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Synthetic study on L-755,807: asymmetric synthesis of the epoxy-ɣ-lactam moiety

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Abstract

The optically active epoxy-ɣ-lactam moiety (−)-**4** of the B_2 selective bradykinin inhibitor L-755,807 **1** was prepared from (*S*)-aldehyde **7** via an *anti* selective aldol reaction as the key step. © 1999 Published by Elsevier Science Ltd. All rights reserved.

There has been increasing interest in naturally occurring epoxy-ɣ-lactam compounds due to their important biological activities.[1–3] For example, L-755,807 **1** was isolated by a Merck research group[1] from the endophytic *Microsphaeropsis* sp. as a new non-peptide bradykinin binding inhibitor[4,5] to bind to a cloned human B_2 receptor (Fig. 1).

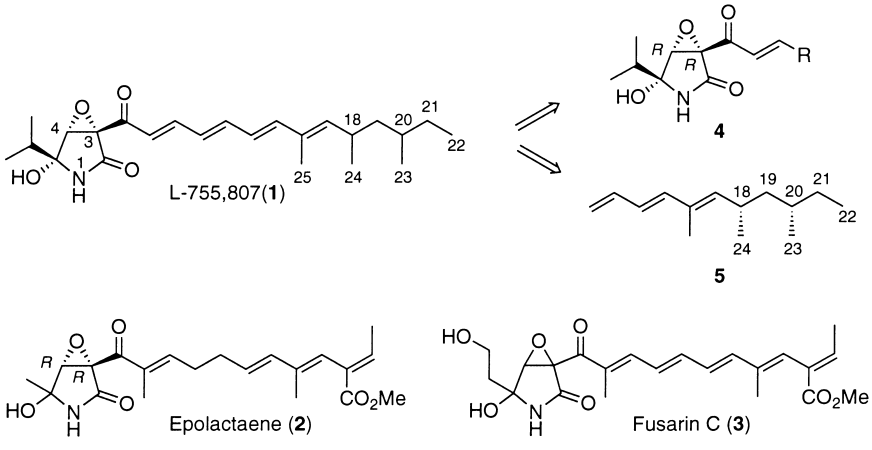

Figure 1.

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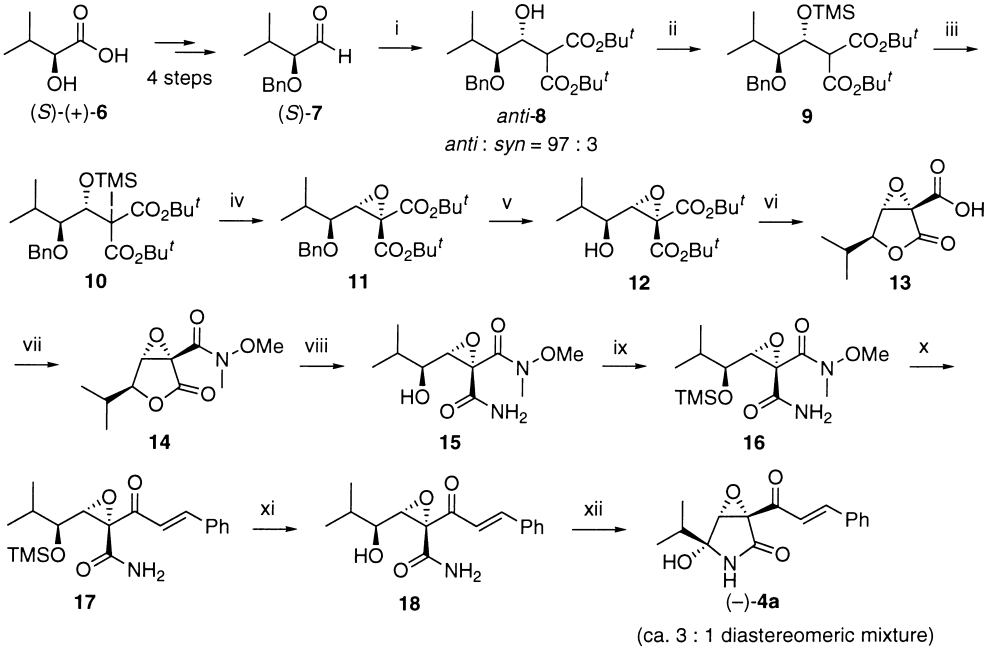
Epolactaene **2** was isolated from the culture broth of a marine microbe and showed potent neurite outgrowth activity,[2] and fusarin C **3** was isolated from fungus as a mutagenic agent.[3a] Additionally, fusarin-related compounds were used to show neurite outgrowth activity similar to that shown in **2**.[3b]

Among these compounds, epolactaene **2** was the only one to be synthesized and for which absolute stereochemistry was determined.[6] Extensive spectroscopic studies elucidated every aspect of the structure of **1** except for the absolute stereochemistry of the epoxy-ɣ-lactam part and the relative configuration of two methyl groups on the side chain (C23 and C24).[1] Recently, Clark and Ellard synthesized the *syn*- and *anti*-**5** corresponding C12–C25 fragments of the side chain of **1**.[7] By comparing the calculated[8] and observed NMR spectra between *syn*-**5**, *anti*-**5**, and **1**, they deduced that the relative configuration of the C23 and C24 methyl groups is *syn*. However, construction of the optically active epoxy-ɣ-lactam moiety still remains to be performed. In this paper we wish to report on the asymmetric synthesis of the epoxy-ɣ-lactam part **4** as a model compound.

We postulated that both **1** and **2** have the same absolute configuration for the epoxy-ɣ-lactam part since both may be biosynthesized through the same pathway starting from amino acid precursors. Therefore, (3*R*,4*R*)-epoxy lactam **4a** (R=Ph) was selected for the target model of **1**. According to our previously reported asymmetric total synthesis of **2** via a *syn* selective aldol reaction,[6a] **4a** was synthesized in 12 steps from the known (*S*)-aldehyde **7** as shown in Scheme 1. This time, the *anti* selective aldol reaction[9] between racemic α-alkoxy aldehyde and malonate ester enolate was applied to optically active aldehyde (*S*)-**7**.



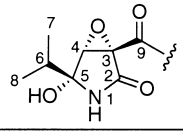
Scheme 1. Reagents and conditions: i, $ZnCl_2$, $LiCH(CO_2Bu^t)_2$, THF, −78°C (75%); ii, Me_3SiOTf, 2,6-lutidine, CH_2Cl_2, 0°C (70%); iii, LiHMDS, THF, −46°C to room temp. then I_2, THF, −46°C; iv, TBAF, THF, −46°C to room temp. (64% from 9); v, $Pd(OH)_2$, H_2, MeOH, 50°C (93%); vi, HCO_2H, room temp.; vii, Me(MeO)NH·HCl, PyBOP®, *i*-Pr_2EtN, CH_2Cl_2, 0°C (84% from **12**); viii, NH_3, MeOH, room temp.; ix, Me_3SiOTf, 2,6-lutidine, CH_2Cl_2, room temp. (73% from **14**); x, (*E*)-BrCH=CHPh, *t*-BuLi, THF, −78°C (80%); xi, 3HF·Et_3N, DMF, room temp. (82%); xii, Dess–Martin reagent, CH_2Cl_2, room temp. then SiO_2, room temp. (89%)

The aldehyde (*S*)-**7**[10] was readily prepared from commercially available (*S*)-(+)-**6** {$[\alpha]_D^{22}$ +18 (*c* 1, $CHCl_3$)} in four steps according to the reported procedure.[11] An aldol reaction between aldehyde

(*S*)-**7** and lithium enolate of di-*tert*-butyl malonate in the presence of zinc chloride in THF at −78°C proceeded with high diastereoselectivity (75% yield as a 97:3 ratio of isomers) to give desired isomer *anti*-**8**, which was easily separable by silica gel flash column chromatography. The pure *anti*-**8** was treated with trimethylsilyltriflate (TMSOTf) in CH_2Cl_2 to give **9** in 70% yield. The *O*-TMS derivative **9** was converted to the anion by treatment with lithium hexamethyldisilazide (LiHMDS) in THF followed by iodination to give α-iodo malonate derivative **10**. Desilylation of iodide **10** with tetrabutylammonium fluoride (TBAF) resulted in cyclization to produce epoxide **11** in 64% yield (from **9**). Cleavage of the *O*-benzyl group by $Pd(OH)_2$ catalyzed hydration provided epoxyalcohol **12** in 93% yield. Treatment of **12** with formic acid afforded lactone carboxylic acid **13**, which was transformed to the Weinreb amide **14** using (1*H*-benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP®)[12] and *N*,*O*-dimethylhydroxylamine in 84% yield from **12**. Ammonolysis of **14** with concentrated ammonia in methanol yielded amide **15** followed by protection of the generated secondary alcohol with the trimethylsilyl group to give **16** (73% yield from **14**). Reaction of the Weinreb amide **16** with 5 equiv. of vinyllithium generated in situ by lithiation of commercially available 2-bromostyrene (*E*:*Z*=ca. 5:1) with *tert*-butyllithium afforded (*E*)-α,β-unsaturated ketone **17** in 80% yield. The stereochemistry of the double bond of **17** was confirmed by the large coupling constant (J=16 Hz) observed in the ^{1}H NMR spectrum. Deprotection of the silyl group with triethylamine trihydrofluoride furnished alcohol **18** in 82% yield. Finally, Dess–Martin oxidation of **18** provided the ketone which underwent lactamization with silica gel to afford (−)-**4a** {$[\alpha]_D^{22}$=−200 (*c* 0.60, MeOH)} in 89% yield, as an inseparable ca. 3:1 diastereomeric mixture at C5.

Table 1 shows a comparison of the ^{1}H and ^{13}C NMR spectra of (−)-**4a** with that of L-755,807 **1** for the lactam moiety. There is good agreement between them. This result suggests that the major isomer of (−)-**4a** has the same relative configuration with L-755,807 **1**. The antipode of (−)-**4a** could be synthesized from commercially available (*R*)-(−)-**6** through the same procedure. The obtained result suggests that fusarin C **3** and its related compounds belonging to the epoxy-γ-lactam family could be synthesized from the appropriate starting materials. Further work towards the total synthesis of **1** is underway.

Table 1
^{13}C (100 MHz) and ^{1}H (400 MHz) chemical shifts for **1** and **4a** in CH_2Cl_2



	L-755,807 (**1**)[a]		**4a**[b]	
Position	δC	δH	δC	δH
1		8.03 (br s)		7.63(br s)
2	169.9		169.5	
3	60.9		61.1	
4	65.8	4.28 (d, *J* = 2.4 Hz)	65.7	4.34 (d, *J* = 1.5 Hz)
5	87.6		87.6	
6	33.3	2.06 (m)	33.8	2.09 (m)
7	17.8	1.16 (d, *J* = 6.8 Hz)	17.9	1.18 (d, *J* = 6.9 Hz)
8	16.2	1.11 (d, *J* = 6.8 Hz)	16.3	1.12 (d, *J* = 6.8 Hz)
9	189.7		190.0	

[a] Ref 1. [b] Major isomer.

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