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

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Abstract

Macrocycles are found in important and diverse molecules such as naturally occurring peptides (e.g., cyclosporine), oligosaccharides (cyclodextrins), and 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 itself.[1] Though often successful and high yielding, this approach is also highly context-dependent and in some cases provides little to none 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, nickel-catalyzed epoxide alkyne reductive coupling, [3] and illustrate its use in the synthesis of the macrolide natural product (−)-gloeosporone (**1**).[4]

Keywords

macrocyclization; reductive coupling; nickel; total synthesis; C-C coupling

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 case described here 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. Previously we described the total synthesis of two amphidinolide T natural products using stereoselective, Ni-catalyzed aldehyde-alkyne reductive coupling reactions to form a 19-membered ring.[6] Montgomery has investigated how the size of the ring being formed affects the regioselectivity of alkyne addition in related reactions.[7] Also utilized in our amphidinolide syntheses was an intermolecular, Ni-catalyzed alkyne-epoxide reductive coupling, a process that we have also used to construct 5- and 6-membered rings. [3] Since success in smaller-ring cases is often not an accurate predictor of the outcome of cyclizations to form larger rings, it was not clear whether these Ni-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**, eq 1 and 2) 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 (not shown) revealed a critical interdependence of the concentrations of substrate and catalyst. To summarize, competing intermolecular reductive coupling processes were minimized under two sets of conditions: $[\mathbf{3a}]_0 = 0.15$ M, 20 mol% $Ni(cod)_2$ and $[\mathbf{3a}]_0 = 0.075$ M, 100 mol% $Ni(cod)_2$. Notably, the optimum initial substrate concentrations were 1–2 orders of magnitude greater than those typically used in macrocyclization reactions.

As shown in Table 1, the number of atoms in the ring targeted is *not* as important as two other factors. Holding the ring size constant but varying the number of CH_2 groups between the ester and alkyne clearly shows the superiority of 3 CH_2 (n = 1) vs. 2 or 4 such units (n = 0 or 2, respectively; entries 1–6). With this requirement satisfied, 12 and 15-membered rings can also be prepared in this fashion, albeit with reduced efficiency (entries 7–10). Also significant is the *orientation* of the ester relative to the alkyne. With the ester oxygen in the tether (entries 11–14), no product was detected, even in cases with the same number of heavy atoms in the tether (3) as in best cases (3 CH_2).

These results strongly suggest that a temporary interaction between Ni and the ester[8,9] is necessary for effective promotion of the macrocyclization, in contrast to Fürstner's observations that certain arrangements of ester functional groups inhibited macrocyclization via ring-closing metathesis.[5h,9c–d]

Since the necessary ester-alkyne relationship corresponded to that in gloeosporone, we hypothesized that this strategy would be well suited for preparing the natural product. Epoxy alcohol **4** was prepared in 4 steps from 7-octen-1-ol, with Jacobsen's hydrolytic kinetic resolution[10] establishing the absolute configuration of the epoxide (Scheme 2). As five methylene groups separate the epoxide and aldehyde, 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 dr 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 via ester formation (DCC/DMAP) provided the substrate (**3**) for the catalytic epoxide-alkyne reductive macrocyclization (Scheme 2). At 20% Ni loading **2** is obtained in 46% yield (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.
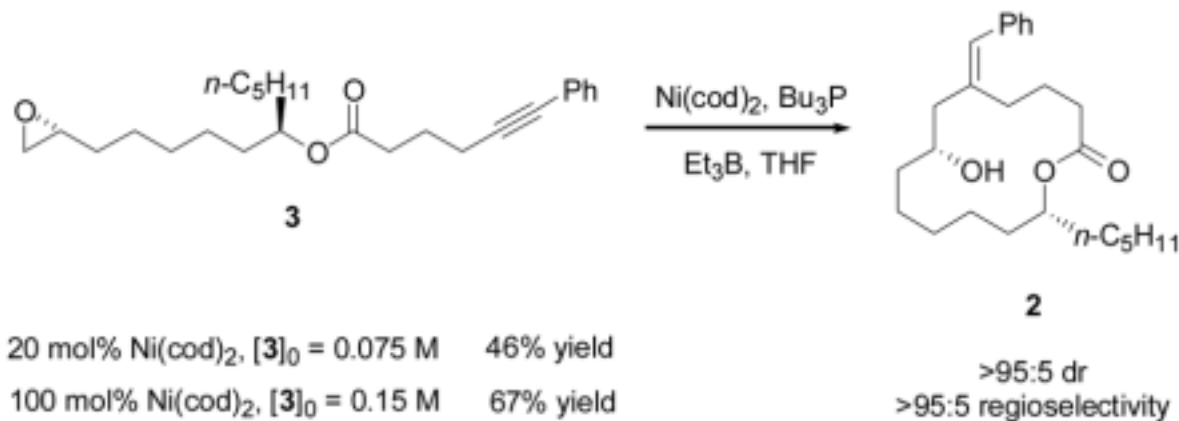
(3)

With the macrocycle in hand, the major remaining challenge in the synthesis of (−)–gloeosporone was site-selective oxidation of the C4 methylene group, rather than 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] Heating **9** in *t*-butoxy-bis(dimethylamino) methane (Bredereck's reagent[14]) generated enamine **10** with excellent regiocontrol (>95:5 site-selectivity[15]) that 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 dioxetane. Removal of the Et_3Si group provided (−)-gloeosporone (**1**) in 90% yield.

In summary, Ni-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 component of the end game was a notably site-selective oxidation using Bredereck's reagent. Other applications of macrocyclization via catalytic epoxide-alkyne reductive coupling are under investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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13. This ketone also undergoes high yielding and highly site-selective soft enolization at C4-C5 (Et_3SiOTf, Et_3N, 90% yield). (Elaboration of this enolsilane to gloeosporone via Rubottom oxidation was unsuccessful.)

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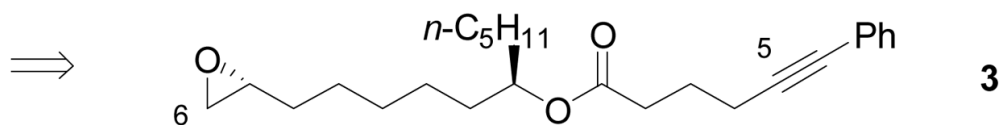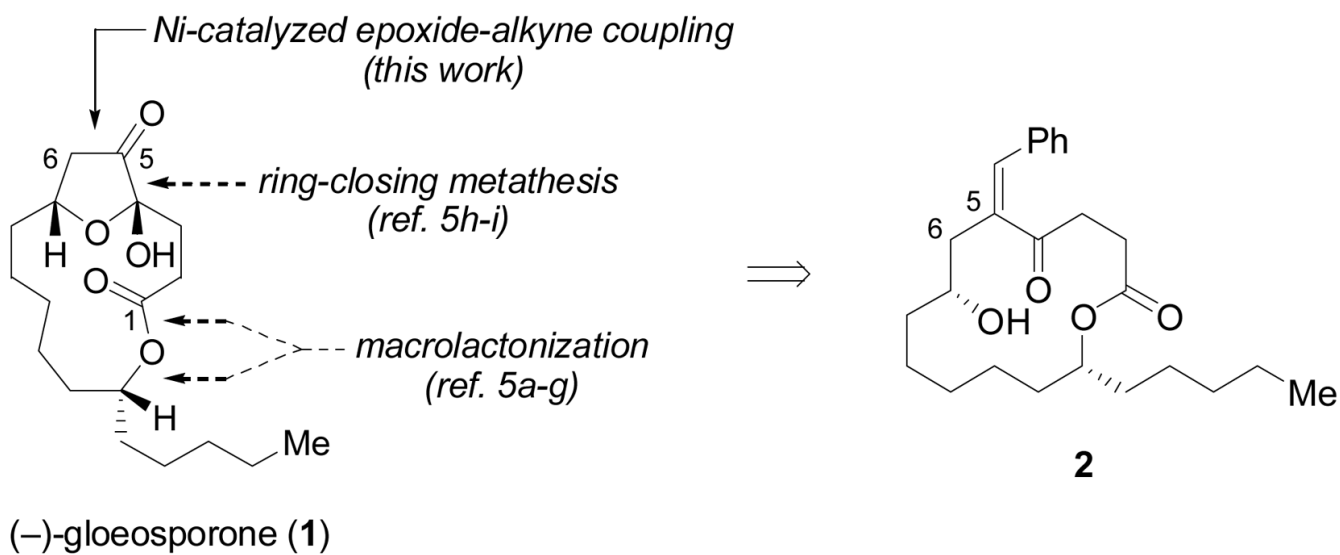
Scheme 1.
Retrosynthetic analysis of (−)-gloeosporone (**1**).
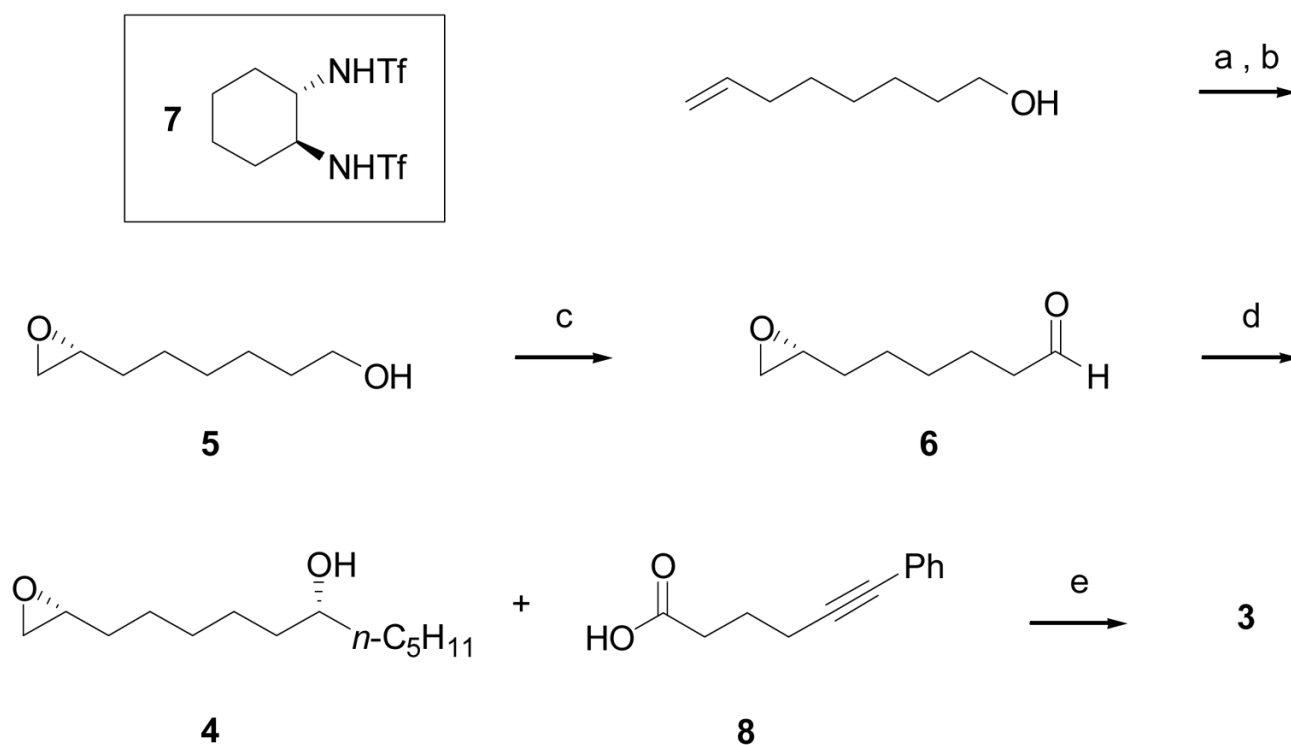
Scheme 2.
Preparation of epoxyalcohol **3**. a) *m*CPBA, CH$_2$Cl$_2$; b) ((*R,R*)-salen)Co–OAc, H$_2$O, 35% over 2 steps, 99% ee; c) *n*Pr$_4$NRuO$_4$, NMO, 3 Å MS, CH$_2$Cl$_2$, 95%; d) **7**, (*n*C$_5$H$_{11}$)$_2$Zn, Ti (O*i*Pr)$_4$, −20 °C, PhMe, 80%, >95 : 5 dr; e) DCC, DMAP, CH$_2$Cl$_2$, 85%. DCC = 1,3-dicyclohexylcarbodiimide, DMAP = 4–dimethylaminopyridine, *m*CPBA = *meta*-chloroperbenzoic acid, MS = molecular sieves, NMO = *N*-methylmorpholine *N*-oxide
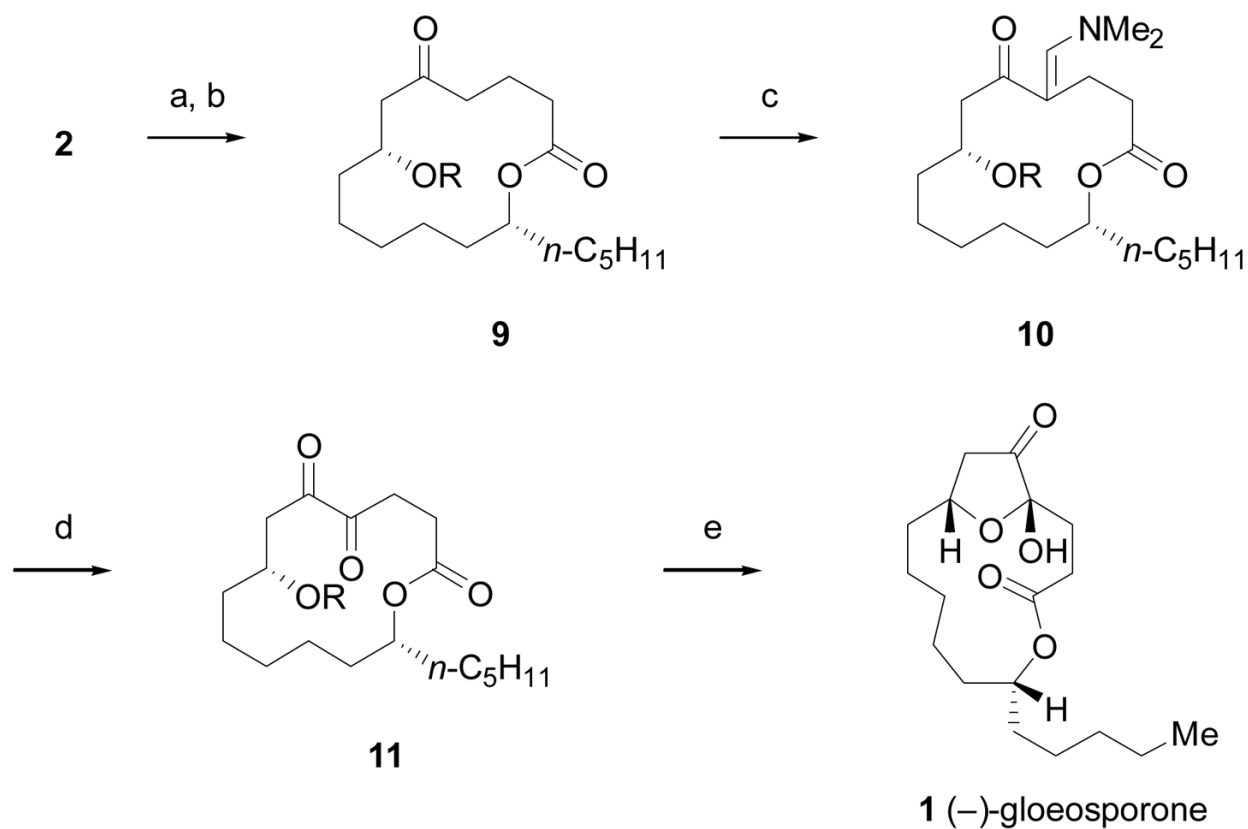
Scheme 3.
Completion of the synthesis of (−)-gloeosporone (**1**). a) O_3, then Ph_3P b) Et_3SiOTf, 2,6–lutidine, 94% yield over 2 steps; c) *t*-butoxybis(dimethylamino)methane, 60 °C, >95 :5 site selectivity; d) O_2, hv, Rose Bengal, CH_2Cl_2, 70% yield over 2 steps; e) HF•pyridine, THF, 90% yield.

Table 1

Nickel-catalyzed reductive macrocyclization.[a,b]
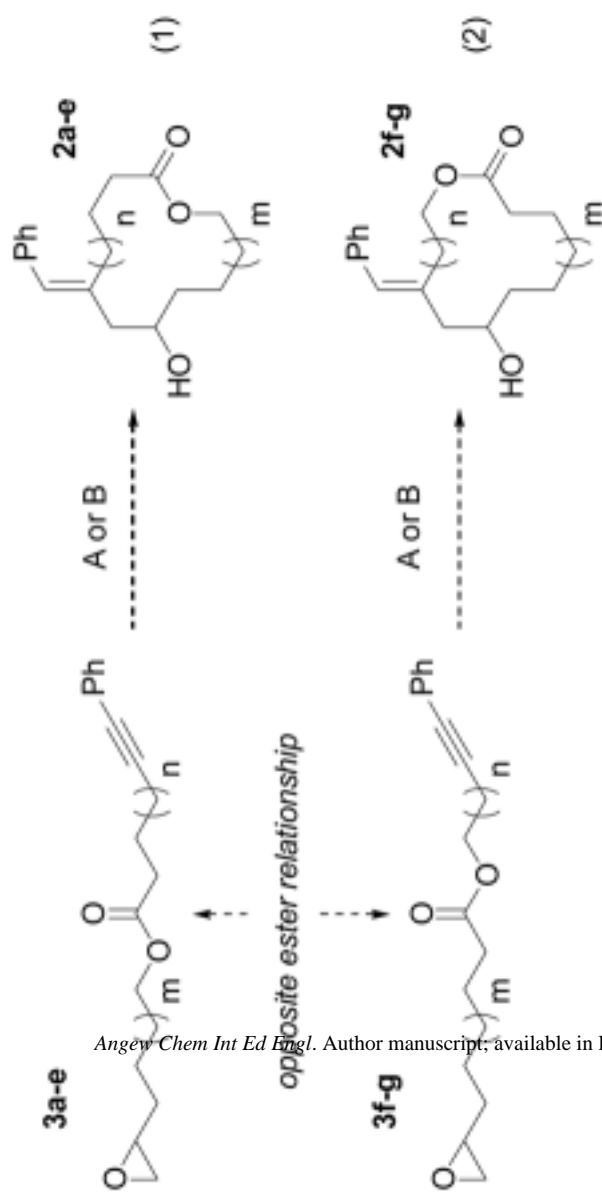
entry	substrate	reaction conditions	m	n	product	ring size	yield (%)
1	3a	A	3	1	2a	14	40
2	3a	B	3	1	2a	14	50
3	3b	A	2	2	2b	14	5
4	3b	B	2	2	2b	14	18
5	3c	A	4	0	2c	14	<5
6	3c	B	4	0	2c	14	<5
7	3d	A	4	1	2d	15	28
8	3d	B	4	1	2d	15	53
9	3e	A	1	1	2e	12	12
10	3e	B	1	1	2e	12	26
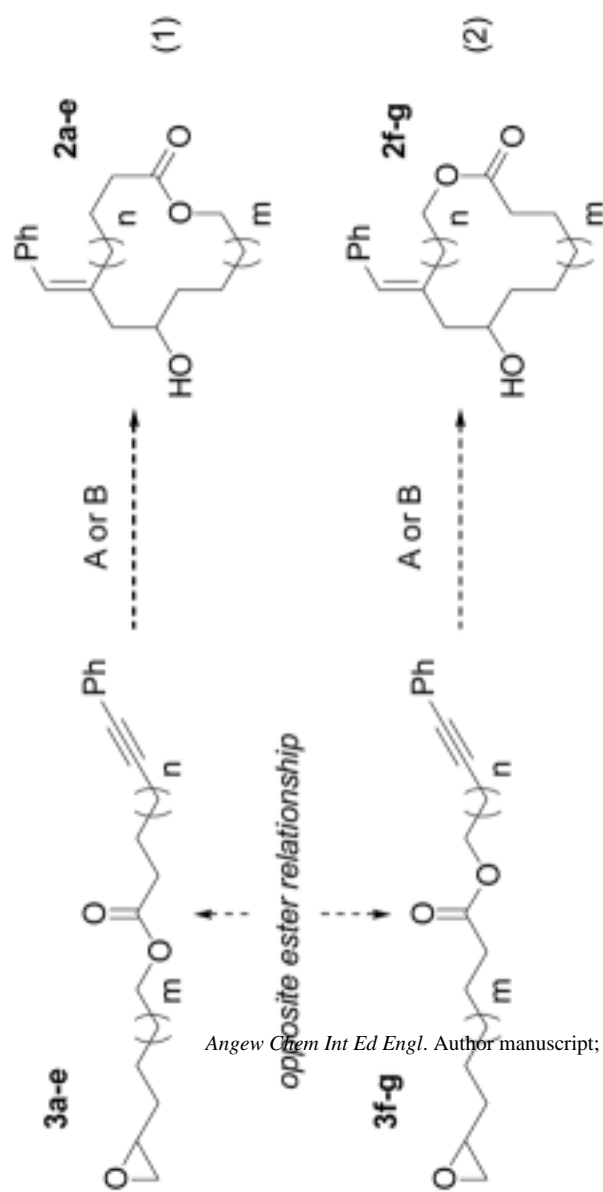
entry	substrate	reaction conditions	m	n	product	ring size	yield (%)
11	3f	A	3	1	2f	14	<5
12	3f	B	3	1	2f	14	<5
13	3g	A	2	2	2g	14	<5
14	3g	B	2	2	2g	14	<5

[a] See Supporting Information and eq. (1) and (2).

[b] Reaction conditions: (A) 20 mol% Ni(cod)$_2$, 40 mol% Bu$_3$P, 1000 mol% Et$_3$B, THF, [SM]$_0$ = 0.15 M; (B) 100 mol% Ni(cod)$_2$, 200 mol% Bu$_3$P, 1000 mol% Et$_3$B, THF, [SM]$_0$ = 0.075 M.