VIP Total Synthesis Very Important Paper

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Total Synthesis of (±)-Gephyrotoxin by Amide-Selective Reductive Nucleophilic Addition**

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Dedicated to Professor Larry E. Overman on the occasion of his 70th birthday

Abstract: *A chemoselective approach for the total synthesis of (±)-gephyrotoxin has been developed. The key to success was the utilization of N-methoxyamides, which enabled the direct coupling of the amide with an aldehyde and selective reductive nucleophilic addition to the amide in the presence of a variety of sensitive and electrophilic functional groups, such as a methyl ester. This chemoselective approach minimized the use of protecting-group manipulations and redox reactions, which resulted in the most concise and efficient total synthesis of (±)-gephyrotoxin described to date.*

Modern applications of organic chemistry in industry and medicine, especially for drug discovery, have resulted in the need for compounds of ever-increasing complexity. However, the reaction of a targeted functional group in such complex molecules often requires extra steps to protect more reactive functional groups, which results in decreases in the total yield. To overcome this issue and to achieve step-economic processes, the development of methods with high chemoselectivities, especially for carbon–carbon bond formation, has become a pivotal goal in synthetic chemistry.[1]

Gephyrotoxin (**1**) was isolated from skin extracts of a tropical poison dart frog, *Dendrobates histrionicus*, and possesses an array of neurological activities, including mild muscarinic activity.[2] The groups of Kishi, Hart, and Overman independently reported landmark total syntheses of gephyrotoxin with their own beautiful approaches (Figure 1).[3–6] However, although we appreciate that their syntheses were achieved more than 30 years ago, they required a number of protecting groups. For example, the construction of the three stereogenic carbon centers that are connected to the nitrogen atom and the installation of the two distinct side chains required extra protecting-group manipulations. To overcome this limitation, we envisioned a chemoselective approach with an amide-selective nucleophilic addition in the presence of a more electrophilic methyl ester (Scheme 1). This key reaction ultimately served to minimize the use of protecting-group manipulations, which resulted in a concise total synthesis of (±)-gephyrotoxin (**1**).

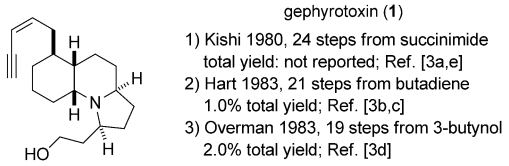
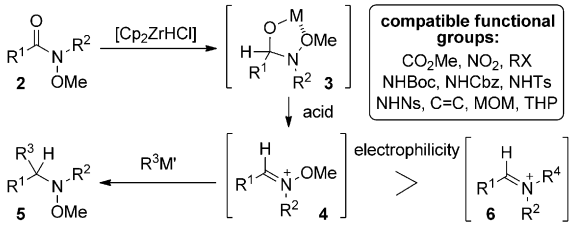


Figure 1. Gephyrotoxin (**1**) and previous total syntheses.



Scheme 1. Chemoselective reductive nucleophilic addition to *N*-methoxyamides. Boc = *tert*-butoxycarbonyl, Cbz = benzyloxycarbonyl, Cp = cyclopentadienyl, MOM = methoxymethyl, Ns = *ortho*-nitrobenzenesulfonyl, THP = 2-tetrahydropyranyl, Ts = 4-toluenesulfonyl.

Before we focused on the overall synthesis, we needed to develop a practical amide-selective nucleophilic addition reaction. Although significant progress has recently been made in the field of nucleophilic addition to inert amides by using reactive nucleophiles, including diisobutylaluminum hydride (DIBAL-H), Grignard reagents, and organolithium reagents,[7–9] functional-group compatibility still remains an unsolved issue.[10–12] De Meijere and co-workers reported that a Kulinkovich-type cyclopropanation of tertiary amides proceeded chemoselectively in the presence of a sterically hindered *tert*-butyl ester.[12b] The groups of Charette[12c] and Huang[12d] described chemoselective transformations of secondary amides into ketimines and ketones via highly electro-

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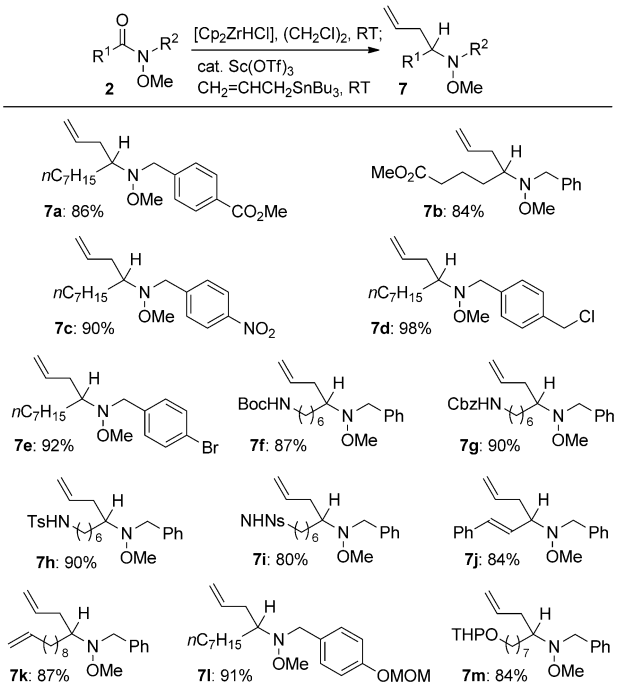
philic imidoyl triflates. This approach was highly general and compatible with a variety of sensitive functional groups, such as esters and ketones. We envisioned a chemoselective reductive nucleophilic addition to *N*-methoxyamides (Scheme 1, **2**→**5**).[13] Exposure of **2** to the Schwartz reagent[14] is known to produce intermediate **3**, which contains a five-membered chelate ring and gives the corresponding aldehyde after hydrolysis.[10b,c] However, our method requires addition of a Lewis acid to **3**, which results in the generation of the *N*-oxyiminium ion **4**. This intermediate would then undergo nucleophilic addition to give substituted amine **5**. The first key to achieving functional-group compatibility is the high reactivity of the Schwartz reagent with amide carbonyl groups. The second important feature of this transformation is the high electrophilicity of *N*-oxyiminium ion **4**. Our previous studies revealed that **4** was more electrophilic than an ordinary *N*-alkyliminium ion **6**, and reacted with mild nucleophiles.[15,16] Combining both of these unique properties, our method became high yielding and compatible with a number of sensitive functional groups.

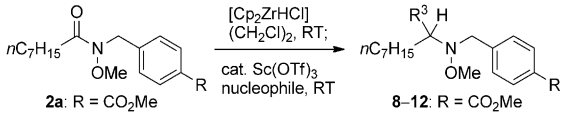
Our hypothesis was confirmed when allyltributylstannane and a catalytic amount of $Sc(OTf)_3$ were employed (Scheme 2). Treatment of an *N*-methoxyamide that also bears a methyl ester with the Schwartz reagent at room temperature, followed by addition of $Sc(OTf)_3$ (20 mol%) and allyltributylstannane (1.2 equiv) provided **7a** in 86% yield. A more electrophilic methyl ester did not interfere with the reaction. This transformation was found to be compatible with a variety of functional groups and proceeded in high yields for a variety of substrates (80–98%). For example, a more reactive aliphatic methyl ester was tolerated (**7b**, 84%). The nitro group remained intact under the reaction conditions (**7c**, 90%). Benzyl and aryl halide moieties within the substrates had no detrimental effects on the yield (**7d**, 98%; **7e**, 92%). Carbamate moieties were completely differentiated from the *N*-methoxyamide despite the high structural similarity; the corresponding products **7f** and **7g** were obtained in 87% and 90% yield, respectively. A sulfonamide with an acidic proton did not disturb the reaction (**7h**, 90%, **7I**, 80%). Initially, we were concerned that using the Schwartz reagent would cause olefin-containing substrates to readily undergo hydrozirconation as a side reaction. However, the reactions of *N*-methoxyamides that contain a cinnamoyl group or a terminal olefin afforded the allylated products without affecting the olefin moieties (**7j**, 84%; **7k**, 87%). The developed conditions were mildly acidic, but did not affect acetal groups (**7l**: 91%; **7m**: 84%).

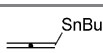
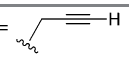
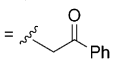
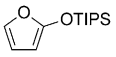
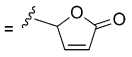
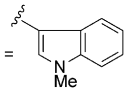


Scheme 2. Scope of the chemoselective reductive allylation of *N*-methoxyamides. Reaction conditions: **2**, [Cp_2ZrHCl] (1.6 equiv), $(CH_2Cl)_2$ (0.1 M), RT, 10 min; then $CH_2=CHCH_2SnBu_3$ (1.2 equiv), $Sc(OTf)_3$ (20 mol%), RT, 1 h. Yields of isolated products after purification by column chromatography are given. Tf = trifluoromethanesulfonyl.

The high electrophilicity of the *N*-oxyiminium ion enabled us to use a variety of nucleophiles without deterioration of chemoselectivity (Table 1). Most nucleophiles, including allenylstannane and TMSCN, required 10 mol% of $Sc(OTf)_3$, although the allylation needed 20 mol% (entries 1 and 2). Mukaiyama-type Mannich reactions with a silyl enol ether or a siloxyfuran proceeded in good yields (entries 3 and 4). The intermolecular Pictet–Spengler-type reaction with *N*-methylindole was performed at −40°C to give **12** in 75% yield (entry 5).

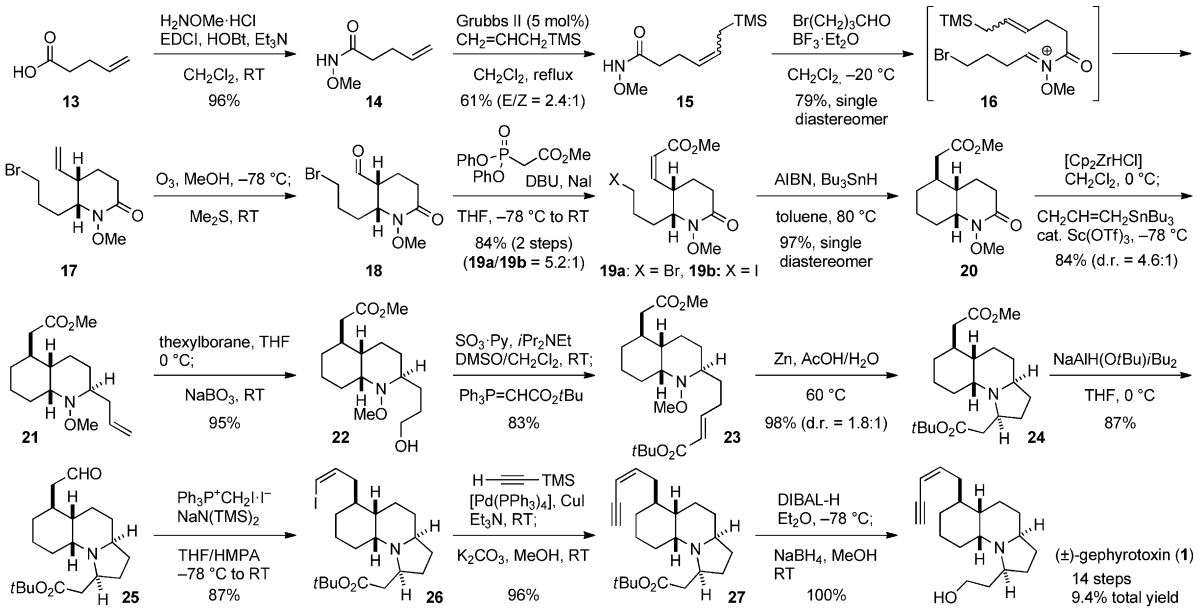
Table 1: Variation of the nucleophile.[a]



Entry	Nucleophile	Product	Yield[b] [%]
1		**8**: R^3 = 	71
2	TMS-CN	**9**: R^3 = 	81
3		**10**: R^3 = 	74
4		**11**: R^3 = 	78 (d.r. = 1.6:1)
5[c]		**12**: R^3 = 	75

[a] **2a**, [Cp_2ZrHCl] (1.6 equiv), $(CH_2Cl)_2$ (0.1 M), RT, 10 min; nucleophile (1.2 equiv), $Sc(OTf)_3$ (10 mol%), RT, 1 h. [b] Yield of isolated product after purification by column chromatography. [c] The reaction was performed with $Sc(OTf)_3$ (20 mol%) at −40°C. TMS = trimethylsilyl, TIPS = triisopropylsilyl.

With suitable conditions for the chemoselective reductive nucleophilic addition to *N*-methoxyamides in hand, we turned our attention to the total synthesis of gephyrotoxin (Scheme 3). Our strategy featured utilization of the *N*-methoxy group as a reactivity control element, which was installed along with the requisite nitrogen atom; The condensation of 4-pentenoic acid (**13**) with *N*-methoxyamine



Scheme 3. Total synthesis of (±)-gephyrotoxin (**1**). AIBN = 2,2′-azobis(isobutyronitrile), DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, DMF = dimethylformamide, DMSO = dimethylsulfoxide, HMPA = hexamethylphosphoramide.

gave *N*-methoxyamide **14** in 96% yield. Subsequent cross-metathesis of **14** with Grubbs' second-generation catalyst at reflux provided **15** as a mixture of diastereomers in 61% yield ($E/Z = 2.4:1$).[17,18] We then attempted the direct coupling of *N*-methoxyamide **15** with 4-bromobutanal, followed by intramolecular allylation of *N*-acyl-*N*-oxyiminium ion **16**. The *N*-methoxy group played a critical role as a reactivity control element in this key reaction. In contrast to the reaction of basic amines, the intermolecular condensation of an ordinary amide with an aldehyde is very challenging because of the poor nucleophilicity of the nitrogen atom of the amide.[19] The assistance of the *N*-methoxy group, however, increased the nucleophilicity of the nitrogen atom to render it more nucleophilic than the oxygen atom and to enable the direct coupling, which afforded 2,3-*cis*-piperidone **17** in 79% yield as a single diastereomer.[20] Interestingly, the identical reaction of the corresponding *N*-methyl-substituted amide did not provide the desired lactam. The terminal olefin **17** was then converted into methyl-*Z*-enoate **19** (**19a**/**19b** = 5.2:1) by ozonolysis and an olefination developed by Ando and coworkers.[21] In the following radical cyclization, this *Z* arrangement of enoate **19** was crucial; **20** was obtained as a single diastereomer in 97% yield, whereas the transformation of the corresponding *E*-enoate gave the product without diastereoselectivity (87%, d.r. = 1:1).

The stage was now set for the key chemoselective reductive allylation (Scheme 3). Treatment of **20** with [Cp_2ZrHCl] at 0 °C gave the five-membered chelate, which underwent subsequent allylation even at −78 °C with allyltributylstannane and a catalytic amount of $Sc(OTf)_3$. The reaction was both chemoselective and stereoselective in the presence of a methyl ester and afforded **21** in 84% yield (d.r. = 4.6:1).[22] It is noteworthy that classical nucleophilic addition in this situation would require a number of extra steps. First, the reduction of the more electrophilic ester would be necessary because no practical protecting group for esters has been reported. Subsequent protection of the generated hydroxy group would then be required prior to the nucleophilic addition, as well as a deprotection afterwards. On the other hand, our chemoselective reaction gave the product in a one-pot process, and ultimately removed the protection/deprotection sequence of the methyl ester from the total synthesis.

With decahydroquinoline **21** in hand, we turned our attention to the construction of the pyrrolidine unit (Scheme 3). Hydroboration of **21** with thexylborane, followed by a one-pot homologation using the Parikh–Doering oxidation and the Wittig olefination[23] provided *E*-enoate **23**. Treatment of **23** with activated zinc in $AcOH/H_2O$ at 60 °C initiated the cleavage of the N–O bond, which was followed by aza-Michael cyclization to form pyrrolidine **24**.[24] For completion of the total synthesis, the installation of the two distinct side chains was still required. After extensive investigation, we succeeded in differentiating the two esters in **24** with NaAlH(O*t*Bu)*i*Bu_2 (SDBBA).[25] Treatment of **24** with SDBBA initiated chemoselective partial reduction of the methyl ester in the presence of the *tert*-butyl ester to afford aldehyde **25**. Wittig reaction of **25** and subsequent Sonogashira coupling installed the *Z*-eneyne side chain to give **27**. Finally, reduction of the remaining *tert*-butyl ester completed the total synthesis of (±)-gephyrotoxin (**1**).

The present synthesis of (±)-gephyrotoxin (**1**) by our chemoselective approach was accomplished in 14 steps with an overall yield of 9.4% from commercially available 4-pentenoic acid, and thus represents the most concise and efficient synthesis that has been described for (±)-gephyrotoxin to date. The key to success was the use of an *N*-methoxy group as the reactivity control element. The *N*-methoxy group increased the nucleophilicity of the nitrogen atom of the amide, which enabled the direct coupling of the *N*-methox-

yamide with an aldehyde (**15**→**16**→**17**). Furthermore, the chelation effect and the increased electrophilicity of the iminium ion enabled amide-selective nucleophilic addition (**20**→**21**) in the presence of the methyl ester. The developed chemoselective strategy is highly practical, as it minimizes the need for protecting-group manipulations as well as redox reactions. We believe that our novel approach will be applicable to the synthesis of a number of complex alkaloids.

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