Organic LETTERS

Letter

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Enantioselective Total Synthesis of (+)-Iso-A82775C, a Proposed Biosynthetic Precursor of Chloropupukeananin

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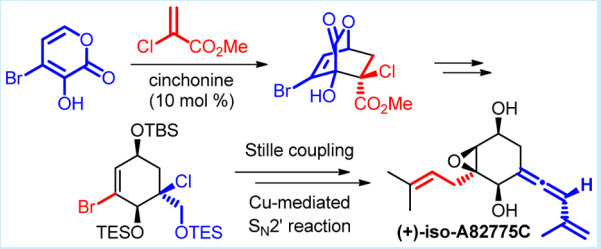
Supporting Information

ABSTRACT: (+)-Iso-A82775C is a proposed biosynthetic precursor of the chloropupukeananin family and an important intermediate for related natural products. The first enantioselective total synthesis of (+)-iso-A82775C (18 steps, 2.2% overall yield) toward the eventual biomimetic total synthesis of chloropupukeananin is described. The key steps are (1) the enantioselective Diels–Alder reaction of 4-bromo-3-hydroxy-2-pyrone with methyl 2-chloroacrylate using cinchonine as an organocatalyst and (2) the *anti*-selective Cu-mediated S_N2' reaction to afford the axially chiral vinylallene moiety.



(+)-Iso-A82775C (**1**) pestheic acid (**2**), and chloropupukeananin (**3**) (Figure 1a) were isolated from the fermentation broth of the plant endophytic fungus *Pestalotiopsis fici* by Che and colleagues in 2008.[1] Their recent studies[2] revealed the biosynthetic diversity of this fungus, resulting in numerous products including chloropestolides A–G. These compounds from the chloropupukeananin family consist of highly functionalized bi- or tricyclic skeletons and show inhibitory activity against HIV-1 replication and cytotoxicity against human tumor cell lines. The proposed biosynthesis of the chloropupukeananin family involves an intermolecular Diels–Alder reaction[3] between **1** and **2** and a subsequent carbonyl–ene reaction. In this context, studies involving the biomimetic synthesis of **3** using model compounds have been reported by Snider's group[4] and by us.[5]

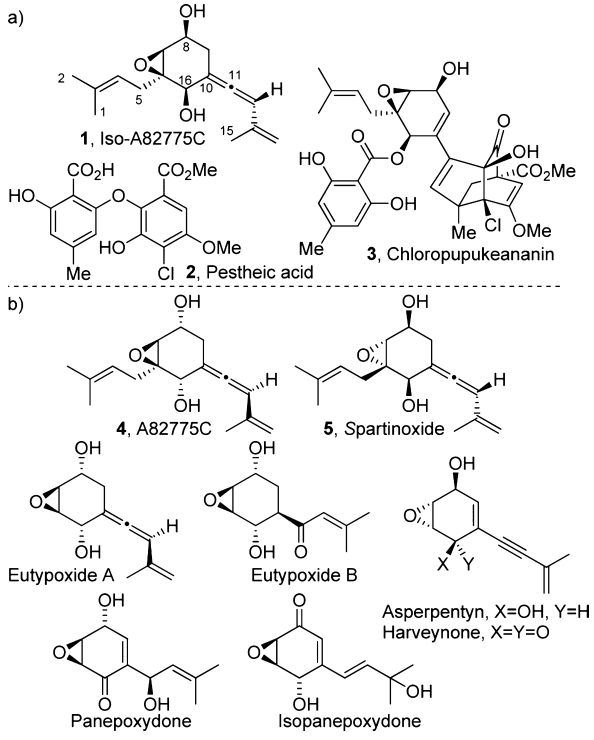


Figure 1. Iso-A82775C and related compounds.

Structurally, (+)-iso-A82775C is a diastereomer of the known fungal natural product A82775C (**4**)[6] and its enantiomer spartinoxide (**5**)[7] (Figure 1b). The former was isolated from an unknown terrestrial fungus collected in Egypt, and the latter was isolated from a marine-derived fungus and identified as an inhibitor of human leukemia elastase in 2010. These compounds are members of a family of naturally occurring cyclohexene epoxides[8] possessing an unsaturated C5 side chain, such as eutypoxides,[9] asperpentyn,[10] harveynone,[11] and panepoxydone.[12] However, only a few examples possess two unsaturated C5 side chains.[13] To the best of our knowledge, there is no compound that possesses both a prenyl group and an axially chiral vinylallene group other than compounds **1**, **4**, and **5**. In addition, **1** is considered to be an important biosynthetic intermediate of the related natural products pestaloficinol A–L[14] and pestalofone A–E[15] (see the Supporting Information). Because of its important role in the biosynthesis of chloropupukeananin as well as its interesting structural features, we attempted the total synthesis of (+)-iso-A82775C.

Received: January 10, 2017

DOI: 10.1021/acs.orglett.7b00085
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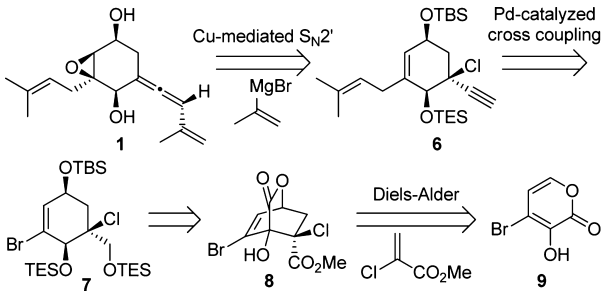
Our retrosynthetic analysis of (+)-iso-A82775C is outlined in Scheme 1. We considered that the stereoselective construction

Scheme 1. Retrosynthetic Analysis of 1

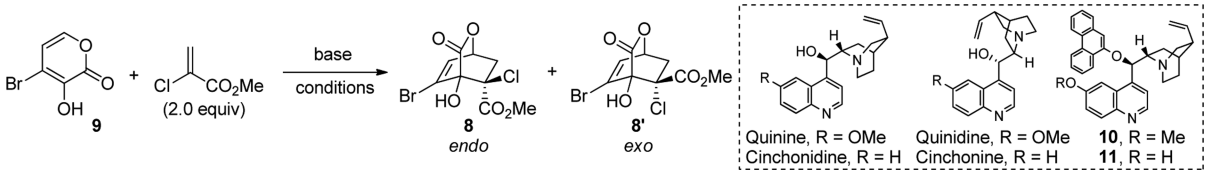


of the labile vinylallene and epoxide groups of **1** in the final stage of the total synthesis could be a serious challenge. The former could be accomplished by an S_N2' reaction to propargyl chloride using a vinylcopper reagent[5b,16] and the latter by neighboring-group-directed catalytic epoxidation. Thus, we set alkyne **6** as a precursor for the final stage, which could also be a common intermediate for both *ent*-**4** and **5**. Installation of the prenyl group of alkyne **6** could be achieved by Pd-catalyzed cross-coupling with bromide **7**. According to Okamura's pioneering work on the total synthesis of eutypoxide B,[17] the base-catalyzed Diels–Alder reaction of 3-hydroxy-2-pyrone and 2-chloroacrylate could construct the requisite stereocenters of bromide **7**. Especially, the tertiary alkyl chloride stereocenter is essential for the stereoselective construction of the vinylallene group. Thus, the Diels–Alder reaction of 4-bromo-3-hydroxy-2-pyrone (**9**) and methyl 2-chloroacrylate using a tertiary amine could give the *endo* cycloadduct **8** stereoselectively. We expected that the optically active cycloadduct **8** could be obtained by the enantioselective Diels–Alder reaction using chiral amines,[18] such as cinchona alkaloids. Herein we report the first enantioselective total synthesis of (+)-iso-A82775C.

We first investigated the intermolecular Diels–Alder reaction of pyrone **9**[19] and methyl 2-chloroacrylate under basic conditions (Table 1). With 0.5 equiv of *i*-Pr_2NEt as a base, the Diels–Alder reaction (in CH_2Cl_2 at 0 °C) gave the cycloadducts in 91% yield as a mixture of *endo* adduct **8** and *exo* adduct **8′** (**8**/**8′** = 2.1:1; Table 1, entry 1). Use of natural cinchona alkaloids as the base (Table 1, entries 2–5) increased the diastereoselectivity to give the desired adduct **8** (dr = 3.0–5.8:1), albeit with moderate enantiomeric excess. According to Deng's work,[18b] quinine-based catalysts (Table 1, entries 6–8) resulted in a slight decrease in the *endo*/*exo* and enantioselectivity. The *endo*/*exo* selectivity was increased to 8.4:1 when 0.5 equiv of quinidine in toluene was used (Table 1, entry 11). A lower catalyst loading (0.1 equiv of quinidine) slightly increased the *endo*/*exo* selectivity; however, the enantiomeric excess was not satisfactory (Table 1, entry 12). On the other hand, the reaction using 0.1 equiv of cinchonine in toluene gave the desired adduct **8** with 67% ee (dr = 3.6:1) (Table 1, entry 13). To our delight, recrystallization of the *endo* cycloadduct **8** (67% ee; Table 1, entry 13) from EtOAc/*n*-hexane gave enantiomerically pure crystalline (−)-**8** (>99% ee) in 42% yield from pyrone **9**. The absolute stereochemistry of cycloadduct (−)-**8** was determined by X-ray crystallographic analysis (Figure 2).[20]

With enantiomerically pure **8** in hand, we focused on its transformation to the cross-coupling precursor **7** (Scheme 2). Selective reduction of the ester group of *endo* adduct **8** with $LiBH_4$ followed by TES protection of the resulting alcohol gave silyl ether **12**.[21] DIBAL reduction of the lactone afforded α-hydroxylactol **13** as a diastereomeric mixture.[22] Criegee oxidation of lactol **13** with $Pb(OAc)_4$ in the presence of $NaHCO_3$ furnished cyclohexenone **14** in 43% overall yield from **8**. TBS protection of the secondary alcohol, deprotection of the primary alcohol, and in situ diastereoselective reduction using $NaBH(OAc)_3$[23] gave 1,3-diol **15** as a single diastereomer. Protection of the 1,3-diol with TES groups (TESCl, imidazole) gave the desired silyl ether **7** in quantitative yield.

Table 1. Diels–Alder Reaction between Pyrone 9 and Methyl 2-Chloroacrylate under Basic Conditions



entry	base (equiv)	solvent	temp (°C)	time (h)	yield (%)	**8**/**8′**[a]	ee of **8** (%)[b]
1	*i*-Pr_2NEt (0.5)	CH_2Cl_2	0	48	91	2.1:1	–
2	quinine (0.5)	CH_2Cl_2	0	39	94	5.7:1	−42
3	cinchonidine (0.5)	CH_2Cl_2	0	40	97	3.0:1	−48
4	quinidine (0.5)	CH_2Cl_2	0	36	93	5.7:1	39
5	cinchonine (0.5)	CH_2Cl_2	0	40	94	3.1:1	49
6	$(DHQD)_2PHAL$ (0.5)	CH_2Cl_2	0	60	90	3.7:1	31
7	**10** (0.5)	CH_2Cl_2	25	72	86	3.1:1	35
8	**11** (0.5)	CH_2Cl_2	0	40	90	1.3:1	45
9	quinidine (0.5)	EtOAc	0	40	99	5.6:1	40
10	quinidine (0.5)	Et_2O	25	64	95	6.2:1	37
11	quinidine (0.5)	toluene	0	40	97	8.4:1	31
12	quinidine (0.1)	toluene	0	40	99	9.2:1	34
13	cinchonine (0.1)	toluene	0	40	99	3.6:1	67

[a]Determined by ^1H NMR analysis. [b]Determined by HPLC analysis.

DOI: 10.1021/acs.orglett.7b00085
Org. Lett. XXXX, XXX, XXX–XXX

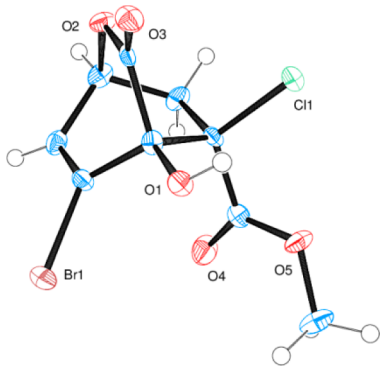
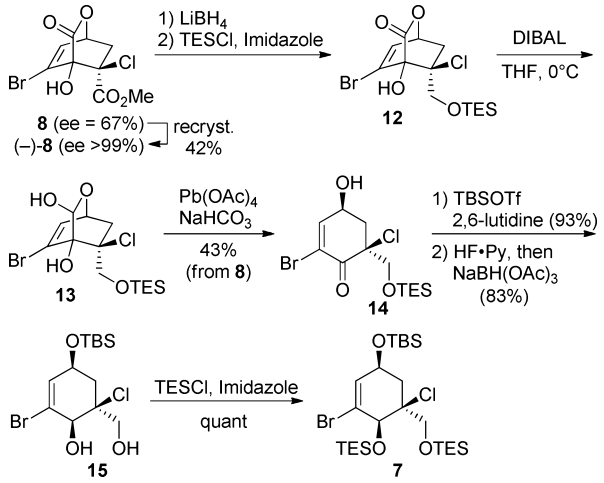


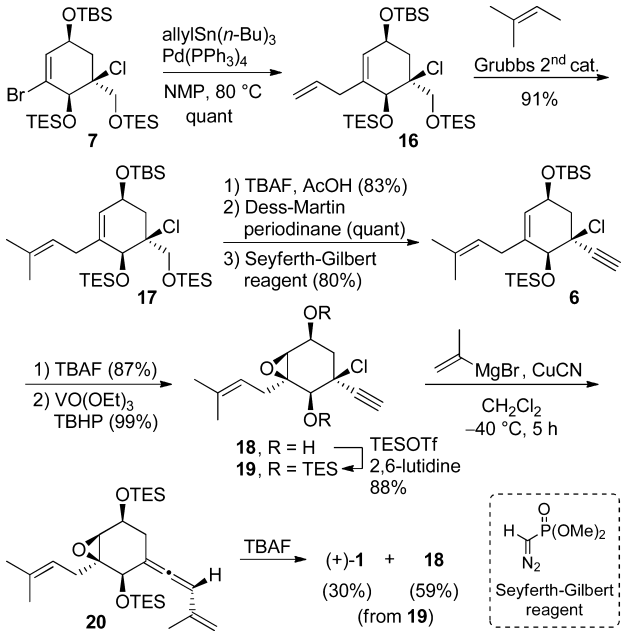
Figure 2. ORTEP drawing of *endo* adduct (−)-**8**.

Scheme 2. Preparation of Cross-Coupling Precursor 7



Next, we attempted the installation of the prenyl side chain by the use of cross-coupling reactions (Scheme 3). Treatment of bromide **7** with various allylmetal reagents, such as Mg and Zn, in the presence of a Pd catalyst gave almost no reaction.

Scheme 3. Completion of the Total Synthesis of (+)-1



Suzuki–Miyaura coupling ($Pd_2(dba)_3$, $P(t\text{-}Bu)_3$)[24] with allylboronic acid pinacol ester afforded allylcyclohexene **16** in 40% yield. Standard Stille coupling conditions (allyl-Sn(n-Bu)$_3$ and $Pd(PPh_3)_4$) using *N*-methyl-2-pyrrolidone (NMP) as a solvent gave **16** in quantitative yield. Unfortunately, the Stille coupling of **7** with prenyl-Sn(n-Bu)$_3$ was unsuccessful, resulting in only a trace amount of **17**. Cross-metathesis of **16** with 2-methylbut-2-ene using Grubbs' second-generation catalyst afforded prenylcyclohexene **17** in 91% yield. The three-step transformation from **17** to terminal alkyne **6** (selective deprotection, Dess–Martin oxidation of the resulting primary alcohol, and Seyferth–Gilbert homologation) was successful in 66% yield, whereas the Ohira–Bestmann reaction resulted in decomposition of the aldehyde.

After the deprotection of alkyne **6** with TBAF, hydroxyl-group-oriented epoxidation of the resulting diol using a catalytic amount of VO(OEt)$_3$ and TBHP[25] afforded epoxide **18** as a single diastereomer. After protection of the diol with TES groups, a Cu-mediated *anti*-S_N2' reaction was best carried out using CuCN and isopropenyl-MgBr to give vinylallene **20** as a single diastereomer along with the starting material **19**.[26] Other methods, including our conditions previously reported in model studies,[4] resulted in decomposition of the epoxide moiety and formation of a terminal allene.[16] Desilylation of the resulting mixture of vinylallene **20** and alkyne **19** provided (+)-**1** (30%, two steps) and diol **18** (59%). Thus, the total synthesis of (+)-**1** was completed in 2.2% overall yield from pyrone **9** (18 steps). All of the spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS, and $[\alpha]_D$) of synthetic (+)-**1** were in good accordance with those of natural (+)-iso-A82775C reported by Che et al.[1]

In conclusion, we have achieved the first total synthesis of (+)-iso-A82775C. Characteristic features of the present synthesis are (1) the enantioselective Diels–Alder reaction of pyrone **9** with methyl 2-chloroacrylate using cinchona alkaloids and (2) the *anti*-selective Cu-mediated S_N2' reaction to afford the labile vinylallene moiety. Our synthetic strategy represents an efficient means for preparing natural products related not only to (+)-iso-A82775C but also to chloropupukeananin. Further investigation toward the biomimetic total synthesis of chloropupukeananin is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00085.

Crystallographic data for (−)-**8** (CIF)
Experimental procedures and ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.7b00085
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■ ACKNOWLEDGMENTS

This research was supported in part by a Grant-in-Aid for Young Scientists (B) (KAKENHI 22790022 and 24790025) from the Japan Society for the Promotion of Science. We thank the Naito Foundation, the Uehara Memorial Foundation, the Kurata Memorial Hitachi Science and Technology Foundation, and the Research Foundation for Pharmaceutical Sciences for financial support.

■ REFERENCES

(1) Liu, L.; Liu, S. C.; Jiang, L. H.; Chen, X. L.; Guo, L. D.; Che, Y. S. *Org. Lett.* **2008**, *10*, 1397−1400.
(2) (a) Liu, L.; Li, Y.; Liu, S. C.; Zheng, Z. H.; Chen, X. L.; Zhang, H.; Guo, L. D.; Che, Y. S. *Org. Lett.* **2009**, *11*, 2836−2839. (b) Liu, L.; Niu, S. B.; Lu, X. H.; Chen, X. L.; Zhang, H.; Guo, L. D.; Che, Y. S. *Chem. Commun.* **2010**, *46*, 460−462. (c) Liu, L.; Bruhn, T.; Guo, L. D.; Gotz, D. C. G.; Brun, R.; Stich, A.; Che, Y. S.; Bringmann, G. *Chem. - Eur. J.* **2011**, *17*, 2604−2613. (d) Liu, L.; Li, Y.; Li, L.; Cao, Y.; Guo, L. D.; Liu, G.; Che, Y. S. *J. Org. Chem.* **2013**, *78*, 2992−3000.
(3) For a recent example of total synthesis using a biomimetic intermolecular Diels−Alder reaction, see: Deng, J.; Zhou, S.; Zhang, W.; Li, J.; Li, R.; Li, A. *J. Am. Chem. Soc.* **2014**, *136*, 8185−8188.
(4) Yu, M.; Snider, B. B. *Tetrahedron* **2011**, *67*, 9473−9478.
(5) (a) Suzuki, T.; Kobayashi, S. *Org. Lett.* **2010**, *12*, 2920−2923. (b) Suzuki, T.; Miyajima, Y.; Suzuki, K.; Iwakiri, K.; Koshimizu, M.; Hirai, G.; Sodeoka, M.; Kobayashi, S. *Org. Lett.* **2013**, *15*, 1748−1751.
(6) Sanson, D. R.; Gracz, H.; Tempesta, M. S.; Fukuda, D. S.; Nakatsukasa, W. M.; Sands, T. H.; Baker, P. J.; Mynderse, J. S. *Tetrahedron* **1991**, *47*, 3633−3644.
(7) Elsebai, M. F.; Kehraus, S.; Gütschow, M.; König, G. M. *Nat. Prod. Commun.* **2010**, *5*, 1071−1076.
(8) For reviews, see: (a) Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84−90. (b) Marco-Contelles, J.; Molina, M. T.; Anjum, S. *Chem. Rev.* **2004**, *104*, 2857−2899.
(9) (a) Renaud, J.-M.; Tsoupras, G.; Stoeckli-Evans, H.; Tabacchi, R. *Helv. Chim. Acta* **1989**, *72*, 1262−1267. (b) Defrancq, E.; Gordon, J.; Brodard, A.; Tabacchi, R. *Helv. Chim. Acta* **1992**, *75*, 276−281.
(10) (a) Kis, Z.; Closse, A.; Sigg, H. P.; Hruban, L.; Snatzke, G. *Helv. Chim. Acta* **1970**, *53*, 1577−1597. (b) Erkel, G.; Anke, T.; Sterner, O. *Biochem. Biophys. Res. Commun.* **1996**, *226*, 214−221.
(11) Nagata, T.; Ando, Y.; Hirota, A. *Biosci., Biotechnol., Biochem.* **1992**, *56*, 810−811.
(12) Mühlenfeld, A.; Achenbacht, H. *Phytochemistry* **1988**, *27*, 3853−3855.
(13) More recently, biscognienyne B was isolated from the lichen *Usnea mutabilis* stirt., which possesses two unsaturated C5 side chains (prenyl and 3-methylbut-3-en-1-ynyl). See: Zhao, H.; Chen, G. D.; Zou, J.; He, R. R.; Qin, S. Y.; Hu, D.; Li, G. Q.; Guo, L. D.; Yao, X. S.; Gao, H. *Org. Lett.* **2017**, *19*, 38−41.
(14) (a) Liu, L.; Tian, R. R.; Liu, S. C.; Chen, X. L.; Guo, L. D.; Che, Y. S. *Bioorg. Med. Chem.* **2008**, *16*, 6021−6026. (b) Liu, L.; Liu, S. C.; Niu, S. B.; Guo, L. D.; Chen, X. L.; Che, Y. S. *J. Nat. Prod.* **2009**, *72*, 1482−1486.
(15) Liu, L.; Liu, S. C.; Chen, X. L.; Guo, L. D.; Che, Y. S. *Bioorg. Med. Chem.* **2009**, *17*, 606−613.
(16) Gordon, J.; Tabacchi, R. *J. Org. Chem.* **1992**, *57*, 4728−4731.
(17) (a) Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron Lett.* **1995**, *36*, 5939−5942. (b) Shimizu, H.; Okamura, H.; Iwagawa, T.; Nakatani, M. *Tetrahedron* **2001**, *57*, 1903−1908.
(18) (a) Okamura, H.; Nakamura, Y.; Iwagawa, T.; Nakatani, M. *Chem. Lett.* **1996**, *25*, 193−194. (b) Wang, Y.; Li, H.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 6364−6365.
(19) Preparation of **9** was carried out by a modification of Mayer's method. See: Mayer, R. *Chem. Ber.* **1957**, *90*, 2369−2372. See the Supporting Information.
(20) See the Supporting Information.
(21) Direct reduction of the ester and lactone groups of **8** with DIBAL or $LiAlH_4$ gave a complex mixture as a result of aromatization of the cyclohexene ring.
(22) The stereochemistry was not identified because of the instability of lactol **13**.
(23) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273−276.
(24) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020−4028.
(25) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−74.
(26) Despite our extensive efforts, the conversion of the S_N2' reaction could not be improved, probably because of competitive deprotonation of the terminal alkyne.

DOI: 10.1021/acs.orglett.7b00085
Org. Lett. XXXX, XXX, XXX−XXX