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Tetrahedron Letters
Tetrahedron Letters 47 (2006) 7711–7713

Total synthesis of aspidophytine

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Received 4 August 2006; revised 23 August 2006; accepted 25 August 2006
Available online 18 September 2006

Abstract—A total synthesis of aspidophytine was accomplished by employing a newly developed strategy for the enantiospecific syntheses of aspidosperma alkaloids. The key steps involve a novel ketene-lactonization reaction of a chiral vinyl sulfoxide (Marino annulation reaction) to set up the chiral quaternary carbon center, and a tandem Michael addition-alkylation reaction sequence to form the polycyclic core structure.

Recently, we reported a total synthesis of (+)-aspidospermidine **1** via the Marino annulation reaction, and demonstrated a new, efficient and highly enantiospecific synthetic strategy for the syntheses of aspidosperma alkaloids.[1,2] In order to further evaluate this new synthetic strategy and exploit the power of Marino annulation reaction for the formation of chiral quaternary carbon centers, we initiated the research toward the construction of a more complex structure aspidophytine **2**.[3] Here, we describe a completed total synthesis of aspidophytine **2**, a potential synthetic precursor for haplophytine **3** (Fig. 1).

Haplophytine **3** is one of the active chemical components of '*La hierba de la cucaracha*', an anticockroach/insecticidal powder extracted from the dried leaves of the plant *Haplophyton Cimicidium*. The degradative product aspidophytine **2** was isolated after haplophytine **3** was subjected to strong proteolytic conditions. Two asymmetric syntheses of aspidophytine **2** were completed by Corey's group in 1999 and by Fukuyama' group in 2003, respectively.[4] Most recently, Padwa's group also successfully synthesized aspidophytine **2** in its racemic form[5].

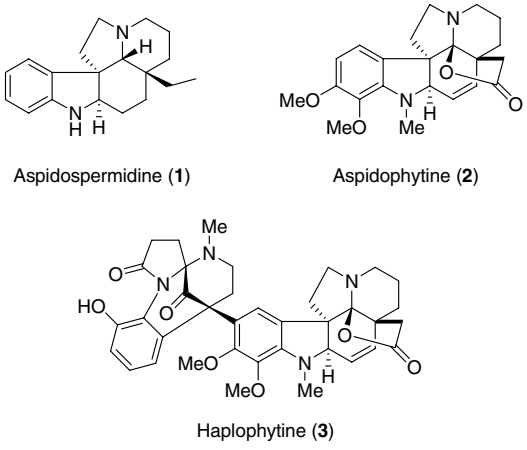

Figure 1.

Our synthesis started with the preparation of a chiral alkynylsulfoxide **9**. A process of dianion alkylation[6] with benzyl 2-iodoethyl ether **4**[7] converted β-ketoester **5** to an exclusively γ-alkylated product **6**. Compound **6** was then β-alkylated with propargyl bromide, followed by decarboxylation, ketal formation to give alkyne **8** in 63% yield over three steps. Treatment of **8** with *n*-BuLi and then $MgBr_2$ formed an alkynyl Grignard reagent, which was added to Evans' chiral *N*-sulfinyloxazolidinone **A**[8] to form chiral alkynyl sulfoxide **9** in 78% yield (Scheme 1).

Once the chiral alkynyl **9** was in hand, it was coupled with an N-protected dimethoxy aniline **10**[9] by being added to the cuprate reagent formed from transmetallation of the ortholithiated intermediate derived from **10**

Keywords: Aspidophytine; Haplophytine; Aspidosperma alkaloids; Quaternary carbon center; Chiral vinyl sulfoxide; Ketene-lactonization; Marino annulation reaction; Enantiospecific; Tandem.
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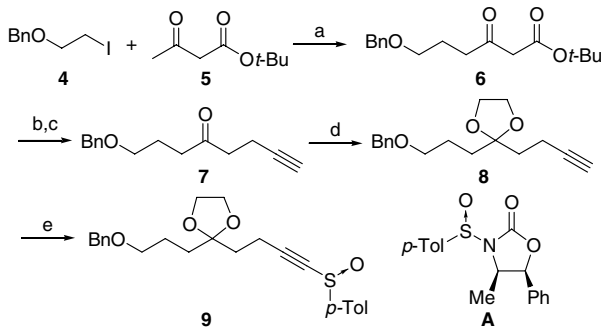
doi:10.1016/j.tetlet.2006.08.115

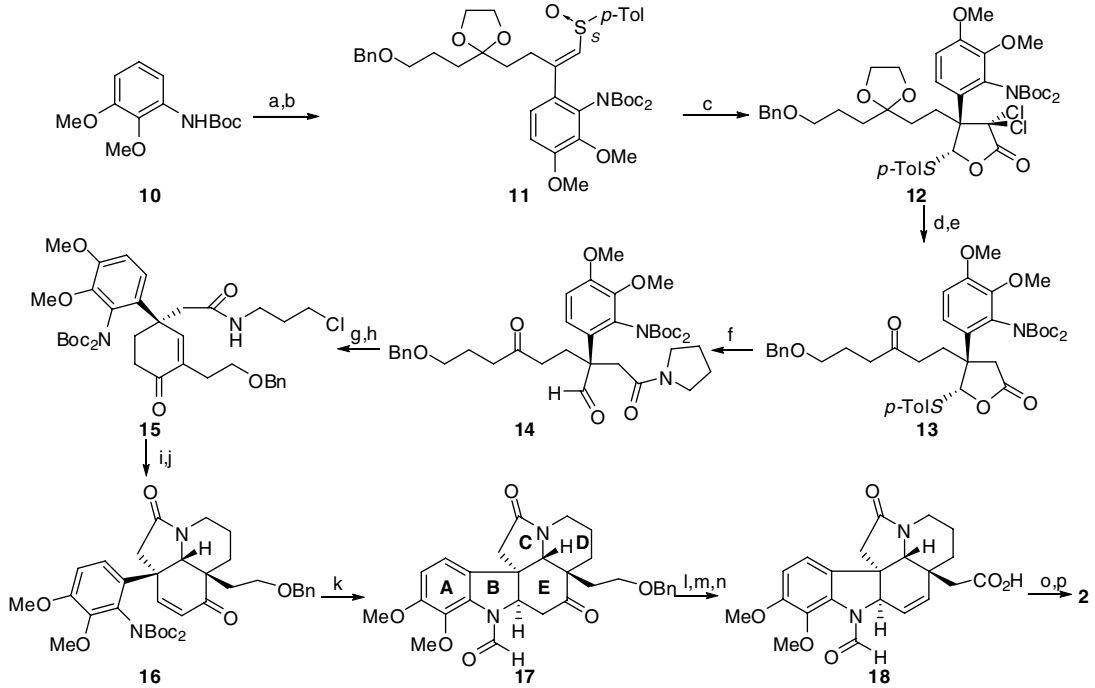


Scheme 1. Reagents and conditions: (a) THF, NaH, 0 °C, *n*-BuLi, −78 °C, 83%. (b) NaOEt/EtOH, 3 equiv proparagyl bromide; (c) TsOH, benzene, reflux; (d) ethylene glycol, TsOH, benzene, reflux, 63% over three steps; (e) THF, *n*-BuLi, −78 °C then $MgBr_2$, 0 °C, then **A**, (4*R*, 5*S*)-4-methyl-5-phenyl-3-[(*R*)-*p*-tolysulfinyl]-2-isoxazolidinone, −78 °C, 78%.

with $CuBr{\cdot}Me_2S$. To the adduct, a second Boc group was introduced and a stereodefined chiral vinyl sulfoxide **11** was obtained. Subsequently, the reaction of this vinyl sulfoxide with the in situ formed dichloroketene from trichloroacetyl chloride and a zinc-copper reagent (Marino annulation reaction), delivered lactone **12** with a chiral quaternary carbon center in 84% yield. After dechlorination with $Et_3B/n\text{-}Bu_3SnH$ and the deprotection of the ketal, lactone **13** was generated. The lactone **13** was then opened by pyrrolidine to afford aldehyde **14** in 86% yield. A subsequent intramolecular aldol condensation process set up the nascent C-ring of aspidophytine, concurrently the pyrrolidine amide was hydrolyzed. By employing the mixed anhydride protocol, the so formed carboxylic acid was linked to 3-chloropropylamine to give amide **15** in 64% over two steps. A tandem conjugate addition-intramolecular alkylation reaction sequence was triggered once amide **15** came into contact with NaH, forming what will become the C- and D-rings of aspidophytine. The product was further oxidized through a modified Saegusa reaction to furnish tricyclic enone **16**. When enone **16** was stirred in formic acid overnight, multiple events occurred and a rather advanced intermediate, pentacyclic structure **17** was obtained in 90% yield. These events included the removal of two Boc groups, N-formylation and an intramolecular Michael addition reaction to form the B-ring. A Stille reduction reaction[4,10] was then applied to transform the ketone functionality in compound **17** to a double bond, and carboxylic acid **18** was secured after the side chain primary alcohol was deprotected and oxidized[11] (Scheme 2).

Finally, the two amide groups in structure **18** were reduced by the combination of Meerwein's salt with $NaBH_4$,[12] and the product was further treated sequentially by $K_3Fe(CN)_6$ and $NaHCO_3$ (oxidative lactone formation conditions invented by Corey) to give aspidophytine **2** in 40% yield over two steps. The spectroscopic data and optical rotation of **2** were consistent with those reported.[4,5]

In summary, we completed an enantiospecific total synthesis of aspidophytine **2**. The synthetic success with both aspidospermidine **1** and aspidophytine **2** further



Scheme 2. Reagents and conditions: (a) 2 equiv *t*-BuLi, 1 equiv $CuBr{\cdot}Me_2S$, then **9**, THF, −78 °C, 75%; (b) MeLi, Boc_2O, THF, −78 °C, 85%. (c) Zn(Cu), Cl_3CCOCl, THF, −45 °C, 84%; (d) $n\text{-}Bu_3SnH$, cat. Et_3B, benzene, reflux, 87%; (e) Acetone, cat. *p*-TsOH, rt, 85%; (f) Pyrrolidine, benzene, rt, 80%; (g) Pyrrolidine, *i*-PrOH, 33% aq AcOH; (h) *i*-BuOCOCl, Et_3N, 3-chloropropylamine hydrochloride, THF, 0 °C, 67%, (two steps); (i) NaH, DMF, 0 °C, 88%; (j) KHMDS, TMSCl, THF, −78 °C, then $Pd(OAc)_2/O_2$, DMSO, 60 °C, 85%; (k) HCO_2H, rt, 90%; (l) THF, −78 °C, KHMDS, $PhN(Tf)_2$, 85%; $Pd(PPh_3)_4$, $(Bu)_3SnH$, 85%; (m) Pd/C, H_2, CH_3OH, 92%; (n) PDC, wet DMF, 75%; (o) Et_3OBF_4, CH_2Cl_2 then $NaBH_4$, EtOH; (p) $K_3Fe(CN)_6$, *t*-BuOH/H_2O then $NaHCO_3$, 40% (two steps).

validated our newly developed strategy for the enantiospecific syntheses of aspidosperma alkaloids.

Acknowledgments

The research on the syntheses of aspidosperma alkaloids was originally supported by NIH (CA22237). G.C. thanks Chemistry Department, University of Michigan, for the financial support.

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