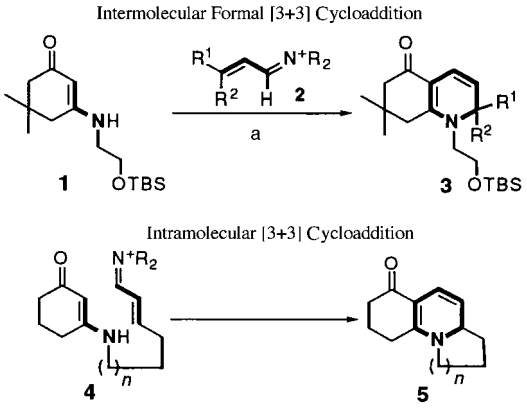
434.2 Hz)) in 1,4-dioxane (6.0 mL) at room temperature for 6 h generated a brown mixture exhibiting a ^{1}H-coupled ^{31}P NMR resonance at $\delta = 123.4$ (singlet).

[17] See Supporting Information for full synthetic details and characterization of new compounds. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-157421. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

A Novel and Highly Stereoselective Intramolecular Formal [3+3] Cycloaddition Reaction of Vinylogous Amides Tethered with α,β-Unsaturated Aldehydes: A Formal Total Synthesis of (+)-Gephyrotoxin**

Lin-Li Wei, Richard P. Hsung,* Heather M. Sklenicka, and Aleksey I. Gerasyuto

We have been exploring reactions of β-diketo equivalents **1** with α,β-unsaturated iminium salts **2** for the construction of heterocycles such as **3** (Scheme 1).[1–3] These reactions involve a sequence consisting of a Knoevenagel condensation followed by a six π-electron electrocyclic ring-closure,[4] thereby constituting a stepwise formal [3+3] cycloaddition[5–7] in which two σ bonds are formed, along with a new stereocenter adjacent to the heteroatom. This cycloaddition protocol can be classified as a sequential anionic–pericyclic strategy for which the significance in natural product synthesis has been elegantly summarized by Tietze and Beifuss.[8] Our recent work on the use of vinylogous amides in this formal cycloaddition[1] has allowed us to envision an intramolecular version of this reaction. Since the vinylogous amide **1**, which contains a functionalized tether, provided the formal cycloadduct **3** in good yields,[1] it is conceivable that the vinylogous amides **4**, which are tethered with an α,β-unsaturated iminium ion, may lead to piperidinyl heterocycles **5**, attractive as intermediates in the syntheses of natural alkaloids (Scheme 1). We report herein the first stereoselective intramolecular formal [3+3] cycloaddition reaction by using vinylogous amides that are tethered with iminium ions, and its application in a formal total synthesis of (+)-gephyrotoxin.[9–11]



Scheme 1. [3+3] Cycloaddition reactions of vinylogous amides and α,β-unsaturated iminium salts. Reagents and conditions: a) EtOAc/toluene 1:2, 150 °C, 15–30 h, 76–80 %; TBS = *tert*-butyldimethylsilyl.

Based on our previous studies, the formation of the α,β-unsaturated iminium salt prior to the addition of a β-diketo nucleophile is crucial to the regio- and chemoselectivity of the intermolecular formal cycloaddition reaction.[1, 2a] Conditions and protocols that generate α,β-unsaturated iminium salts in the presence of the β-diketo nucleophile lead to low yields of the desired products, and/or to synthetically less useful by-products resulting from various competing reaction pathways.[7b–e] However, the enal precursor to α,β-unsaturated iminium ions in the intramolecular variant also contains a vinylogous amide. Thus, controlling the extent of iminium ion formation before competing reactions take place is a major challenge.

To demonstrate the feasibility of an intramolecular formal [3+3] cycloaddition, the vinylogous amides **6** and **7** were prepared[12, 13] and treated with piperidine (2.0 equiv) and Ac_2O (2.0 equiv) in EtOAc/toluene (1:2; concentration of vinylogous amides: 0.03–0.30 M) at 85 °C for 1 h (Scheme 2). These are the standard reaction conditions that have been consistently employed for the formation of iminium salts.[1, 2] Subsequent heating at 150 °C in a sealed tube led to the isolation of the desired heterocycles **8** and **9** in yields of 80 and 68 %, respectively. Furthermore, the chiral vinylogous amide **10**[12] led to the desired tricycle **11** in 55 % yield as a single diastereomer under the same reaction conditions. The stereochemistry of **11** was assigned by NOESY experiments.

These examples suggest that our initial concern regarding the extent of iminium salt formation was not necessary; under conditions that do not promote the formation of iminium ions, these reactions were essentially arrested. This control study suggests that even a low concentration of the iminium species is sufficient to promote this intramolecular formal [3+3] cycloaddition reaction. On the other hand, under the same standard reaction conditions, the vinylogous amide **12** did not provide the desired cycloadduct **13** in useful yields (Scheme 2). We were, however, able to observe the formation of **13** by ^{1}H NMR spectroscopy; thus our inability to isolate **13** from **12** may be a result of the instability of **13** under the reaction conditions and/or under the work-up conditions. This prompted us to explore other protocols suitable for generating iminium salts.

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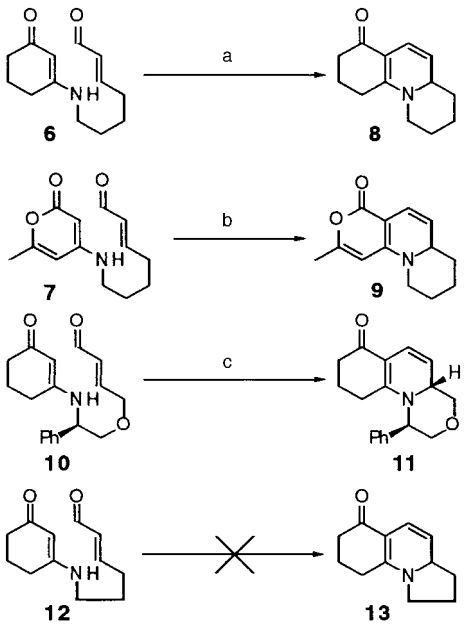
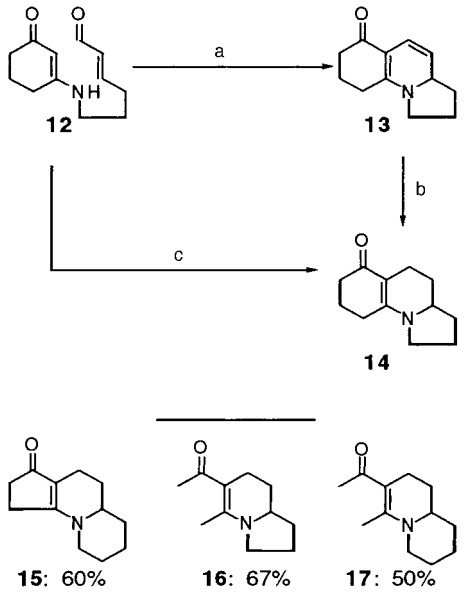


Scheme 2. Intramolecular [3+3] cycloaddition reaction to give piperidinyl heterocycles. Reagents and conditions: a) 1) piperidine, Ac_2O, EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 3 h, 80% over two steps; b) 1) piperidine, Ac_2O, EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 3 h, 68% over two steps; c) 1) piperidine, Ac_2O, EtOAc/toluene 1:2, 85 °C, 1 h, 2) 150 °C, 23 h, 55% over two steps (≥95:5).

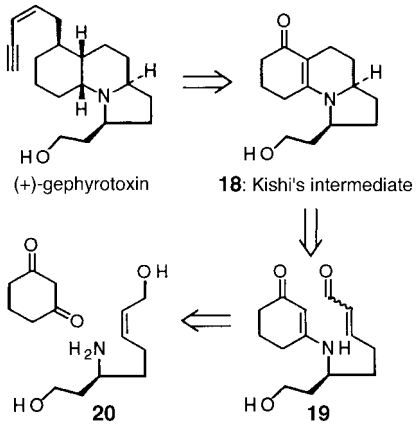
After extensive screening, the desired cycloadduct **13** was isolated in 71% yield after **12** was heated at 90–110 °C for 1–2 h in the presence of 0.5–1.0 equivalents of piperidinium acetate salt[14] (Scheme 3). Under these conditions, the reaction proceeded more quickly, and the product was purified by column chromatography. Compound **13** was less stable than anticipated, but to improve its stability, **13** was hydrogenated to give the tricyclic heterocycle **14** in 70% yield.



Scheme 3. Optimized intramolecular [3+3] cycloaddition reactions. Reagents and conditions: a) EtOAc, Na_2SO_4, piperidinium acetate (0.5–1 equiv), 90–110 °C, 1–2 h, 71%; b) 5% Pd/C, H_2, EtOAc, 70%; c) EtOAc, Na_2SO_4, piperidinium acetate (0.1 equiv), 80 °C, 1–2 h, then 5% Pd/C, H_2, 65%.

This two-step sequence was further optimized by decreasing the amount of piperidinium salt to 0.1 equivalents and decreasing the temperature to 80 °C. Most significantly, the crude reaction mixture was directly submitted to standard hydrogenation conditions, thereby avoiding the isolation of the sensitive heterocycle **13**. This one-pot protocol provided **14** in 65% yield from **12**. This new reaction protocol was general for the successful examples described in Scheme 2 and, more significantly, worked well in the syntheses of **15**–**17** (Scheme 3), which were difficult to prepare under the standard conditions. Successful preparations of **16** and **17** allowed us to design syntheses of natural products from the indolizidine and quinolizidine families.[15]

Access to the tricyclic heterocycle **14** from **12** provides an efficient entry to the tricyclic frame of gephyrotoxin.[9] Of the three known total syntheses of (±)-gephyrotoxin,[10] the synthesis reported by Kishi and co-workers involved the intermediate **18** (Scheme 4).[10a] The only enantioselective

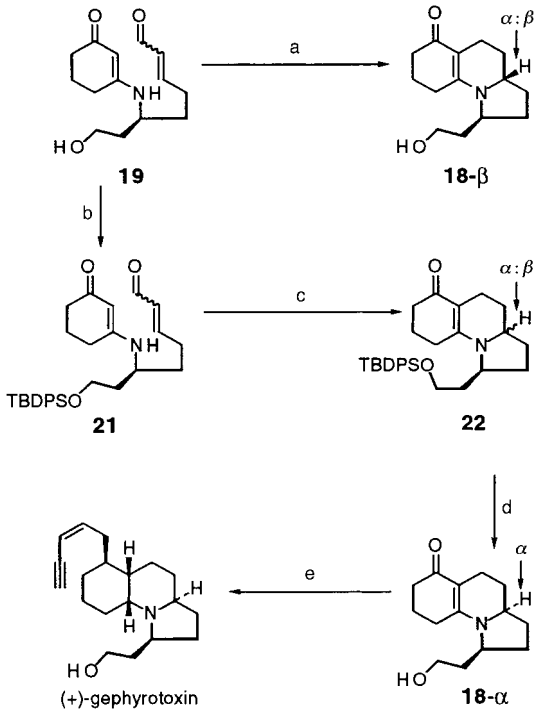


Scheme 4. Retrosynthetic analysis of gephyrotoxin.

synthesis of (+)-gephyrotoxin, which was reported by Kishi and Fujimoto, utilized the optically active **18**, which was prepared in 18 steps.[11] We envisioned an opportunity to intercept Kishi's intermediate **18** by using our stereoselective intramolecular formal [3+3] cycloaddition reaction of the chiral vinylogous amide **19**. Compound **19**[12] was obtained by condensation of the chiral amino diol **20**[12] with 1,3-cyclohexanedione.

Subjecting the vinylogous amide **19** to very similar conditions to those described in Scheme 3 led to the tricyclic compound **18** in 50% yield overall (Scheme 5). The diastereomeric ratio was very high (≥93:7) and the major isomer was assigned as **18**-β ($[\alpha]_D^{20} = -51°$) by using NOESY experiments. However, **18** did not exhibit the same ^{1}H NMR spectroscopic or optical rotation properties as Kishi's intermediate[11]. We speculated that the unprotected primary alcohol could play a role in controlling the conformation of **19** through hydrogen bonding with the nitrogen atom. This interaction could distort the conformation of the transition state, thus leading to the observed but undesired stereochemical outcome of the reaction.

To verify this notion, we explored a range of different silyl protecting groups and found that the reaction of *tert*-



Scheme 5. Synthesis of gephyrotoxin precursor **18**. Reagents and conditions: a) EtOAc/EtOH, Na_2SO_4, piperidinium acetate (0.5–1 equiv), 100 °C, 1–2 h, then 5% Pd/C, H_2, 50% ($[\alpha]_D^{20} = -51°$, $\alpha/\beta \leq 7{:}93$); b) TBDPSCl, imidazole; c) toluene/EtOH, Na_2SO_4, piperidinium acetate (1.0 equiv), 150 °C, 1–2 h, then 5% Pd/C, H_2, 60% from **19**, (α/β 60:40–41:59); d) 1) TBAF, CH_2Cl_2, 0 °C, 80%, 2) separation; e) Kishi's route, 11 steps.

butyldiphenylsilyl (TBDPS)-protected **21** provided the best ratio for **22**-α/**22**-β, which ranged from 60:40 to 41:59. The TBDPS group in **22** was removed by using tetrabutylammonium fluoride (TBAF) in CH_2Cl_2 at 0 °C, leading to a mixture of isomers **18**-α and **18**-β in 80% yield with the same ratio. Subsequent chromatographic separation of the two isomers on silica gel led to the isolation of the tricyclic compound **18**-α, which matched Kishi's intermediate. Although the stereoselectivity in the formal [3+3] cycloaddition reaction should be improved to pursue a potential total synthesis of gephyrotoxin, the overall sequence to Kishi's intermediate is short, and demonstrates the synthetic potential of this intramolecular formal [3+3] cycloaddition reaction in the synthesis of natural products.

We have described herein a unique intramolecular formal [3+3] cycloaddition reaction that uses vinylogous amides tethered with an enal functional group to give complex piperidinyl heterocycles. For example, the method has been applied to a formal total synthesis of (+)-gephyrotoxin.

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