

Macrocyclization by Nickel-Catalyzed, Ester-Promoted, Epoxide–Alkyne Reductive Coupling: Total Synthesis of (–)-Gloeosporone**

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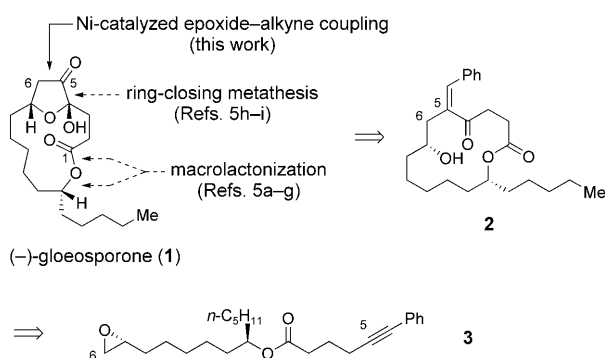
Macrocycles are found in important and diverse molecules such as naturally occurring peptides (e.g., cyclosporine), oligosaccharides (cyclodextrins), polyketides (erythromycin), and synthetic compounds such as crown ethers and polyenes. The most common strategy to prepare macrocyclic lactones (macrolides) is by intramolecular C–O bond formation to provide the lactone functional group.^[1] Although it is often successful and high-yielding, this approach is also highly context-dependent and in some cases provides negligible amounts of the desired macrocycle.^[1] The development of methods for macrocyclization has thus received much attention.^[2] Herein, we report a new C–C bond-forming strategy for macrocyclization, namely nickel-catalyzed epoxide alkyne reductive coupling,^[3] and illustrate its use in the synthesis of the macrolide natural product (–)-gloeosporone (**1**).^[4]

In the eight reported syntheses of gloeosporone, the 14-membered ring was constructed by either macrolactonization^[5a–g] or ring-closing metathesis (Scheme 1).^[5h–i] The nickel-catalyzed approach described herein represents a departure

from these strategies, and, for the first time, uses the C5–C6 bond as the site of macrocyclization, whereby the homoallylic alcohol product (**2**) of an epoxide–alkyne reductive coupling reaction corresponds to the β -hydroxyketone pattern in gloeosporone. We previously described the use of stereoselective, nickel-catalyzed aldehyde–alkyne reductive coupling reactions to form a 19-membered ring in the total synthesis of two amphidinolide T natural products.^[6] Montgomery and co-workers have investigated how the size of the formed ring affects the regioselectivity of alkyne addition in related reactions.^[7] An intermolecular nickel-catalyzed alkyne–epoxide reductive coupling, which is a process that we have also used to construct 5- and 6-membered rings, was also utilized in our amphidinolide syntheses.^[3] Since the successful formation of small rings often does not accurately predict the outcome of cyclizations to form larger rings, it was not clear whether these nickel-catalyzed coupling reactions could be extrapolated to the case of gloeosporone.

Thus, we began our investigation of this question with a series of esters [**3a–g**, Eqs. (1) and (2), Table 1], which were selected to determine not only the suitability of the macrocyclization to the synthesis of gloeosporone, but also the generality of this strategy (Table 1). A preliminary survey of reaction conditions (data not shown) revealed a critical interdependence of the concentrations of substrate and catalyst. In summary, competing intermolecular reductive coupling processes were minimized under two sets of conditions: [**3a**]₀ = 0.15 M, 20 mol % [Ni(cod)₂], and [**3a**]₀ = 0.075 M, 100 mol % [Ni(cod)₂] (cod = cyclooctadiene). Notably, the optimum initial substrate concentrations were one to two orders of magnitude greater than those typically used in macrocyclization reactions.

As shown in Table 1, the number of atoms in the targeted ring is not as important as two other variables. When the ring size was kept constant but the number of CH₂ groups between the ester and alkyne was varied, the superiority of three CH₂ units ($n = 1$) versus two or four such units was observed ($n = 0$ or 2, respectively; Table 1, entries 1–6). With this requirement satisfied, 12- and 15-membered rings could also be prepared in this fashion, albeit with reduced efficiency (Table 1, entries 7–10). The orientation of the ester group relative to the alkyne group is also significant. When the ester oxygen atom is situated in the tether (Table 1, entries 11–14), no product was detected, even in cases with the number of atoms in the tether backbone (three) was the same as in the cases that gave the best results (three CH₂ groups). These observations strongly suggest that a temporary interaction between Ni and the ester^[8,9] is necessary for effective promotion of the macrocyclization, and is in contrast with reports by Fürstner et al., who observed that certain arrange-



Scheme 1. Retrosynthetic analysis of (–)-gloeosporone (**1**).

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Table 1: Nickel-catalyzed reductive macrocyclization.^[a]

Entry	Substrate	Reaction conditions ^[b]	<i>m</i>	<i>n</i>	Product	Ring size	Yield [%]
1	3a	a	3	1	2a	14	40
2	3a	b	3	1	2a	14	50
3	3b	a	2	2	2b	14	5
4	3b	b	2	2	2b	14	18
5	3c	a	4	0	2c	14	< 5
6	3c	b	4	0	2c	14	< 5
7	3d	a	4	1	2d	15	28
8	3d	b	4	1	2d	15	53
9	3e	a	1	1	2e	12	12
10	3e	b	1	1	2e	12	26
11	3f	a	3	1	2f	14	< 5
12	3f	b	3	1	2f	14	< 5
13	3g	a	2	2	2g	14	< 5
14	3g	b	2	2	2g	14	< 5

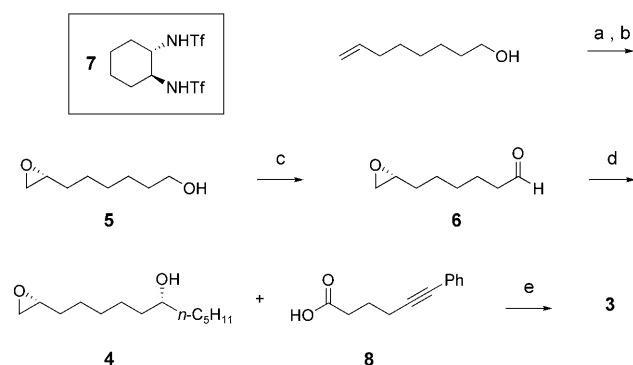
[a] See the Supporting Information and Equations (1) and (2). [b] Reaction conditions: a) 20 mol% [Ni(cod)₂], 40 mol% Bu₃P, 1000 mol% Et₃B, THF, initial concentration of starting material = 0.15 M; b) 100 mol% [Ni(cod)₂], 200 mol% Bu₃P, 1000 mol% Et₃B, THF, initial concentration of starting material = 0.075 M.

ments of ester functional groups inhibited macrocyclization by ring-closing metathesis.^[5h,9c-d]

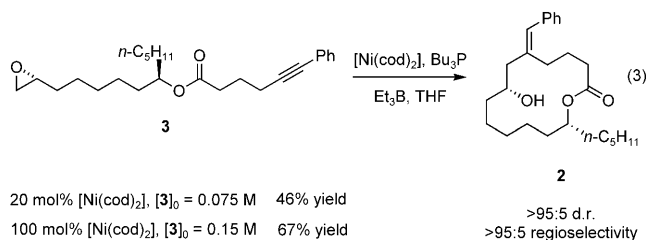
Since the necessary ester–alkyne relationship corresponded to that found in gloeosporone, we hypothesized that this strategy would be well-suited to the preparation of the natural product. Epoxy alcohol **4** was prepared in four steps from 7-octen-1-ol; Jacobsen's hydrolytic kinetic resolution^[10] was used to establish the absolute configuration of the epoxide (Scheme 2). As five methylene groups separate the epoxide and aldehyde groups, carbonyl addition reactions of **6** proceeded with no detectable diastereoselection (not shown). However, a reagent-controlled addition of diamylzinc afforded alcohol **4** in > 95:5 d.r. and 80% yield.^[11,12]

Hexynoic acid **8** was prepared from commercially available 5-hexyn-1-ol in two steps in 80% overall yield. Fragment coupling by ester formation (DCC/DMAP) provided the substrate (**3**) for the catalytic epoxide–alkyne reductive macrocyclization (Scheme 2). Compound **2** was obtained in 46% yield at 20% Ni loading [Eq. (3)]. Use of stoichiometric amounts of nickel provided **2** with improved efficiency (67% yield). When compared to the studies in Table 1 (entries 1 and 2, respectively), these results indicate that the amyl group plays a small yet beneficial role in the macrocyclization.

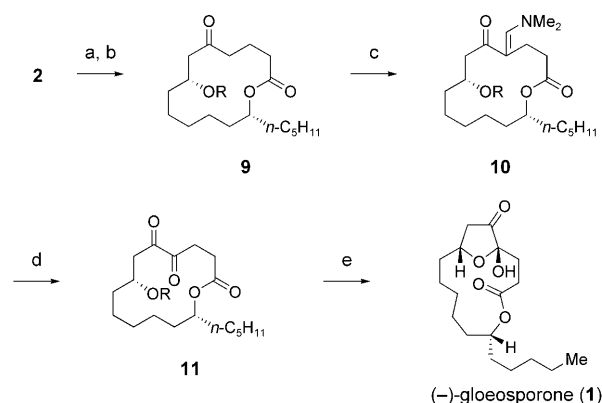
With the macrocycle in hand, the major remaining challenge in the synthesis of (–)-gloeosporone was site-selective oxidation of the methylene group at C4, rather than



Scheme 2. Preparation of epoxyalcohol **3**. a) *m*CPBA, CH₂Cl₂; b) (*R,R*)-[Co(salen)(OAc)], H₂O, 35% over 2 steps, 99% *ee*; c) *n*Pr₄NRuO₄, NMO, 3 Å M.S., CH₂Cl₂, 95%; d) **7**, (*n*-C₅H₁₁)₂Zn, Ti(O*i*Pr)₄, –20 °C, PhMe, 80%, > 95:5 d.r.; e) DCC, DMAP, CH₂Cl₂, 85%. DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, *m*CPBA = *meta*-chloroperbenzoic acid, M.S. = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide.



that at C6. Ozonolytic cleavage of the alkene in **2** and protection of the secondary alcohol afforded **9** in 94% yield over the two steps (Scheme 3).^[13] When **9** was heated in *tert*-butoxy-bis(dimethylamino)methane (Bredereck's reagent^[14]), enamine **10** was generated with excellent regio-control (> 95:5 site-selectivity^[15]), and was immediately exposed to singlet oxygen.^[16] The ensuing [2+2] and retro-[2+2] cycloaddition reactions afforded the desired 1,2-diketone **11** in 70% overall yield (two steps) by way of a



Scheme 3. Completion of the synthesis of (–)-gloeosporone (**1**). a) O₃, then Ph₃P; b) Et₃SiOTf, 2,6-lutidine, 94% yield over 2 steps; c) *tert*-butoxy-bis(dimethylamino)methane, 60 °C, > 95:5 site selectivity; d) O₂, *hν*, Rose Bengal, CH₂Cl₂, 70% yield over 2 steps; e) HF-pyridine, THF, 90% yield.

dioxetane. Removal of the Et_3Si group provided (–)-gloeosporone (**1**) in 90% yield.

In summary, nickel-catalyzed epoxide–alkyne reductive coupling represents a novel strategy for the preparation of large rings and proceeds with high regioselectivity for both alkyne and epoxide components. This approach enabled the synthesis of (–)-gloeosporone in 10 steps (longest linear sequence) and 6% overall yield at 20% catalyst loading in the macrocyclization (9% overall yield at 100 mol% loading). A critical step of the target synthesis was the oxidation of an enamine that was introduced using Brederick's reagent with notable site selectivity. Other applications of macrocyclization by catalytic epoxide–alkyne reductive coupling are under investigation.

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