Tetrahedron Letters 51 (2010) 3294–3296

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient construction of the core framework of lysidicin A via three Claisen rearrangements including a cascade reaction

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ARTICLE INFO

Article history:
Received 8 March 2010
Revised 10 April 2010
Accepted 19 April 2010
Available online 22 April 2010

Keywords:
Lysidicin A
Vasodilation activity
Claisen rearrangement
Cascade reaction

ABSTRACT

A model compound (**6**) with the core skeleton of lysidicin A was synthesized as a racemate. The key step (**8**→**7**) includes three Claisen rearrangements of the triether with phloroglucinols; two of which rearranged in a cascade manner and the other was a simple rearrangement. This one-pot reaction enabled the introduction of three phloroglucinol units at the correct positions and makes the synthetic approach significantly efficient.

Lysidicins A–E (**1**–**5**) were isolated from Chinese medicinal plant, *Lysidice rhodostegia* Hance (Fabaceae) which has been used for the treatment of ache, fractures, and hemorrhage for a long time by local folks in China (Fig. 1).[1,2] Among the lysidicin family, lysidicins A–C were reported to exhibit vasodilation activity.[1] However, the full details of biological activity of lysidicins have not been clarified yet. Lysidicin A (**1**) has the most unique and complicated structure in which two acetals form spiro[furan–furofuran] ring system. However, only the relative configuration of **1** was determined. Additionally, any other compounds possessing this unique structure have not been isolated. That prompted us to embark on the total synthesis of lysidicin A. Herein, we report an efficient construction of the acetalic framework of lysidicin A.

We set up **6** as a model compound and our synthetic strategy of **6** (and lysidicin A) is shown in Scheme 1. Compound **6** would be synthesized from diene **7** by oxidative cleavage of two *exo*-olefins and subsequent intramolecular acetalization. Diene **7** would be obtained from triether **8** by Claisen rearrangements including a cascade reaction. Triether **8** would be obtained from phloroglucinol derivative **9** and triol **10**. Triol **10** would be obtained from dimethyl itaconate **11** and ketone **12**. The key step (**8**→**7**) enables the introduction of three phloroglucinol units at the correct positions in a single operation and makes our synthesis significantly efficient.

The precursor **8** for the Claisen rearrangements was prepared as shown in Scheme 2. First of all, **11** was reduced to diol by DIBAL-H,[3] which was submitted to monosilylation to give a mixture of **13a** and **13b** (1:1). After SiO_2 separation, iodination of the desired alcohol **13a** followed by treatment with triphenylphosphine afforded phosphonium salt **14**. Subsequent Wittig reaction with known ketone **12**[4,5] gave coupling product, whose protective groups were removed under mild acidic condition to afford corresponding triol **10**. Under the Mitsunobu condition, triol **10** was then converted to the precursor of the key reaction, triether **8**, in 51% yield along with 30% of intramolecularly O-alkylated product (**15**).

With key intermediate **8** in hand, Claisen rearrangement was examined as summarized in Table 1. Thermal conditions resulted in decomposition (entries 1 and 2).[6,7] The reaction using diethylaluminum chloride as a Lewis acid afforded only the partially rearranged products and the desired **7** was not detected (entries 3 and 4).[8] Triisobutylaluminum was also unsatisfactory (only a trace amount of **7** was observed on silica gel TLC, entry 5).[9] In contrast, trimethylaluminum and water dramatically accelerated the Claisen rearrangement and **7** was obtained in excellent yield (entry 6).[10]

After the successful key step, model compound **6** was synthesized via oxidation and subsequent acetalization (Scheme 3). Three phenolic hydroxy groups of **7** were temporarily acetylated, and the product **16** was submitted to ozonolysis to give desired diketone **17** in good yield. On the other hand, ozonolysis of **7** resulted in decomposition due to the competitive oxidation of the aromatic rings. Finally, removal of acetyl groups of **17** and subsequent acid treatment afforded model compound **6** successfully as a major product (47% in two steps) along with a small amount of diastereomer **6′** (5%). ^{1}H NMR coupling patterns of **6** showed good accordance with those of lysidicin A[1,11] and the relative stereochemistry of **6** was confirmed by X-ray analysis.[12]

In summary, by use of the three Claisen rearrangements in one-pot, model compound **6** with a core framework of lysidicin A (**1**)

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doi:10.1016/j.tetlet.2010.04.073

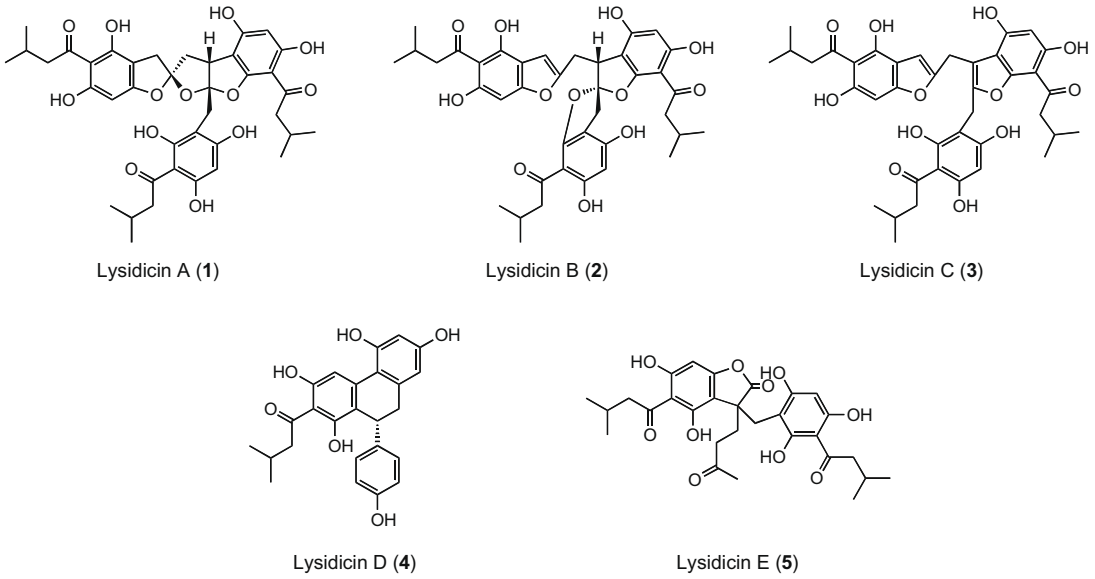
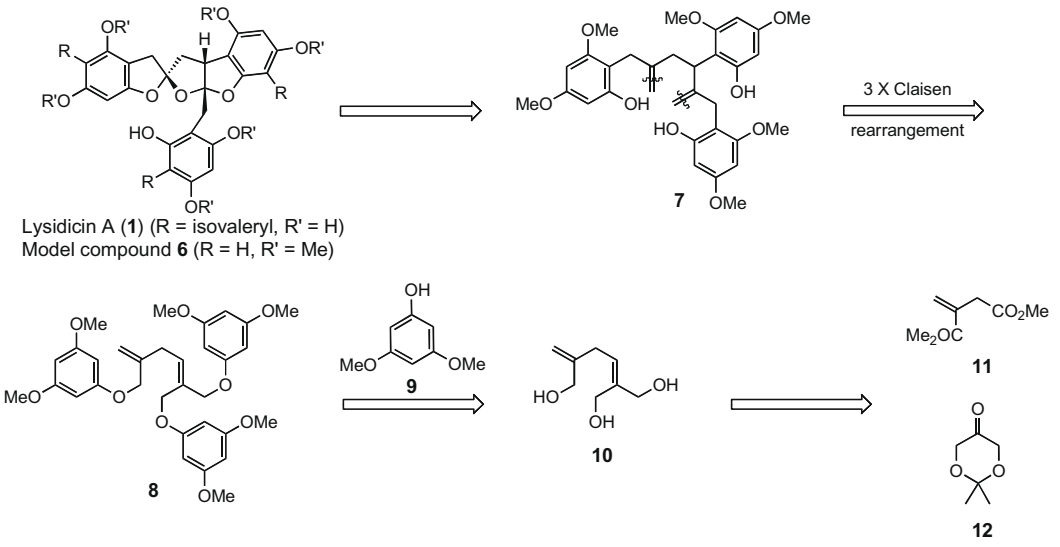
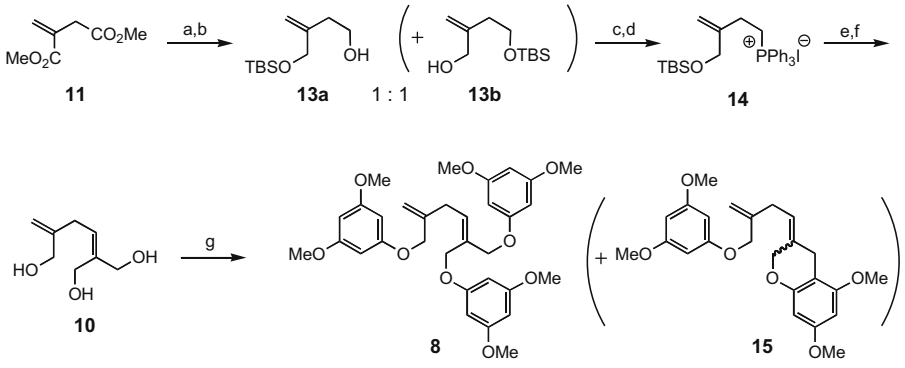


Figure 1. Structures of lysidicin family.

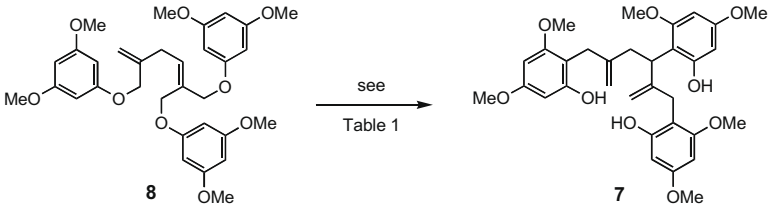


Scheme 1. Retrosynthetic analysis.



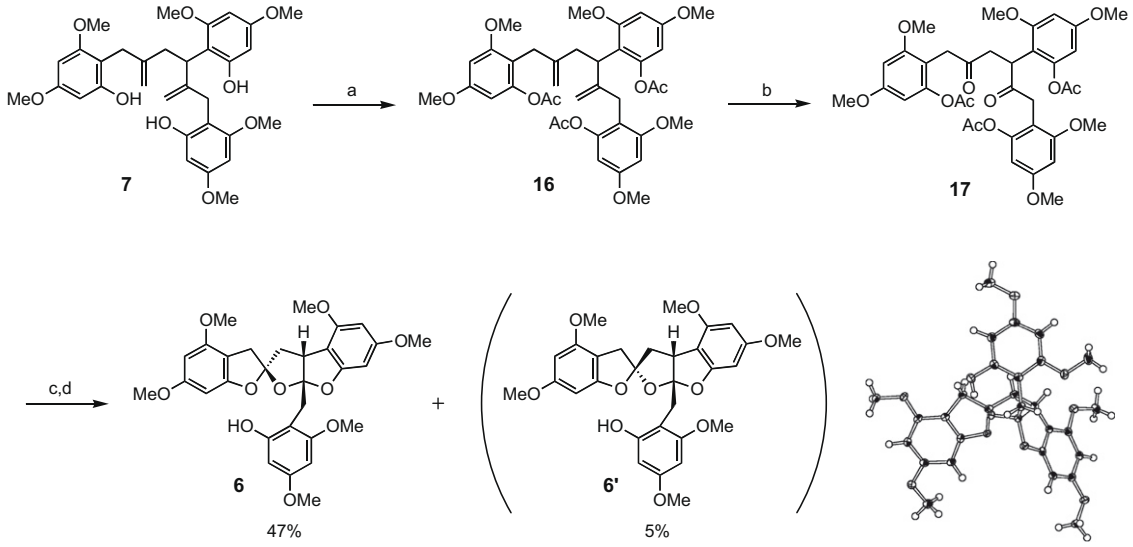
Scheme 2. Preparation of triether **8**. Reagents and conditions: (a) DIBAL-H, THF, −78 °C to rt, 95%; (b) TBSCl, NaH, THF, −10 °C, 43% (and 43% of **13b**); (c) I_2, Imid., PPh_3, CH_3CN/ether = 1:3, rt, 96%; (d) PPh_3, CH_3CN, reflux; (e) *n*-BuLi, DME, then **12**, −78 °C to 0 °C , 80% in two steps; (f) AcOH/H_2O/THF = 1:1:1, rt, 84%; (g) **9**, DEAD, PPh_3, THF, 0 °C to rt, 51%.

Table 1
Examination of Claisen rearrangement



Entry	Catalyst	Solvent	Temperature	Time (h)	Result
1	—	Decalin®	Reflux	17	Decomposition
2	—	*N*,*N*-Dimethylaniline	160 °C	24	Decomposition
3	Et_2AlCl	CH_2Cl_2	−78 °C	3	Incompletion
4	Et_2AlCl	CH_2Cl_2	0 °C	3	Incompletion
5	$(i\text{-}Bu)_3Al$	CH_2Cl_2	0 °C to rt	2.5	Incompletion
6	Me_3Al/H_2O[a]	CH_2Cl_2	Reflux	4	83%

[a] Me_3Al (16 equiv), H_2O (4 equiv).



Scheme 3. Synthesis of model compound **6**. Reagents and conditions: (a) Ac_2O, NaH, THF, 0 °C, 92%; (b) O_3, CH_2Cl_2, −78 °C, then PPh_3, 69%; (c) K_2CO_3, MeOH, 0 °C; (d) TsOH, CH_2Cl_2, 0 °C to rt, 47% in two steps.

was synthesized in 12 steps from dimethyl itaconate (**11**). This approach would provide an efficient synthetic way for analogous compounds as well as lysidicin A itself. Total synthesis of lysidicin A (**1**) is now in progress and will be reported in due course.

Acknowledgment

We thank Mr. M. Bando of Otsuka Pharmaceutical Co., Ltd for X-ray analysis.

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11. Physical and spectral data of model compound **6** : mp 194–196 °C (recrystallized from hex/EtOAc = 10:1), ^1H NMR (500 MHz $CDCl_3$) δ 7.16 (1H, s), 6.18 (1H, d, J = 2.4 Hz), 6.15 (1H, d, J = 2.1 Hz), 6.08 (1H, d, J = 2.4 Hz), 6.07 (1H, d, J = 2.1 Hz), 5.98 (1H, d, J = 1.8 Hz), 5.81 (1H, d, J = 1.8 Hz), 3.94 (1H, d, J = 8.7 Hz), 3.81 (3H, s), 3.77 (9H, s), 3.76 (3H, s), 3.68 (3H, s), 3.40 (1H, d, J = 15.0 Hz), 3.27 (1H, d, J = 15.0 Hz), 3.26 (1H, d, J = 16.8 Hz), 3.07 (1H, d, J = 16.8 Hz), 2.63 (1H, d, J = 13.2 Hz), 2.07 (1H, dd, J = 8.7 Hz, 13.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.09, 161.45, 160.67, 159.73, 159.39, 159.38, 157.60, 156.42, 156.31, 124.22, 120.06, 108.47, 103.89, 102.33, 94.91, 92.05, 91.95, 91.83, 89.00, 88.63, 55.85, 55.48, 45.35, 42.02, 36.77, 30.52. IR (KBr) ν = 3676–3153 (br), 2941, 2841, 2081, 1740, 1613, 1453 cm^{-1}. ESI-HRMS m/z calcd for $C_{30}H_{32}NaO_{10}$ $[M+Na]^+$ 575.1888, found 575.1876.
12. Crystallographic data (excluding structure factors) for the structures of **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 768120. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).