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Total Synthesis of (−)-L-755,807: Establishment of Relative and Absolute Configurations

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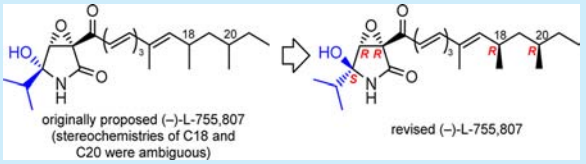
Supporting Information

ABSTRACT: The first total synthesis of (−)-L-755,807 and its three stereoisomers was achieved by our Horner−Wadsworth−Emmons reaction for stereoselective formation of trisubstituted olefins, highly diastereoselective Darzens condensation to construct the epoxy-γ-lactam ring, and late-stage coupling of the ring and side-chain segments for efficient convergent synthesis. This synthesis shows that the originally proposed structure of natural (−)-L-755,807 was incorrect and establishes its relative and absolute configurations.



Alzheimer disease (AD) is an incurable neurodegenerative disorder. Acetylcholinesterase inhibitors, such as donepezil (Aricept), galanthamine (Reminyl), rivastigmine (Exelon), and tacrine (Cognex), are used to treat AD.[1] These drugs improve AD symptoms, although they do not cure the disease. Therefore, researchers are looking for seed compounds with new mechanisms of action from natural sources.[2] Over the past 20 years, several natural products containing an epoxy-γ-lactam ring have been isolated.[3−6] Epolactaene[3] and a fusarin C derivative[4] induce neurite outgrowth and are regarded as potential therapeutic agents for AD (Figure 1).[7] Therefore, natural products containing an epoxy-γ-lactam ring have attracted intense interest from chemists and biologists.

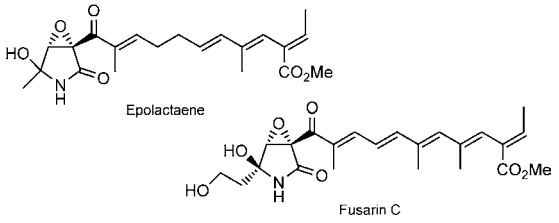


Figure 1. Structures of epolactaene and fusarin C.

L-755,807 (original proposed structure **1**, Figure 2) was isolated in 1996 by Merck from an endophytic fungus, *Microsphaeropsis* sp., and was identified as a bradykinin binding inhibitor with an IC_{50} of 71 μM.[8] Antagonistic bradykinin receptor activity is related to inflammatory diseases and is also effective for treating neurodegenerative diseases such as AD.[9,10] Additionally, L-755,807 (**1**) may exhibit neurite outgrowth activity because it contains an epoxy-γ-lactam ring, and **1** may be a candidate seed compound for developing drugs to treat dementia caused by AD.

L-755,807 (**1**) consists of an epoxy-γ-lactam moiety, which contains three contiguous stereocenters, and a conjugated tetraene moiety, which contains two stereocenters. The gross

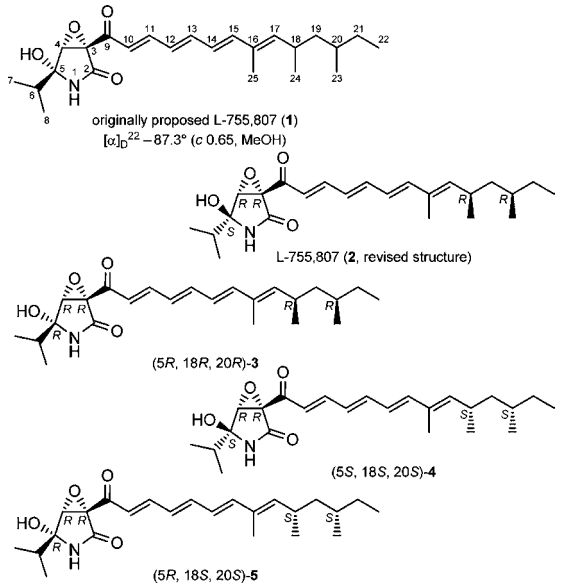


Figure 2. Structures of originally proposed L-755,807 (**1**) and synthetic compounds **2**−**5**.

structure of **1** was deduced by an extensive NMR study, and the relative configuration of the epoxy-γ-lactam moiety was confirmed by the NOESY correlation between H4 and H7/H8.[8] However, the stereochemistries of C18 and C20 in the side chain remain ambiguous. Although L-755,807 (**1**) is an attractive synthetic target because of its molecular structure and promising biological activity, its total synthesis has not been reported.[11,12] In this work, we have accomplished the first asymmetric total synthesis of L-755,807 (**2**, revised structure) and its three stereoisomers **3**, **4**, and **5** with different configurations at C5, C18, and C20, and we describe the

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reassignment of the relative and absolute configurations of L-755,807.

Prior to this work, two research groups independently reported synthetic studies and structural elucidation of **1** (Figure 3).[11] In 1998, Clark and Ellard reported the relative

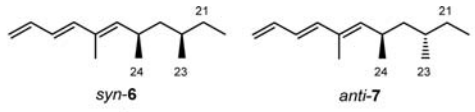
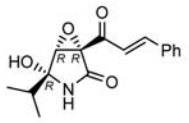


Table ^{13}C NMR shifts of L-755,807, *syn*-**6**, and *anti*-**7**

position	L-755,807	*syn*-**6**	*anti*-**7**
C21	30.4	30.4	29.5
C23	19.2	19.1	19.5
C24	21.4	21.6	20.8



model compound **8**

$[\alpha]_D^{22}$ −200° (*c* 0.60, MeOH)

Figure 3. Model compounds for L-755,807.

configuration of the side-chain moiety in **1** (Figure 3).[11a] They prepared two model compounds with side-chain trienes, *syn*-**6** and *anti*-**7**. Comparison of the ^{13}C NMR spectra of *syn*-**6** and *anti*-**7** with the natural product indicated that the relative configuration of the C23 and C24 methyl groups of L-755,807 (**1**) is *syn*, and these results were supported by MM3/SOS-DFPT/IGLO calculations.[13]

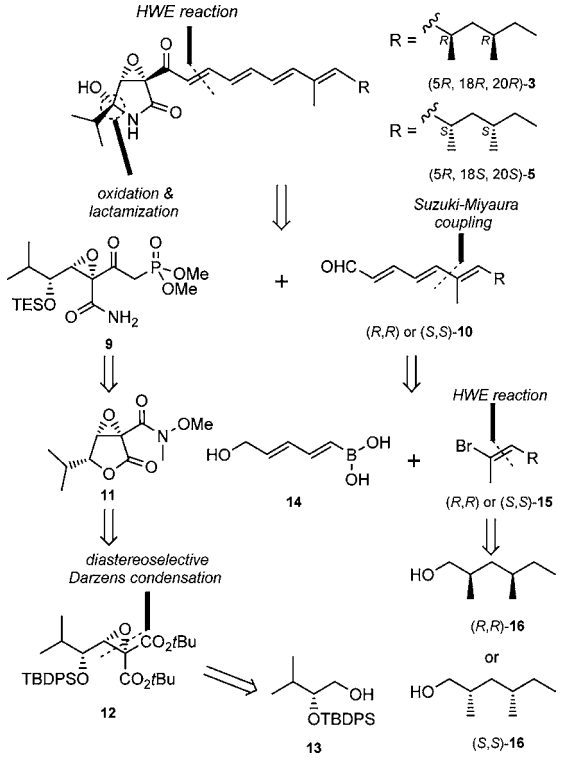
We previously synthesized model epoxy-γ-lactam **8** (Figure 3).[11b] Both ^{1}H and ^{13}C NMR spectra of **8** are in good agreement with the natural product spectra, and the optical rotation of **8** had the same sign as **1**. Accordingly, the absolute configuration of the epoxy-γ-lactam ring in **1** was deduced as shown in Figure 2.

Based on these findings, we planned to synthesize putative structures **3** and **5** (Figure 2) to elucidate the correct structure of natural L-755,807.

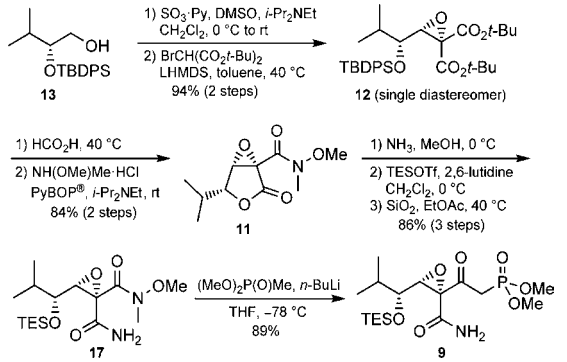
Our convergent retrosynthetic strategy for **3** and **5** is outlined in Scheme 1. To make these two compounds efficiently, we envisioned the late-stage coupling of phosphonate **9** with conjugated triene aldehydes (*R*,*R*)- and (*S*,*S*)-**10**. Phosphonate **9** could be derived from epoxide **12** via lactone **11**. Epoxide **12** can be retrosynthetically converted to alcohol **13** by diastereoselective Darzens condensation using bromo di-*tert*-butyl malonate.[14,15] Conjugated triene aldehydes (*R*,*R*)- and (*S*,*S*)-**10** would be prepared from boronic acid **14**[16] and (*E*)-vinyl bromides (*R*,*R*)- and (*S*,*S*)-**15**, respectively, by Suzuki−Miyaura coupling. To make (*R*,*R*)- and (*S*,*S*)-**15** from known alcohols (*R*,*R*)- and (*S*,*S*)-**16**, respectively, we used the Horner−Wadsworth−Emmons (HWE) reaction[17] and subsequent reduction of the ester to a methyl group.

Alcohol **13**, which was prepared from D-valine in four steps by following a known procedure,[11b,18] was converted to an aldehyde by Parikh−Doering oxidation (Scheme 2). The aldehyde can be converted to epoxide **12** by our previous method, consisting of a stereoselective aldol reaction, TMS protection, iodination, and epoxide formation, which was accompanied by undesirable β-elimination.[11b,18] To decrease the number of reaction steps and avoid the side reaction, we developed a diastereoselective Darzens condensation.[14] Thus, the reaction of an aldehyde derived from oxidation of alcohol

Scheme 1. Retrosynthetic Analysis



Scheme 2. Synthesis of Epoxy-γ-lactam Precursor Segment 9



13 with bromo di-*tert*-butyl malonate pretreated with lithium bis(trimethylsilyl)amide (LHMDS) proceeded cleanly to give only desired diastereomer **12** in high yield. Interestingly, the Darzens reaction proceeded via *syn*-selective addition of di-*tert*-butyl malonate to the aldehyde through an *anti*-Felkin−Anh transition state,[14] whereas a related aldol reaction in our previous study showed high *anti*-stereoselectivity.[11b,18] Epoxide **12** was treated with formic acid to remove the silyl group and form mono acid via spontaneous lactonization. The carboxylic acid was converted to corresponding Weinreb amide **11** with (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N*,*O*-dimethylhydroxyamine, and *i*-Pr_2NEt in 84% yield from **12**. Treatment of Weinreb amide **11** with 7 N NH_3 in methanol and protection of the resultant secondary alcohol with triethylsilyl (TES) group afforded **17**. In this step, bis-TES ether formation of both the hydroxy and amide groups was observed by TLC analysis. When the crude product was heated with silica gel in EtOAc at 40 °C, cleavage of the TES ether in the amide group occurred to give **17** in 86% yield.[19] Amide **17** was then reacted with dimethyl methyl-

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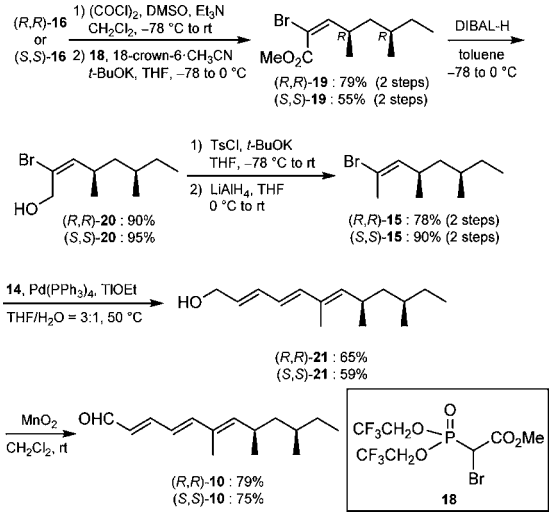
phosphonate pretreated with *n*-BuLi at −78 °C to deliver phosphonate **9** in 89% yield.

The side-chain segments (*R*,*R*)- and (*S*,*S*)-**10** were prepared as follows (Scheme 3). The HWE reaction using methyl 2-

Scheme 3. Synthesis of Side-Chain Segments (*R*,*R*)- and (*S*,*S*)-10

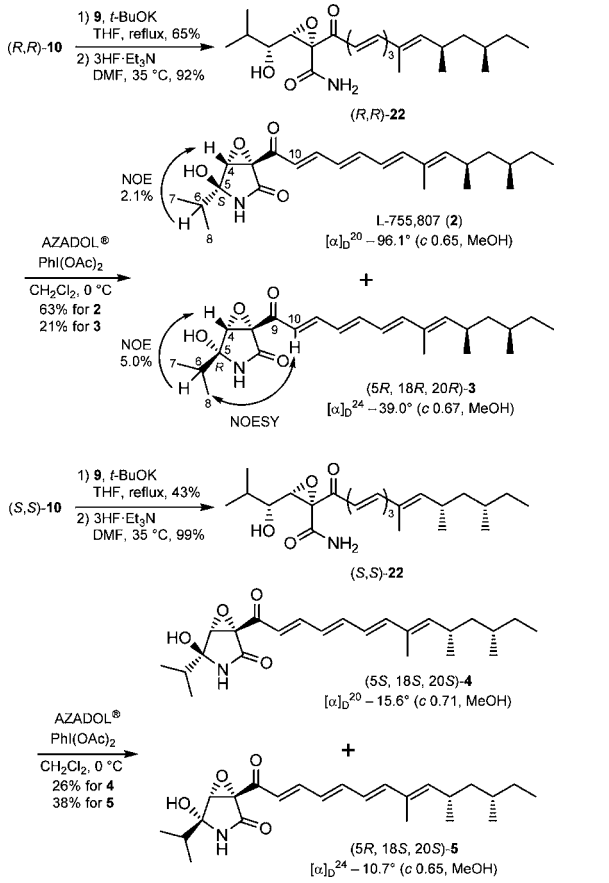


(bis(2,2,2-trifluoroethoxy)phosphoryl)-2-bromoacetate (**18**)[17] and aldehydes, which were prepared from known alcohols (*R*,*R*)- and (*S*,*S*)-**16**[20] by Swern oxidation, proceeded with complete stereoselectivity to give (*E*)-α-bromoacrylate derivatives (*R*,*R*)- and (*S*,*S*)-**19**. The ester group of (*R*,*R*)- and (*S*,*S*)-**19** was then reduced to a methyl group by DIBAL-H reduction, tosylation, and $LiAlH_4$ reduction to give vinyl bromides (*R*,*R*)- and (*S*,*S*)-**15**. The Suzuki−Miyaura coupling[21] of vinyl bromides (*R*,*R*)- and (*S*,*S*)-**15** and boronic acid **14**[16] was followed by MnO_2 oxidation to yield side-chain segments (*R*,*R*)- and (*S*,*S*)-**10** in 79% and 75% yield, respectively.

With all segments in hand, our attention turned to coupling of the epoxy-γ-lactam ring and the side-chain segments by the HWE reaction (Scheme 4). We found that a high concentration was essential to produce a good yield in this reaction, and thus, the crucial HWE reaction of aldehydes (*R*,*R*)- and (*S*,*S*)-**10** with phosphonate **9** afforded the desired coupling products in 65% and 43% yield, respectively. Coupling products were treated with 3HF·Et_3N to yield alcohols (*R*,*R*)- and (*S*,*S*)-**22**. Finally, secondary alcohol (*R*,*R*)-**22** was oxidized to furnish **2** and **3** with concomitant hemiaminal formation.[22] The crude product in this reaction included compounds **2** and **3** in the ratio of 1.3:1, as judged by ^1H NMR. Repetition of column chromatography gave **2** and **3** in 63% and 21% yield, respectively. Oxidation of (*S*,*S*)-**22** similarly provided **4** and **5** in 26% and 38% yield, respectively. In this oxidation, only the oxidant AZADOL gave the desired products.[23]

We initially compared the ^1H and ^{13}C NMR spectra of synthetic compounds **2**−**5** with those for natural L-755,807, which indicated that **2** or **4** was the most likely match for L-755,807. The difference between **2** and **4** in the NMR spectra was unclear. Measurement of the optical rotations of **2** and **4** allowed us to determine the structure of L-755,807; the value of **2** ($[\alpha]_D^{20}$ − 96.1 (*c* 0.65, MeOH)) was most similar to that of the natural product ($[\alpha]_D^{22}$ −87.3 (*c* 0.65, MeOH)), whereas **4** had a comparatively small absolute value ($[\alpha]_D^{24}$ = −15.6 (*c* 0.71, MeOH)). Hence, we concluded that L-755,807 was

Scheme 4. Completion of the Total Synthesis of L-755,807 (2) and Its Stereoisomers 3−5



compound **2** and confirmed the NOESY and NOE correlations to verify the stereostructure of synthetic **2**. The Merck group assigned the relative configuration of the lactam ring in **1** (Figure 1) by NOESY correlations between H4 and H7/H8.[8] However, we were puzzled after the NOESY experiment because both diastereomers **2** and **3** showed the same correlations. Further analysis of NOE experiments solved the stereochemical problem; a strong NOE enhancement (5.0%) of H4 with H6 in **3** was observed relative to compound **2** (2.1%), which meant that H4 and the isopropyl group are *trans* in **2** and *cis* in **3**. An additional NOESY correlation between H8 (or H7) and H10 in **3** supported this result.[24,25] Finally, we can revise the incorrect structure of **1** reported by Merck and establish the relative and absolute configurations of (−)-L-755,807 (**2**, revised structure).

In conclusion, we have accomplished the first total synthesis of (−)-L-755,807 (**2**, revised structure) and its stereoisomers (**3**, **4**, and **5**). This study allowed us to revise the structure proposed by Merck and to establish the relative and absolute configurations of natural (−)-L-755,807. Our synthetic strategy featured a highly diastreoselective Darzens condensation[14] for constructing the epoxy-γ-lactam ring, a highly stereoselective construction of the trisubstituted olefin moiety via (*E*)-α-bromoacrylate by use of our reagent **18**, and an HWE reaction to connect the ring and side-chain segments; this strategy can be used in the synthesis of other natural products such as epolactaene and fusarin C. We intend to synthesize various compounds based on (−)-L-755,807 by using this synthetic strategy and to determine the structure−neurite outgrowth

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activity relationships to develop a therapeutic drug candidate for AD.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00758.

Copies of ^{1}H and ^{13}C NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(24) In addition to NOESY and NOE correlations, we also noticed that steric compression shifts were observed at C6 in **2**, and C7/C8 and C9 in **3** on ^{13}C NMR spectra, which should support the structures of compounds **2** and **3**.

(25) Since the NMR spectra of isomers **4** and **5** are similar to those of **2** and **3**, respectively, the stereostructures of **4** and **5** were deduced as depicted in Scheme 4.

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