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Extension of Pd-Mediated One-Pot Ketone Synthesis to Macrocyclization: Application to a New Convergent Synthesis of Eribulin

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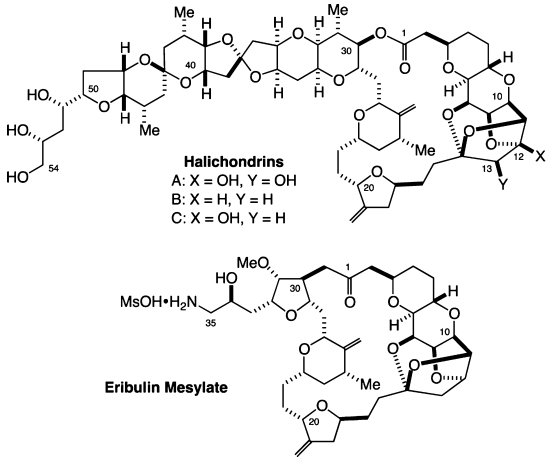
Supporting Information

ABSTRACT: Recently reported Pd-mediated one-pot ketone synthesis from an unactivated alkyl bromide and a thioester has been extended to a macrocyclic ketone synthesis. In situ generation of alkylzinc halide via single electron transfer (SET), using $NbCpCl_4$ and $CrCl_3$, was the key for the success of macrocyclization. A new convergent synthesis of eribulin has been achieved, using (1) catalytic asymmetric Ni/Cr-mediated coupling to form the C19−C20 bond, (2) base-induced cyclization to form the methylenetetrahydrofuran ring, and (3) Pd-mediated one-pot ketone synthesis to form the macrocyclic ketone.

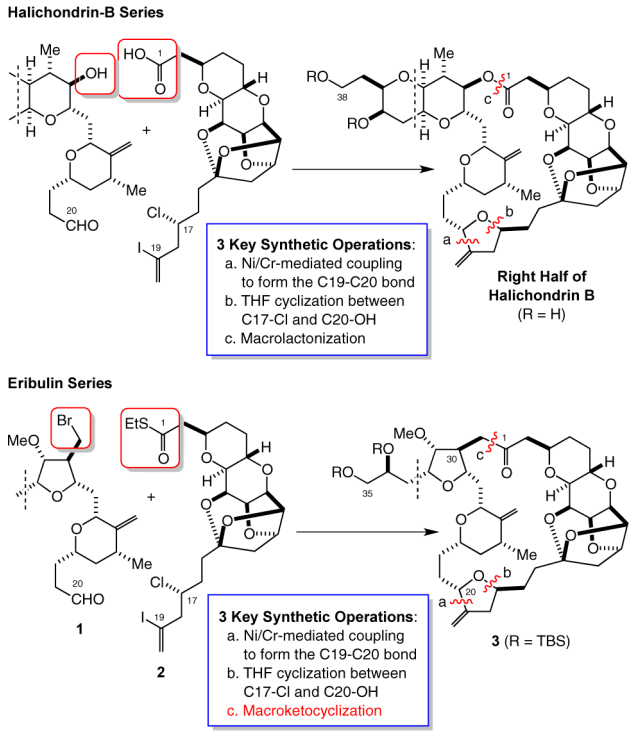
Halichondrins are polyether macrolides, originally isolated from the marine sponge *Halichondria okadai* by Uemura, Hirata, and co-workers.[1] This class of natural products displays interesting structure diversities on the oxidation state at C12 and C13, cf., halichondrins A−C in Scheme 1. We chose halichondrin B as a synthetic target and began the experimental work, which led us to the first total synthesis of halichondrin B in 1992. On completion of the synthesis,[2] we asked (the late) Dr. Suffness at the National Cancer Institute (NCI) and Dr. Littlefield at Eisai Research Institute (ERI) to test antitumor activities of the totally synthetic halichondrins, along with several synthetic intermediates. The results were sensational: their experiments clearly demonstrated that the antitumor activities of halichondrin B resided in the right portion of the molecule, which served as the foundation for successful development of the antitumor drug Halaven (eribulin mesylate) by Eisai.[3−5]

Recently, we reported a unified, convergent synthesis of this class of marine natural products, using (1) Ni/Cr-mediated coupling to form the C19−C20 bond, (2) THF S_N2 cyclization between C17−Cl and C20-OH, and (3) macrolactonization (Scheme 2).[6] We were interested in extending this synthetic strategy to the synthesis of eribulin, in which the first two key synthetic transformations could be achieved by use of the chemistry developed for the unified synthesis of halichondrins. The third key synthetic transformation is the cyclization to form the macrolactone in the halichondrin series, whereas it is

Scheme 1. Structure of Halichondrins A−C and Eribulin Mesylate



Scheme 2. Three Key Transformations Employed in the Unified Convergent Synthesis of Halichondrins



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the cyclization to form the macrocyclic ketone in the eribulin series. Macrolactonization is a well-precedented synthetic transformation. On the contrary, except for a few limited cases,[7] cyclization to form a macrocyclic ketone, referred to as macroketocyclization in this paper, is an unexploited synthetic transformation.[8] In this communication, we report a macroketocyclization between a unactivated alkyl bromide with a thioester and its application to a synthesis of eribulin.

Related to this work, we recently developed a Pd-mediated one-pot ketone synthesis from unactivated alkyl bromides and thioesters, with an intention of extending it to a macroketocyclization.[9] In this connection, we should note that the efficiency of this method is excellent, even with use of a ~ 1:1 molar ratio of two coupling partners. However, to translate the one-pot ketone synthesis to a macroketocyclization, we need to address one additional question, that is how to eliminate, or suppress, an intermolecular coupling. For the case of macrolactonization, a high-dilution technique is commonly employed to achieve this goal.

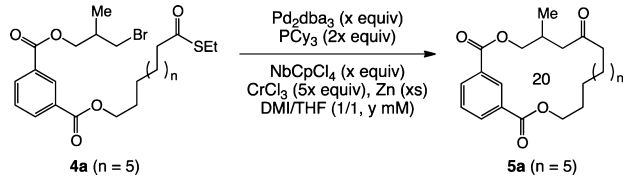
Pd-Mediated ketone synthesis is generally considered to involve three distinct steps: (1) oxidative addition of a Pd(0)-catalyst to a thioester to form RCO-Pd(II)X, (2) transmetalation from an alkylzinc halide to the resultant Pd(II) species, and (3) reductive elimination, leading to a ketone and regenerating the Pd(0)-catalyst. Among these steps, we speculated the second step (transmetalation) to be most critical to effectively achieve the macroketocyclization under a high-dilution condition. Upon dilution, an intramolecular transmetalation would be favored over the intermolecular transmetalation, but would be disfavored over undesired side-reactions due to a higher probability of wasting radical and/or organometallic species.[10]

Experimentally, it was found that catalytic intermolecular ketone synthesis proceeded well even at 25 mM. Among three conditions, Condition **C** [(Pd_2dba_3 (10 mol %), PCy_3 (20 mol %), $CrCl_2$ (0.5 equiv), $NbCpCl_4$ (10 mol %), LiI (1 equiv), TESCl (1.5 equiv), Zn (xs) in DMI)] gave the best conversion.[11,12]

Being encouraged with this observation, we chose substrate **4a** to study the feasibility of macroketocyclization (Table 1). In this study, **4a** was subjected to a specified condition, and a yield of **5a** was estimated from a ^{1}H NMR analysis of crude product.[12] At 50 mM concentration, which was effective for intermolecular ketone synthesis (vide ante), **4a** gave the debrominated product and dimer as major products (entry 1). Considering that the activity of reagents might diminish by dilution, we then tested the macroketocyclization in the presence of a stoichiometric amount of metals, thereby demonstrating that the desired ketone **5a** was indeed formed as a major product at 10 mM concentration with only a small amount of debrominated product, although the dimer was still detected in more than 10% (entry 2). Under the stoichiometric conditions, $CrCl_2$ and $NbCpCl_4$ were essential (entries 4 and 5), but LiI and TESCl were not (entry 3). Also, reducing the amount of $NbCpCl_4$ resulted in a lower yield (entry 6). These observations implicate that SET activation and the early transition metals (TM) are critical for macroketocyclization. Interestingly, this coupling condition corresponds to Condition C for intermolecular one-pot ketone synthesis. At present, we do not have experimental supports to suggest a specific role(s) of early transition metals. However, we would speculate that both metals play the same role(s) in both intra- and intermolecular couplings.[13] Lastly, it was found that Cr(III)Cl_3 was more effective than Cr(II)Cl_2 to lower the concentration further (entries 9–11). Under these conditions, the desired product was formed, accompanied by only a trace amount of debrominated product.[12]

We then carried out the macroketocyclization of **4a** under the condition of entry 10 in a preparative scale (0.2 mmol) (Scheme 3). To achieve the macroketocyclization effectively, it has become evident that two conditions must be met: (1) to maintain Pd-, Nb-, and Cr-reagents in a stoichiometric amount and (2) to maintain the substrate-concentration above 5 mmol.

Table 1. Macroketocyclization: Optimization[a]

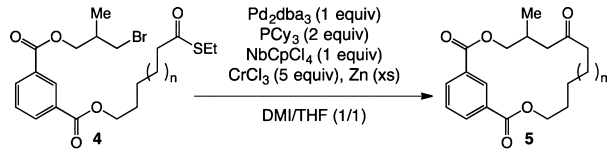


4a (n = 5) **5a** (n = 5)

entry	conditions (equiv)	yield (%)[b]
1[c]	LiI (1), $CrCl_2$ (0.5), $NbCpCl_4$ (0.1), TESCl (1.5), 50 mM	<10[d]
2	LiI (10), $CrCl_2$ (5), $NbCpCl_4$ (1), TESCl (1.5), 10 mM	40
3[e]	$CrCl_2$ (5), $NbCpCl_4$ (1), 10 mM	45[f]
4	LiI (10), $CrCl_2$ (5), TESCl (1.5), 10 mM	<5[d]
5	LiI (10), $NbCpCl_4$ (1), TESCl (1.5), 10 mM	<5[d]
6	$CrCl_2$ (5), $NbCpCl_4$ (0.7), TESCl (1.5), 10 mM	25
7	$CrCl_2$ (5), $NbCpCl_4$ (1), 15 mM	35[g]
8	$CrCl_2$(5), $NbCpCl_4$(1), 7 mM	25[h]
9	$CrCl_3$ (5), $NbCpCl_4$ (1), 10 mM	50[f]
10	$CrCl_3$(5), $NbCpCl_4$(1),5 mM	50[f]
11	$CrCl_3$ (5), $NbCpCl_4$ (1), 2.5 mM	40[h]

[a]Conditions: To Pd_2dba_3 (0.04 mmol) and PCy_3 (0.08 mmol) in DMI (2 mL) were added Zn (0) (xs), $CrCl_3$ (0.2 mmol), and $NbCpCl_4$ (0.04 mmol) at rt in a glovebox. Then, if needed, LiI (0.4 mmol) and TESCl (0.06 mmol) were added to the reaction mixture followed by SM in THF (2 mL). [b]Roughly estimated yield based on a ratio of **5a** to side products (debrominated RH and dimer) in a crude ^{1}H NMR.[12] [c]Pd_2dba_3 (0.1 equiv), PCy_3 (0.2 equiv) were used. [d]RH was a major product. [e]Reduction of Zn (20–40 equiv) provided slightly lower yield. [f]Trace amount of RH. [g]Lower yield mainly due to dimer. [h]Lower yield mainly due to debromination, yet dimer-formation was not noticeably reduced. Abbreviation: DMI = 1,3-dimethyl-2-imidazolidinone; $NbCpCl_4$ = tetrachloro(cyclopentadienyl)niobium; Pd_2dba_3 = tris(dibenzyli-deneacetone)dipalladium(0); PCy_3 = tricyclohexylphosphine.

Scheme 3. Preparative Macroketocyclization



4 **5**

4a (n = 5) → **5a** (ring size = 20) | **4b** (n = 1) → **5b** (ring size = 16)

1/2 loading of reagents[a]: 58% isolated yield | 57% isolated yield

1/4 loading of reagents[b]: 55% isolated yield | 57% isolated yield

1/8 loading of reagents[b]: 55% isolated yield | 57% isolated yield

[a]Conditions: To Pd_2dba_3 (0.1 mmol) and PCy_3 (0.2 mmol) in DMI/THF (10 mL/5 mL) were added $CrCl_3$ (0.5 mmol), Zn (xs), and $NbCpCl_4$ (0.5 mmol) at rt in a glovebox. SM (0.2 mmol) was added to the reagent mixture in two portions. First, one-half (0.1 mmol) of SM in THF (2.5 mL) was added to the reagent mixture and stirred at rt. After 7 h, the remaining half (0.1 mmol) of SM in THF (2.5 mL) was added and stirred overnight. [b]See Supporting Information for details.

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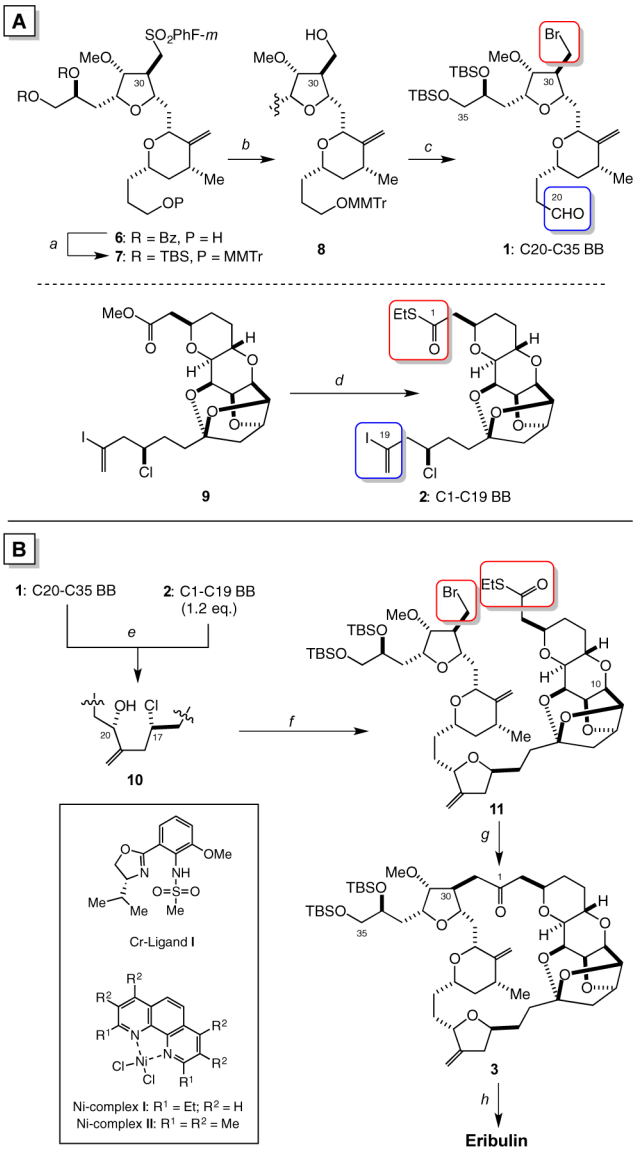
From a practical point of view, it would be more attractive if an amount of Pd-, Nb-, and Cr-reagents could be reduced.[14] To address this issue, we tested the possibility of recycling the reagents mixture in one-pot. Specifically, one-half of substrate **4a** was added into one half of the stoichiometric amount of reagent mixture used for the stoichiometric conditions and, after 7 h, the remaining half of **4a** was added to the same reaction mixture. Under this setting, the cyclization completed to give **5a** in 58% isolated yield after chromatographic purification. Thus, the macroketocyclization was effective with use of one half of the stoichiometric amount of reagent mixture at the cost of time, i.e., 7 vs 14 h. Similarly, the macroketocyclization was tested by adding 1/4- and 1/8-amounts of **4a** into a 1/4- and 1/8-amount of the reagents mixture, respectively, every 7 h, to give **5a** in 55%. Overall, under these conditions, the cyclization was achieved with use of ∼30% and ∼15% of the reagents mixture, at the cost of time, i.e., 7 h vs 28 and 56 h.[15] This procedure was also found effective for 16-membered ketone **5b** to give 57% yield from **4b**. In both cases, dimers and debrominated products were detected, but only in insignificant amounts (<10%).

Having demonstrated the feasibility of one-pot macroketocyclization, we shifted our focus onto its application to a synthesis of eribulin (Scheme 2). The synthesis of aldehyde **1** was started from the known sulfone **6**.[16] Protecting group manipulation, hydroxylation of sulfone **7** to alcohol **8**,[16] followed by tosylation and bromide substitution proceeded uneventfully (Scheme 4). However, deprotection of 4-methoxytrityl (MMTr) ether required an optimization, because of a concomitant deprotection of the primary TBS group; 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), which was known effective for selective deprotection of 4,4-dimethoxytrityl (DMTr),[17] resulted in only partial deprotection of MMTr at 40 °C. Assuming that a MMTr-cation acceptor might enhance the deprotection, we eventually found that an addition of water (HFIP/H_2O = 40/1) allowed us selectively to complete the required deprotection at rt. Then, the resulting alcohol was oxidized to aldehyde **1**. On the other hand, thioester **2** was straightforwardly prepared from the known methyl ester **9** in two-steps:[6] hydrolysis by Me_3SnOH[18] and coupling with EtSH by DCC.

With both aldehyde **1** and vinyl iodide **2** in hand, we studied the C19−20 Ni/Cr-mediated coupling. Initially, the condition optimized for the synthesis of halichondrin A was applied for coupling of **1** and **2** with Ni-complex **I**,[2b] but gave the desired product **10** only in a modest yield (∼40%). We speculated that the low yield might be attributed to a poor selectivity in activation of the C19-vinyl iodide: note the presence of an alkyl bromide as well as a thioester, which might potentially be activated with low-valent Ni. With this speculation, we searched for a Ni-catalyst, which would allow us selectively to activate the C19-vinyl iodide and consequently improve the efficiency of Ni/Cr-mediated coupling of **2** with **1**. Through this search, it was found that a combination of Ni-complex **II**, prepared from electron-rich 2,3,4,7,8,9-hexamethyl-1,10-phenanthroline, and Cr-catalyst, prepared from *unnat-i*-Pr/Me/OMe sulfonamide **I**, gave a satisfactorily high coupling yield (86% yield; dr = ∼ 10:1 (^{1}H NMR)).[19]

The next task was to cyclize **10** to **11**, which had been done with AgOTf/Ag_2O in the synthesis of halichondrin A. Apparently, this condition was not suitable to the substrate **10** because of the presence of thioester- and bromide-groups. Thus, we tested the cyclization conditions reported by Britton (100 °C in water),[20] which gave the desired product **11**, although accompanied by a large amount of unidentified decomposition products. We speculated that the liberated HCl might have caused the decomposition, and began an extensive search for a suitable base, leading us to a satisfactory condition: $SrCO_3$(s) at 95 °C.[22] Under the optimized conditions, **11** was isolated in 87% yield and fully characterized.

Scheme 4. New Convergent Synthesis of Eribulin[a]



[a]Reagents and Conditions: *a*. 1. MMTrCl, *i*-Pr_2NEt, CH_2Cl_2, 93%. 2. K_2CO_3, MeOH. 3. TBSCl, imidazole, 88% for 2 steps. *b*. *n*-BuLi, THF, −78 °C; $HBSia_2$, −10 °C to rt, >12 h; H_2O_2, 3 M NaOH, 0 °C, 81%. *c*. 1. TsCl, DMAP (cat.), Et_3N, CH_2Cl_2, 88%. 2. NaBr, Bu_4NBr (cat.), acetone, reflux, 90%. 3. $(CF_3)_2CHOH/H_2O$ = 40/1, 3 h, 90%. 4. Dess-Martin Ox., 90%. *d*. 1. Me_3SnOH, 80−85 °C, DCE; 0.1 N HCl. 2. EtSH, DCC, DMAP, 94%. *e*. $CrCl_2$ (20 mol %), Cr-Ligand **I** (24 mol %), proton sponge (24 mol %), Ni-complex **II** (5 mol %), LiCl, Mn, $ZrCp_2Cl_2$, CH_3CN/EtOAc = 3/1 (0.15 M), 86%. *f*. $SrCO_3$ (xs), *t*-BuOH/H_2O = 20/1 (4 mM), 95 °C, open to air, 87%. *g*. Pd_2dba_3 (1 equiv), $PCyp_3$ (2 equiv),[21] $CrCl_3$ (5 equiv), $NbCpCl_4$ (1 equiv), Zn (0) (xs), DMI/THF (1/1, 27 mM), 64%. *h*. see ref 24. Abbreviation: BB = building block; DCC = dicyclohexylcarbodiimide; $PCyp_3$ = tricyclopentylphosphine.

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Finally, **11** was subjected to macroketocyclization under the stoichiometric conditions. It is worthwhile noting that, contrary to model compounds **4a,b**, the major side-reaction in this series was the reductive quenching of $-CH_2Br$ to CH_3 rather than the dimerization, thereby suggesting the possibility of using a higher concentration. We assume that the difference in behavior might be attributed to the difference in conformational property of **11**, compared to **4**; namely, **11** might have adopted a favorable conformation required for the macroketocyclization. Consistent with this assumption, the macroketocyclization was effective, without noticeable dimerization, even at 27 mM concentration, to furnish ketone **3** in 64% yield (52 mg scale).[23] Spectroscopic comparisons (^{1}H- and ^{13}C NMR, HR-MS) firmly established that **3** thus obtained was identical with the authentic sample.[3,5] Lastly, macrocyclic ketone **3** was converted into eribulin in three steps.[24]

In summary, a method has been developed for macroketocyclization between an alkyl bromide and a thioester under mild conditions. $NbCpCl_4$ and $CrCl_3$ are key components not only for in situ activation of alkyl bromide to alkylzinc halide via a SET process but also for acceleration of Pd-mediated coupling. Notably, this unique macroketocyclization does not require any special template or functional group to be removed after cyclization. Overall, the newly developed macroketocyclization has allowed us to synthesize eribulin with the same synthetic strategy as the one used in the halichondrins.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b11663.

Additional data for Table 1, experimental procedures, characterization data, and copies of spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(10) We hoped to suppress undesired side-reactions by either slow activation of RX and/or acceleration of transmetalation to avoid accumulation of generated alkylzinc halides.

(11) The conversion was 58%, 71% and 80% under Conditions A, B and C, respectively.

(12) See Supporting Information for details.

(13) For the case of intermolecular ketone coupling, we have suggested a possibility that the early transition metals might shift equilibrium from stable RZnX to higher-order orgnozincates and/or might break Pd-Zn to restore Pd reactivity, respectively.

(14) There was one additional benefit in reducing an amount of the reagent, i.e., isolation of the product was much easier with a lesser amount of the reagent.

(15) These experimental data should allow us to identify a proper setting for use of a syringe-pump.

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(19) With the Cr-catalyst derived from *unnat-i*-Pr/$PhCl_2$/$OCy(Me)_2$ sulfonamide, the dr observed for this Ni/Cr-mediated coupling was around 20:1 in the halichondrin series: see ref 2b and Guo, H.; Dong, C.-G.; Kim, D.-S.; Urabe, D.; Wang, J.; Kim, J. T.; Liu, X.; Sasaki, T.; Kishi, Y. *J. Am. Chem. Soc.* **2009**, *131*, 15387.

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(21) $PCyp_3$ is better than PCy_3 for this type of substrates, see ref 9.

(22) Interestingly, soluble amine bases gave complicated side reactions such as halide exchange.

(23) Reductive debromination was observed at 18 mM concentration, but not at 25 mM concentration. On the other hand, dimerization was not observed even at 27 mM concentration.

(24) See (a) ref 3. (b) ref 5. (c) Kaburagi, Y.; Kishi, Y. *Tetrahedron Lett.* **2007**, *48*, 8967.

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