A Two-Step Synthesis of the Bioprotective Agent JP4-039 from *N*-Boc-*L*-Leucinal.

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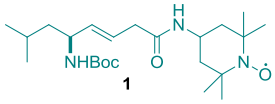
INTRODUCTION

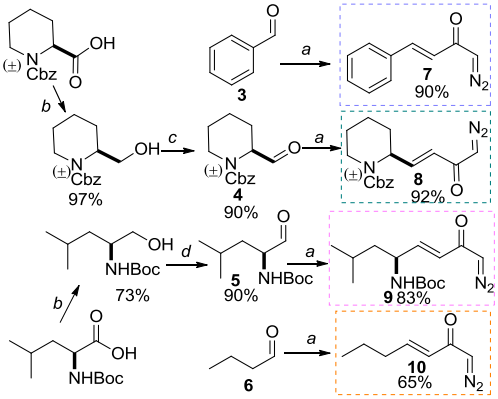
JP4-039 **1** (scheme 1) is a novel nitroxide conjugate capable of crossing lipid bilayer membranes and scavenging reactive oxygen species (ROS)[1]. Only one synthesis is described in the literature, which consists of six steps and involves a one-pot hydrozirconation-transmetalation-addition[1] to a chiral sulfinimine as the key step. As our group has been recently exploiting the chemistry of α,β-unsaturated diazoketones[2–4], we were interested in investigating these platforms for the direct synthesis of β,γ-unsaturated amides and apply the methodology to prepare the bioprotective agent JP4-039 in just one step from them.



Scheme 1. Bioprotective agent JP4-039.

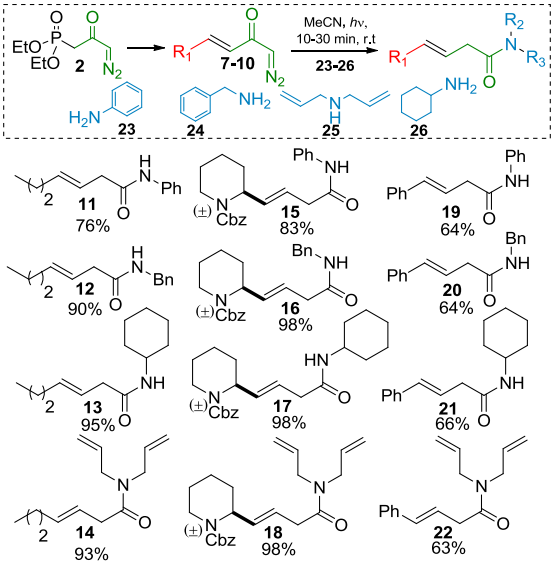
RESULTS AND DISCUSSION

We started our work by preparing key unsaturated diazoketones **7-10** after a Horner-Wadsworth-Emmons reaction between diazophosphonate **2** and aminoaldehydes **3**-**6** (Scheme 2).

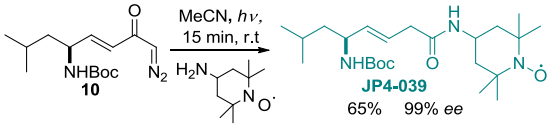


Scheme 2. *Reagents and conditions:a)* diazophosphonate **2**, NaH, THF, 5 min., 0 °C. Then, aldehyde, THF -78 to -30 (**8**) -40°C (**9**) °C; b) $BH_3.SMe_2$, THF, 25 °C, 12h; c) Swern oxidation; d) Parikh-Doering oxidation.

After the preparation of unsaturated diazoketones **7-10**, we turned our attention to the synthesis of β,γ-unsaturated amides **11-22** (63-98%) employing a photochemical Wolff Rearrangement in the presence of amines **23-26** (1 eq.) and acetonitrile (scheme 3). In order to show the applicability of the present method, diazoketone **10** was readily converted into the bioprotective agent JP4-039 in the presence of the 4-amino-TEMPO derivative radical (scheme 4). Chiral HPLC studies showed that no epimerization occurred during the HWE and Wolff rearrangement steps.



Scheme 3. β,γ-unsaturated amides **11-22** from **7-9**.



Scheme 4. One-step synthesis of JP4-039 from **10**.

CONCLUSION

An expedited synthesis of the bioprotective agent JP4-039 is described from *N*-Boc-*L*-Leucinal in 50% overall yield. The synthesis involves the use of an α,β-unsaturated diazoketone as the key intermediate, followed by a photochemical Wolff rearrangement in the presence of 4-amino-Tempo.

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