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Unexpected Diels–Alder/Carbonyl-ene Cascade toward the Biomimetic Synthesis of Chloropupukeananin

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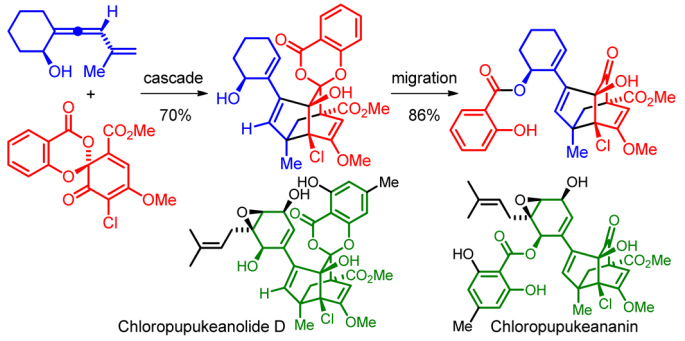
ABSTRACT



The biomimetic synthesis of the advanced model compound of chloropupukeananin has been achieved. The present synthesis features an unexpected enantiomer-differentiating Diels–Alder/carbonyl-ene cascade under high-pressure conditions and a base-promoted migration of the salicyl group.

Chloropupukeananin (**1**), an inhibitor of HIV-1 replication, was originally isolated from the plant endophytic fungus *Pestalotiopsis fici* by Che and colleagues as the first chlorinated pupukeanane derivative, along with its proposed biosynthetic precursors, *iso*-A82775C (**2**) and pestheic acid (**3**) (Figure 1).[1] They also reported the isolation of the congeners of **1**, such as chloropestolide A (**4**), chloropupukeanolide C (**5**) and D (**6**), from the same fermentation extract.[2] Structurally, these natural products possess a highly functionalized tricyclo[4.3.1.$0^{3,7}$]decane or bicyclo[2.2.2]octane, comprised of **2** and **3** by a reverse electron-demand Diels–Alder reaction (REDDA). Inspired by the structural complexity and diversity of this class of compounds, we investigated a synthetic study of chloropupukeananine.[3]

In the previous paper,[3] we proposed a biosynthetic pathway to **1** and **4** from **2** and maldoxin **7** (Scheme 1a).[4,5] Recent isolation of chloropupukeanolide C and D also supports our proposed biosynthetic pathway. In addition, we described the biomimetic synthesis of the core skeleton of chloropupukeananin by a REDDA reaction and carbonyl-ene reaction from masked *o*-benzoquinone (MOB)[6] **10**

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(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.

(3) Suzuki, T.; Kobayashi, S. *Org. Lett.* **2010**, *12*, 2920–2923.

(4) Although stereochemistry of the allene moiety of **2** and the acetal moiety of **7** have not been determined, we postulated that those are *S* and *R*, as shown in Scheme 1a, from the structure of **4**-**6**.

(5) In this manuscript the stereochemical course of the REDDA is classified as "*endo*" or "*exo*". "*Endo*" and "*exo*" represent the *syn* and *anti*-orientation of α-keto-acetal and allene moiety, respectively.

(6) For reviews on MOBs, see: (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856–866. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383–1429. (c) Liao, C.-C. *Pure Appl. Chem.* **2005**, *77*, 1221–1234. (d) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068–4093.

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and vinylallene **9** (Scheme 1b).[7] We report here the synthesis of advanced model compound **18** from spirolactone-type MOB **15** and vinylallene **14** (Scheme 2). Significant features of the present study include; (i) a biomimetic cascade reaction (REDDA and carbonyl-ene reaction) proceeded under high-pressure conditions, and (ii) the desired REDDA occurs in a stereoselective and an enantiomer-differentiating manners.

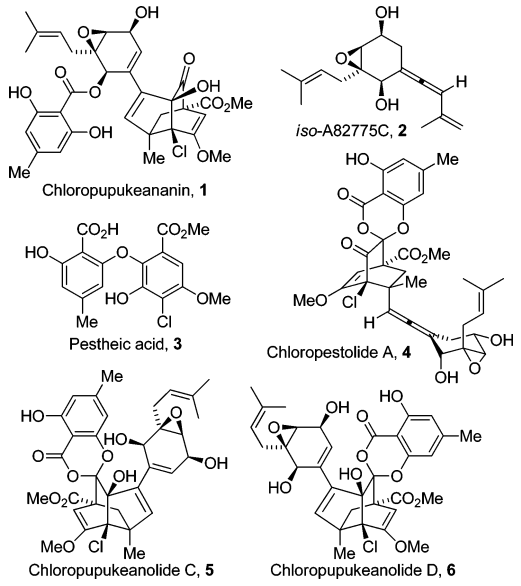
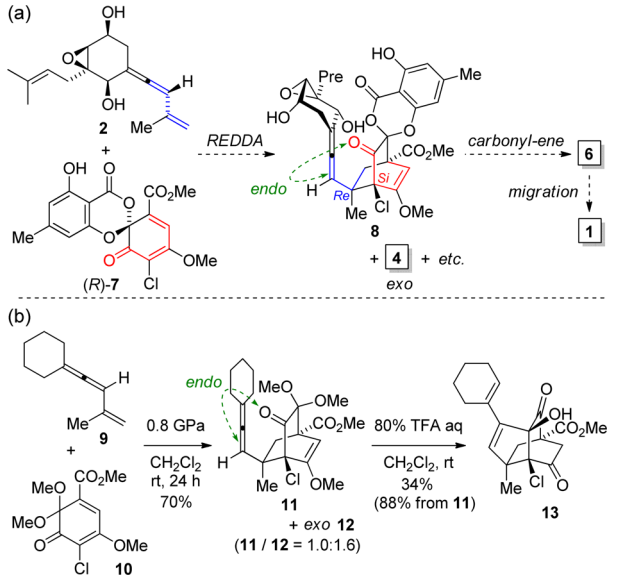


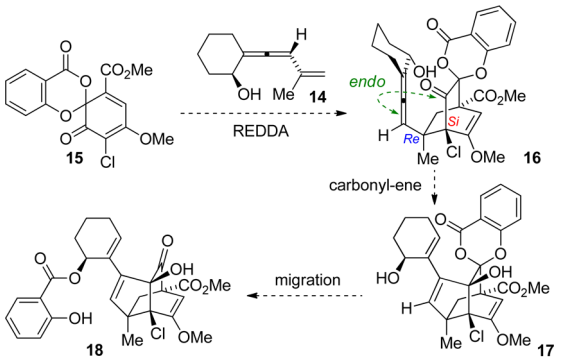
Figure 1. Chloropupukeananin, **1**, and its related compounds.

Scheme 1. Our Proposed Biosynthesis Involving (a) Maldoxin and (b) Our Previous Results



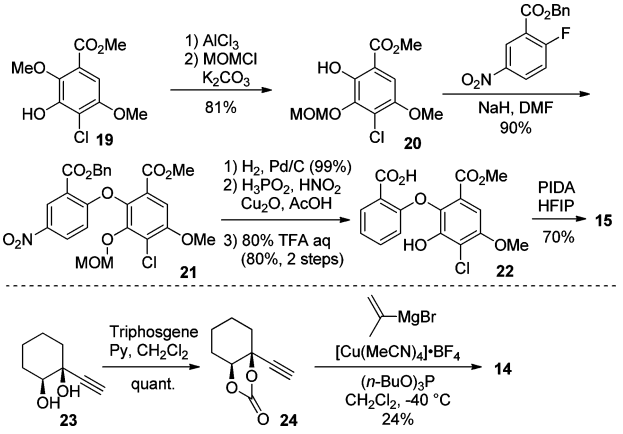
The preparation of MOB precursor **15** was commenced with the removal of the Me group of chlorophenol **19**[3]

Scheme 2. Synthetic Strategy toward Advanced Model Compound **18**



(Scheme 3). Selective protection of the resulting catechol gave phenol **20**, which was subjected to S_NAr reaction with benzyl 2-fluoro-5-nitrobenzoate[8] to give diaryl ether **21** in high yield. Diaryl ether **21** was transformed to **22** by a conventional three step sequence of reactions. The oxidative dearomatization of diaryl ether **22** with PIDA afforded MOB **15** possessing a salicylic acid ketal. Vinylallene **14** was prepared in 2 steps from *cis*-1-ethynylcyclohexane-1,2-diol **23**.[9] Treatment of diol **23** with triphosgene gave carbonate **24**. Cu-promoted *anti*-selective S_N2' reaction[10] with isopropenylmagnesium bromide in the presence of $(n\text{-BuO})_3P$ gave vinylallene **14** as a single diastereomer albeit in low yield.[11]

Scheme 3. Preparation of MOB **15** and Vinylallene **14**



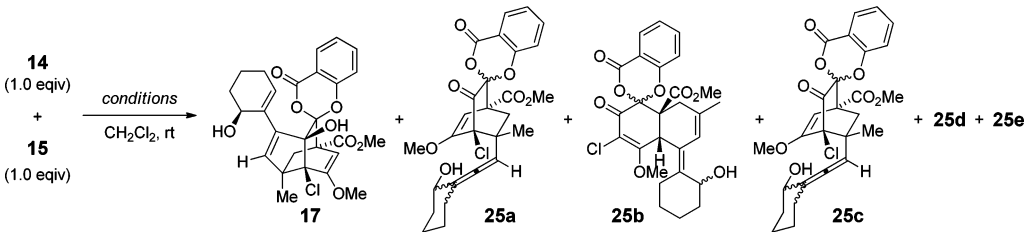
(7) Yu and Snider have also reported the synthesis of (±)-maldoxin and its thermal Diels–Alder reaction with allene **9**, see: (a) Yu, M.; Snider, B. B. *Org. Lett.* **2011**, *13*, 4224–4227. (b) Yu, M.; Snider, B. B. *Tetrahedron* **2011**, *67*, 9473–9478.

(8) South, M. S.; Case, B. L.; Dice, T. A.; Franklin, G. W.; Hayes, M. J.; Jones, D. E.; Lindmark, R. J.; Zeng, Q. P.; Parlow, J. J. *Comb. Chem. High Throughput Screening* **2000**, *3*, 139–151.

(9) Battistini, C.; Crotti, P.; Macchia, F. *J. Org. Chem.* **1981**, *46*, 434–436.

(10) Tang, X. P.; Woodward, S.; Krause, N. *Eur. J. Org. Chem.* **2009**, 2836–2844.

Table 1. High Pressure REDDA Reaction



			yield (%)				
entry	pressure (GPa)	time (h)	**17**[a]	**25a**[b]	**25b**[b]	**25c**[c]	**25d**+**25e**[c]
1	0.5	24	12	7	16	12	35
2	0.8	24	32	24	10	18	14
3	1.0	24	37	18	11	21	13
4	1.0	3	17	16	9	14	39
5	1.0	48	47	21	9	19	3
6	1.0	96	48	24	9	15	0

[a] Isolated yield. [b] Calculated yield from the ratio of a mixture **25a** and **25b**. [c] Calculated yield from the ratio of a mixture of **25c**, **25d**, and **25e**.

With (±)-**15** and (±)-**14** in hand, we conducted a high pressure REDDA reaction. The REDDA reaction of racemic pair was predicted to generate eight possible isomers. Although the use of enantiomerically pure precursors will give only four isomers, REDDA reaction of a pair of racemates was first conducted to obtain any information on the reactivity of **15** and **14**.

Using our previous conditions (0.8 GPa, 0.1 M, CH_2Cl_2, rt, 24h, Table 1, entry 2), the REDDA reaction afforded at least six products **17** and **25a**−**e**. NMR studies showed that these products possess both salicylic acid ketal and cyclohexanol moieties. Surprisingly and to our delight, the X-ray crystallographic analysis of the major product **17** showed it to be the desired tricyclo[4.3.1.$0^{3,7}$]decane with the same stereochemistry as that of chloropupukeanolide D (Figure 2).[12] This result indicated that the REDDA adduct **16** underwent a carbonyl-ene reaction under high-pressure conditions. The yield of product **17** clearly depended on the pressure (entries 1−3) and reaction time (entries 3−6). The highest yield (48%) was obtained by treatment of an equimolecular amount of MOB **15** and allene **14** under 1.0 GPa for 96h (entry 6).

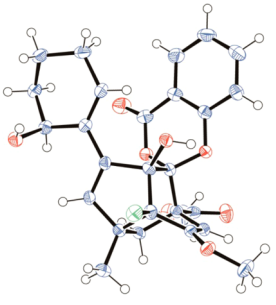


Figure 2. Ortep drawing of tricyclic compond **17**.

The structures of the other products have not been fully established. Products **25a**−**c** are assumed to be exo-REDDA adducts (**25a** and **25c**) and a normal-electron-demand Diels−Alder adduct (**25b**) by NMR studies.[13] Two other cycloadducts **25d** and **25e** could not be purified in order to determine their structures. However, either **25d** or **25e** is the initially expected Diels−Alder adduct **16** because ene product **17** was obtained by the treatment of the mixture of **25c**, **25d** and **25e** under high-pressure conditions. This was supported by the fact that prolonged reaction time increased the yield of **17** with a decrease in the combined yield of **25d** and **25e**.

Direct formation of the desired tricyclo[4.3.1.$0^{3,7}$]decane **17** in 48% yield under high-pressure conditions is interesting for the following three reasons: (i) the REDDA reaction of a racemic pair predominantly afforded the most desired adduct **16** among eight possible isomers; (ii) the REDDA reaction was almost complete after just 3 h, in contrast to our previous results; and (iii) the carbonyl-ene reaction of *endo*-cycloadduct **16** occurred in a biomimetic manner. The unexpectedly predominant formation of cycloadduct **16** might be the outcome of several factors (Scheme 4). For the facial selectivity of the MOB **15**, dienophile **14** tends to approach from the same face as the spirolactone carbonyl of MOB **15** by analogy to the

(11) Despite of our efforts to improve the yield, any condition was failed.

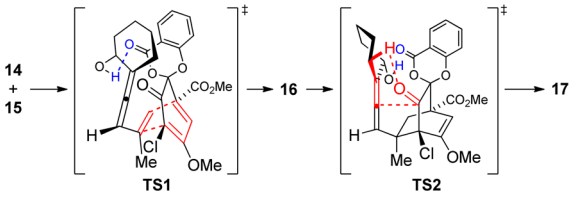
(12) CCDC 919015 (for **17**) and CCDC919016 (for (−)-(*R*)-**15**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(13) Further structural determination was impeded by the isolated stereocenters on the cyclohexane ring and salicylic acid ketal. Use of wavy bonds in **25a**−**c** means unknown facial selectivity of **14** and **15**, not implying that a diastereomer mixture of **14** was used. Probable structures of **25a** and **25c** were illustrated in Supporting Information.

(14) Drutu, I.; Njardarson, J. T.; Wood, J. L. *Org. Lett.* **2002**, *4*, 493–496. Similar facial selectivity was observed by Snider and Yu. See also ref 7b.

pioneering work by Wood et al.[14] In addition, the hydrogen bonding between the hydroxyl group of dienophile **14** and spirolactone carbonyl of **15** might also contribute to the desired selectivity (**TS1**). With regard to the reaction rate, the lower LUMO energy level of the diene of MOB **15** caused by the salicyclic acid ketal moiety might accelerate the REDDA reaction (Table 1, entry 4; REDDA reaction was almost complete within 3 h). This moiety may also lower the LUMO energy level of the carbonyl group of *endo* adduct **16**. As a result, the cascade carbonyl-ene reaction took place.[15] Hydrogen bonding between cyclohexanol and the spirolactone carbonyl moiety might also result in the close proximity of the carbonyl and olefin moiety (**TS2**).

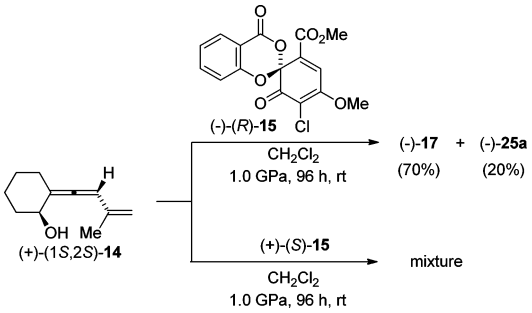
Scheme 4. Proposed Transition State of REDDA Reaction and Carbonyl-ene Reaction



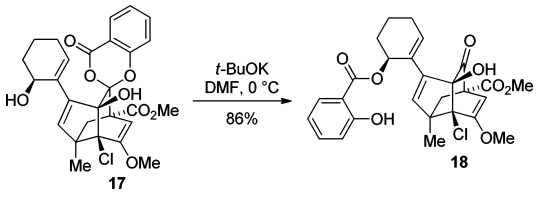
We next examined the cascade reaction with the enantiomerically pure precursors. The resolution of racemic MOB **15** was performed by chiral column HPLC (CHIRALPAK IC, Hex/EtOH/$CHCl_3$ = 2/1/1). The (+)-(1*S*,2*S*)-**14** was prepared from enantiopure diol (−)-**23** obtained by the separation of mandelic acid derivatives.[16,17] Both enantiomers of MOB, (−)-(*R*)- and (+)-(*S*)-**15**,[12,18] were subjected to the Diels−Alder/carbonyl-ene cascade reaction with (+)-(1*S*,2*S*)-**14** under the high-pressure conditions (Scheme 5). The reaction of (−)-(*R*)-**15** and (+)-(1*S*,2*S*)-**14** (natural combination) afforded the desired product (−)-**17** (70%) and (−)-**25a** (20%), whereas the reaction of (+)-(1*S*,2*S*)-**14** and (+)-(*S*)-**15** (unnatural combination) resulted in the formation of a mixture of cycloadducts. The difference in the selectivity between the natural and unnatural combination is interesting, although the degree of enantiomer-differentiation is not high.[19]

Finally, the migration of salicyl group in **17** was examined (Scheme 6). This was best carried out by the treatment

Scheme 5. REDDA/Carbonyl-ene Cascade Reaction with Enantiomerically Pure Precursors



Scheme 6. Migration of Salicyl Group



of **17** with *t*-BuOK in DMF to afford salicylate **18** in 86% yield. The ^{1}H and ^{13}C NMR spectral data of salicylate **18** are in good accordance with those of chloropupukeananin.

In conclusion, we were able to achieve the synthesis of an advanced model of chloropupukeananin by employing a biomimetic Diels−Alder/carbonyl-ene cascade reaction under high pressure conditions. Further study toward the asymmetric total synthesis of chloropupukeananin is currently underway.

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Supporting Information Available. Detail experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(15) To the best of our knowledge, only two examples of carbonyl-ene reaction under high-pressure condition have been reported: (a) Jurczak, J.; Kozluk, T.; Pikul, S.; Salanski, P. *J. Chem. Soc. Chem. Comm.* **1983**, 1447–1448. (b) Dauben, W. G.; Hendricks, R. T. *Tetrahedron Lett.* **1992**, *33*, 603–606.

(16) Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548–3551.

(17) Absolute stereochemistry of (−)-**23** was determined by modified Mosher method. See Supporting Information.

(18) Absolute stereochemistry of (−)-**15** was determined by X-ray crystallographic analysis. See Supporting Information.

(19) See Supporting Information for HPLC analysis of these reactions.