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

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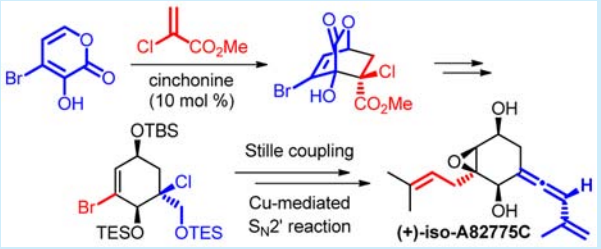
Supporting Information

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]

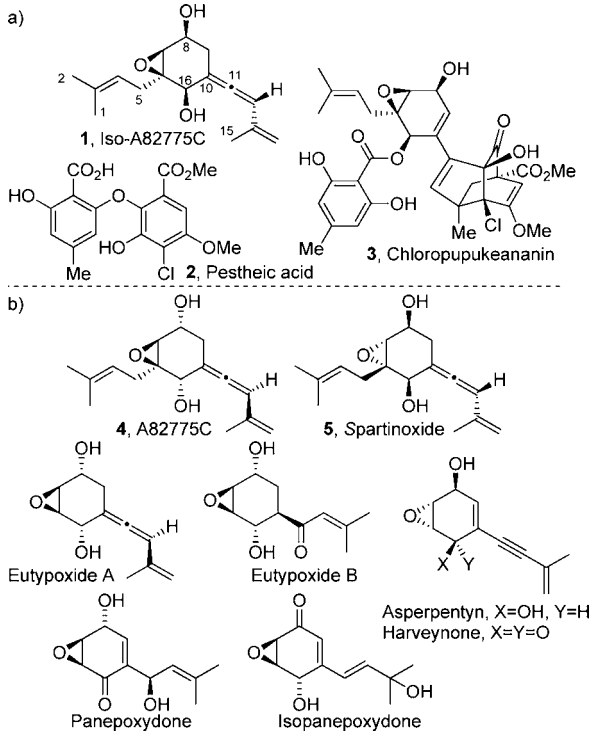


Figure 1. Iso-A82775C and related compounds.

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.

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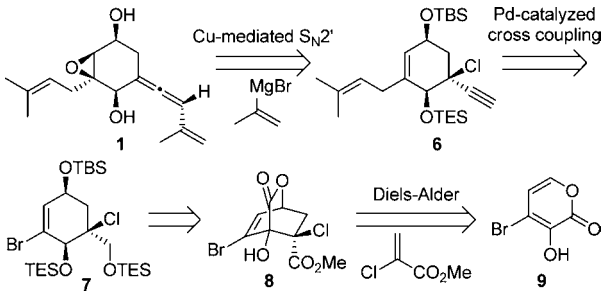
Org. Lett. 2017, 19, 922−925

Our retrosynthetic analysis of (+)-iso-A82775C is outlined in Scheme 1. We considered that the stereoselective construction

Scheme 1. Retrosynthetic Analysis of 1

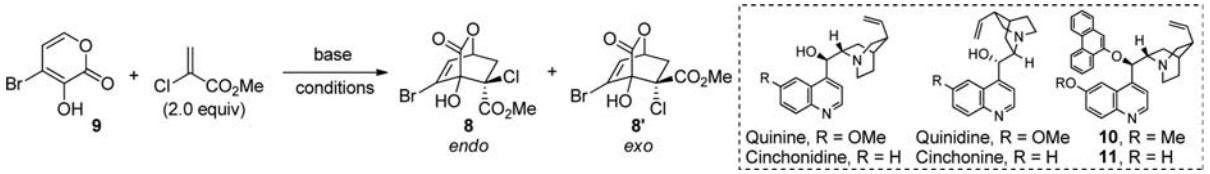


of the labile vinylallene and epoxide groups of **1** in the final stage of the total synthesis could be a serious challenge. The former could be accomplished by an S_N2' reaction to propargyl chloride using a vinylcopper reagent[5b,16] and the latter by neighboring-group-directed catalytic epoxidation. 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.

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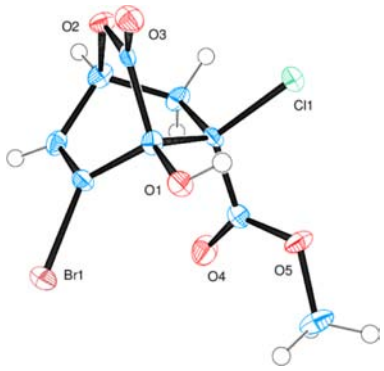
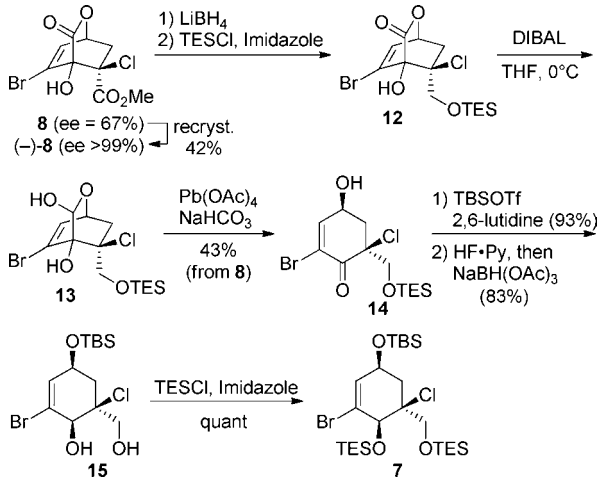


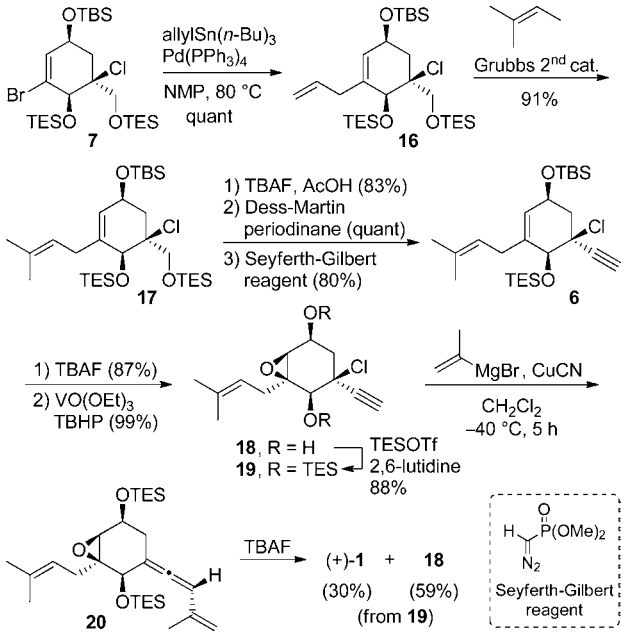
Figure 2. ORTEP drawing of *endo* adduct (−)-**8**.

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.

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