}C NMR, respectively. The generation of the second olefinic arm would form the RCM precursor **9**. The replacement of the Alloc group with

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acryl performed using the two-step reaction of N-deprotection with Pd(0) in compound **8** followed by the installment of the acryl group in the nitrogen atom without the purification of the corresponding amine intermediate. This resulted in the formation of compound **9** with an average yield of 83% for each step. Although proven with all other methods (i.e., mass, ^{13}C NMR, 1D and 2D NMR), the disappearance of the methylene hydrogens in 'OCH_2 -olefin' of the Alloc group, at δ = 4.50–4.60 ppm, was the easiest way to prove that we performed the reaction correctly. Obviously, we also expected to see another carbonyl peak in ^{13}C NMR for the acryl group, which appeared at δ = 155.7 ppm. In the last stage of our synthesis, the RCM reaction using the first-generation Grubbs catalyst on **9** cleanly afforded pyrrolo[1,2-*a*]quinoline **1** in the 80% yield. The structure of this tricyclic compound containing α,β-unsaturated γ-lactam was comprehensively studied by mass, 1D NMR, 2D NMR, and finally with X-ray crystallography. ^1H NMR showed the olefinic (α,β-unsaturated) hydrogens at δ = 6.38 and 7.28 ppm. However, the best sign for a successful RCM reaction is the expulsion of the ethylene molecule, which resulted in fewer number of hydrogen and carbon atoms by six and two, respectively. The counted H and C atoms in 1D NMR spectra proved this.

The pyrroloquinoline compound **1** under recrystallization, using an EtOAc–CH_2Cl_2–hexanes system, resulted in a dark yellow crystal. The X-ray crystallography enabled the ultimate assignment (Figure 2). Interestingly, the pyrrolidine ring was forced slightly (around 10°) out of the quinoline plane as predicted by Reinhoudt in early 1990s.[7] The sophisticated synthesis of pyrrolo[1,2-*a*]quinoline system in his group was performed via the *tert*-amino effect involving an intramolecular [1,5]-H transfer.[8] Due to its harsh conditions used, such as refluxing in toluene or benzene in a long period of time, this approach is not suitable for the synthesis of the relatively sensitive compounds. Furthermore, it lacks the complexity and necessary substitution for the corresponded solid-phase synthesis (such as an α,β-unsaturated system and the anchoring site). Our RCM approach using the same starting material, however, can be applied for the solution-phase synthesis of both pyrrolo- and pyranoquinoline systems in addition to the solid-phase synthesis of the pyrroloquinoline compound.

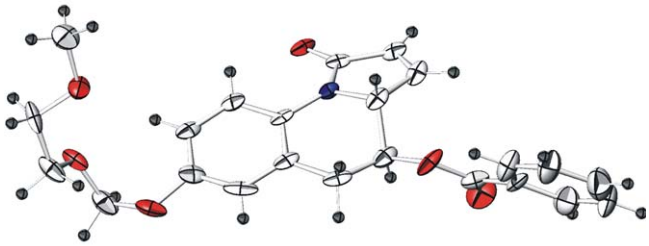
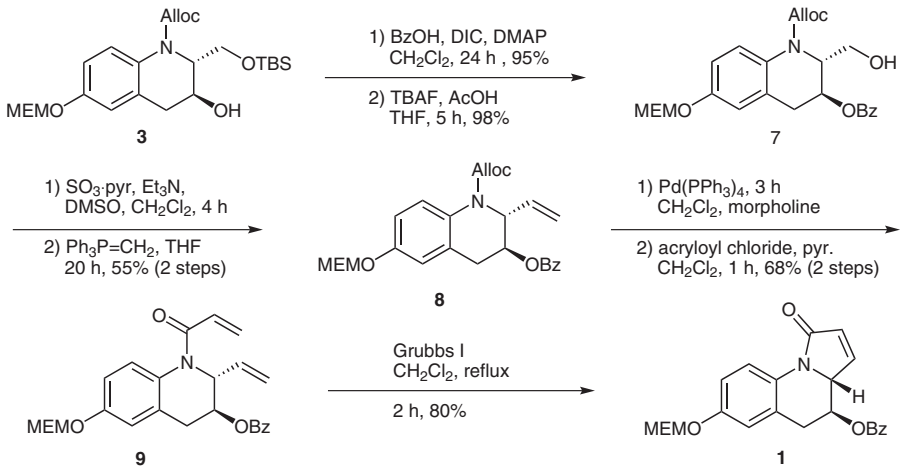


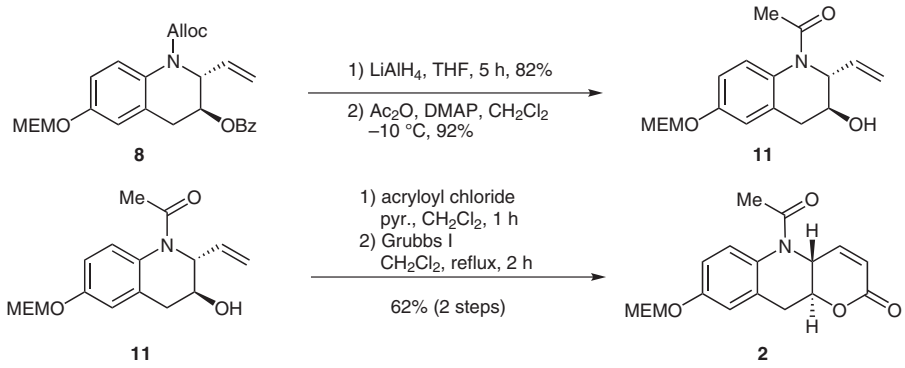
Figure 2 X-ray crystal structure of compound **1**[9]

Earlier the starting material **3** for both syntheses of tricyclics **1** and **2** was shown. However, for the synthesis of pyranoquinoline **2**, the experimental target was prepared using compound **8** (which its formation explained above) and could save four steps. For this investigation, the approach to the synthesis of the pyrano[3,2-*b*]quinoline system again was a RCM reaction, although no other method was found for the synthesis of this system in the literature. Since the terminal olefin has already been installed in the C-2 position of the tetrahydroquinoline compound **8**, an acryl group was used for the proceeding by the RCM reaction. Scheme 2 details the steps for this synthesis. A reduction by lithium aluminum hydride on **8** successfully removed both the Alloc (amide) and benzoyl (ester) groups. The provided amino alcohol **10** (not shown) was also isolated and fully characterized. The disappearance of two carbonyl peaks in ^{13}C NMR indicated that the Alloc and benzoyl groups had been removed.

The secondary amine in this amino alcohol **10** was selectively acyl-protected using acetic anhydride and 4-dimethylaminopyridine (DMAP) as the base to afford **11**. The peaks for acetyl group appeared in ^1H NMR, that is, δ = 2.07 ppm (s, 3 H) for O=CCH_3 and δ = 170.9 ppm in ^{13}C NMR for the carbonyl group. Alcohol **11** then protected as an acryl by the acryloyl chloride–pyridine system to form



Scheme 1 Synthesis of pyrrolo[1,2-*a*]quinoline **1**



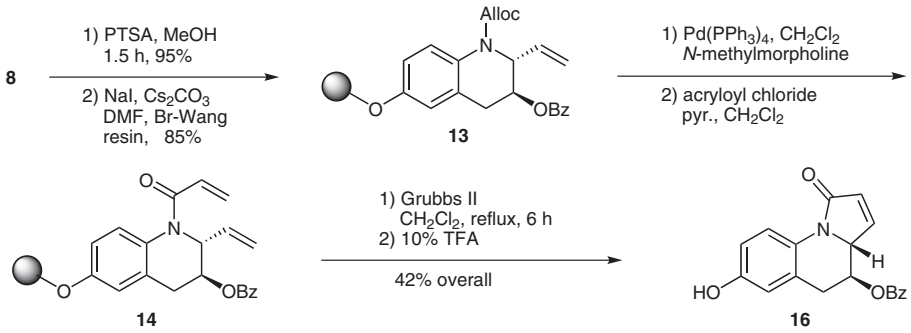
Scheme 2 Synthesis of pyrano[3,2-*b*]]quinoline **2**

the second olefinic arm required for the RCM reaction. Similar to the previous implemented system, the first-generation Grubbs catalyst was used for the cyclization reaction in the refluxed CH_2Cl_2. The appearance of M + 1 (*m/z* = 348.2) peak in the mass spectrum provided the first approval. This tricyclic compound **2** containing α,β-unsaturated δ-lactone showed the olefinic hydrogens at δ = 6.36 ppm (1 H) and 7.22 ppm (1 H) in ^{1}H NMR and the lactone carbonyl at δ = 170.1 ppm in ^{13}C NMR.

The RCM reaction was also the preferred method for our solid-phase synthesis. Above, we pointed out that, for preparing our second tricyclic system, one of our intermediates from the first synthesis was used (i.e., compound **8**). For the solid-phase synthesis of the pyrrolo[1,2-*a*]quinoline system, again, we started with the same intermediate **8** because it had all of the characteristics needed for a successful solid-phase synthesis, including orthogonal protecting groups and potential anchoring site. Furthermore, it had one arm already equipped with an olefin moiety suitable for the RCM reaction. Treatment of the tetrahydroquinoline **8** with PTSA (Scheme 3) in methanol produced an excellent yield of the phenolic compound **12** (not shown). Loading was performed on this phenolic compound using treatment with bromo Wang resin in the presence of sodium iodide and cesium carbonate. The yield for loading was 85%, which was considered to be a very good yield. Resin-loaded compound **13** was our starting material in the solid phase. As indicated above, the formation of a second olefinic arm at the nitrogen position, which is needed for the RCM reaction, can be achieved by the replacement of Alloc with acryl group. The Alloc group was removed by using a typical palladium(0)–methylmorpholine system and the acryl group replaced it using acryloyl chloride–pyridine to form RCM precursor **14**. It should be remembered that each step was checked using mass spectroscopy. The RCM reaction was performed on precursor **14** using a second-generation Grubbs catalyst in refluxed CH_2Cl_2 for six hours. The prepared compound **15** (not shown) was treated with TFA, which cleaved the resin, and subsequently purified by column chromatography. The overall yield was calculated and found to be 42% (four steps). In spite of the limited amount of pyrroloquinoline **16** formed, we were able to characterize it completely. Comparing with tricyclic compound **1**, full sets of protons in **16** were observed using NMR. As expected, the difference was the disappearance of MEM protons and carbon atoms in ^{1}H NMR spectrum. The 2D NMR spectra were also used for the ultimate assignment. For instance, the COSY spectrum of **16** showed a pattern similar to **1**.

In summary, we explained the solution- and solid-phase synthesis of tetrahydroquinoline system pyrrolo[1,2-*a*]quinoline and also solution-phase synthesis of pyrano[3,2-*b*]quinoline. Using this approach, further work is in progress for the library generation from these two scaffolds, and the results of this work will be reported as they are available.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett. Included are experimental procedures and analysis of 1D and 2D NMR spectra of compounds **1**, **2**, and **6**–**16**, and also crystal data for compound **1**.



Scheme 3 Solid-phase synthesis of pyrrolo[1,2-*a*]quinoline **16**

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(9) Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no CCDC 730001. Copies of the data can be obtained, free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or email: deposit@ccdc.cam.ac.uk].