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Synthesis of the C9-C25 fragment of L-755,807. Evidence for the relative configuration of the side-chain.

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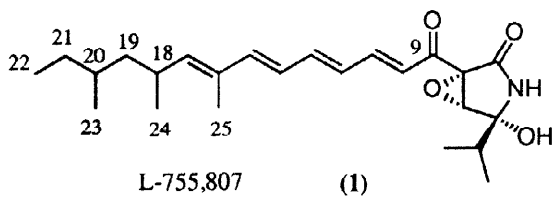
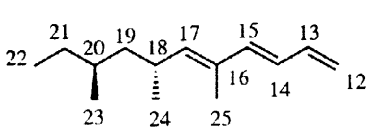
Abstract: Both diastereomers of the side-chain model (**2**) and C9-C25 fragment (**3**) of the B2 selective Bradykinin inhibitor L-755,807 have been prepared and their ^{13}C data compared to those of the natural product and those theoretically predicted by a combination of molecular mechanics and SOS-DFPT/IGLO calculations. The data suggest that the relative configuration of the C23 and C24 methyl groups is *syn*.

Keywords: Stereochemistry; polyenes; natural products; coupling reactions.

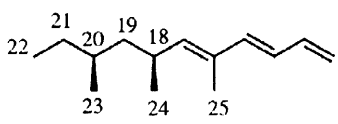


L-755,807 (**1**)

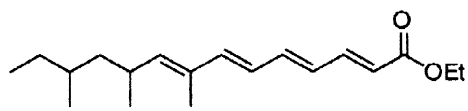
In 1996 a new non-peptide bradykinin antagonist (**1**) was isolated by Lam.[1] They reported an IC_{50} value of 71μM in binding to a cloned human B2 receptor. They elucidated the structure of (**1**) by detailed spectroscopic studies but were unable to identify the relative stereochemistry of the two methyl groups on the side-chain (C23, C24). By comparing theoretically calculated ^{13}C chemical shifts of the C21, C23 and C24 carbons of the *anti* (**2a**) and *syn* (**2s**) trienes with the natural product Frenking *et al*[2] recently predicted that the methyl groups had a *syn* relationship. The ^{13}C NMR chemical shifts were calculated by a combination of molecular mechanics (MM3) and density functional (SOS-DFPT/IGLO) methods, followed by Boltzmann averaging of the calculated chemical shifts. We wish to report the synthesis of both diastereomers of (**2**) as well as the complete side-chain (**3**) in order to a) determine the accuracy of the theoretical method reported for the calculation of the ^{13}C NMR shifts of 1,3-dimethylated hydrocarbons and b) to gain further evidence into the relative stereochemistry of the side-chain of L755,807.



(**2a**)



(**2s**)



(**3**)

The atom numbering of (**1**) is also used for the model compounds (**2**) and (**3**).

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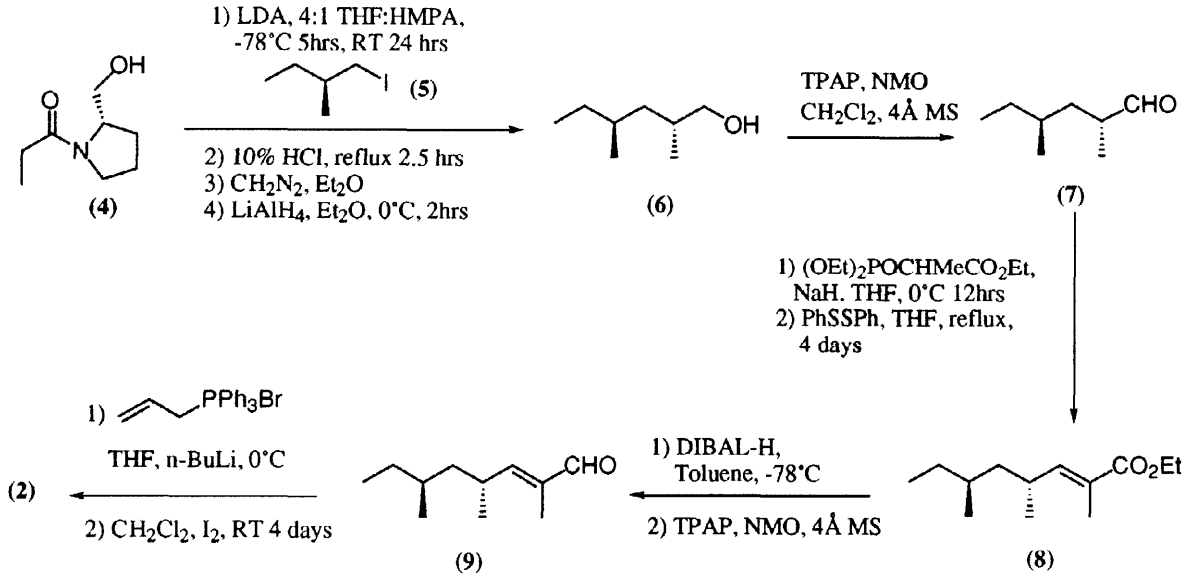
Synthesis of the triene models (2a) and (2s).

The known *anti* alcohol (**6**)[3]was prepared by modification of the literature procedure using the Evans auxiliary (**4**)[4]. Hence alkylation of (S)-hydroxymethyl pyrrolidinone (**4**) with readily available (S)-(+)-1-iodo-2-methylbutane (**5**)[5] furnished 2-(hydroxymethyl)-1-(2-,4-dimethylhexanoyl)pyrrolidine as 9:1 ratio of *anti:syn* diastereomers (as determined by GC).

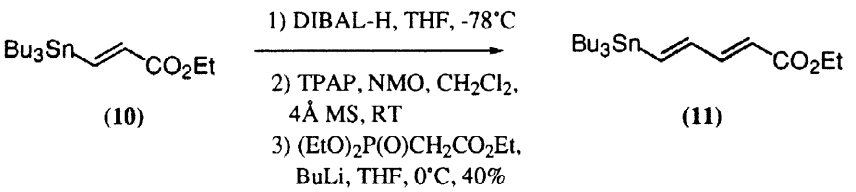


(Scheme 1)

Removal of the amide auxiliary using 10% HCl, esterification of the resulting acid with diazomethane followed by $LiAlH_4$ reduction furnished (2R,4S)-(**6**) in 34% overall yield from (**4**). Oxidation using TPAP[6] and N-methylmorpholine N-oxide furnished the desired aldehyde (**7**) in quantitative yield. Horner-Emmons homologation of this unstable aldehyde (**7**) using triethyl 2-phosphonopropionate and NaH in THF at room temperature gave the tri-substituted ester (**8**) as a 1:3 mixture of *(E):(Z)*-isomers. This mixture was isomerised to give the *(E)*-isomer predominantly by heating with a catalytic amount of diphenyldisulphide for 4 days in dry THF. Reduction of the ester (**8**) with DIBAL-H followed by oxidation of the resulting alcohol with TPAP/NMO furnished the unsaturated aldehyde (**9**) in 21% yield from alcohol (**6**). Wittig reaction using allyltriphenylphosphonium bromide and butyl lithium furnished the model triene (**2a**) as a 8:3 mixture of 14-*(E)*:14-*(Z)* isomers (L-755,807 numbering). The desired *(E,E,E)*-triene (**2a**) was isolated after isomerisation with iodine at room temperature. Repetition of the above synthesis with a 1.5:1 mixture of the *syn/anti* aldehyde (**7**)[7] allowed the NMR data for both the *anti* and *syn* diastereomers to be compared to the published theoretical predictions and to those of the natural product.

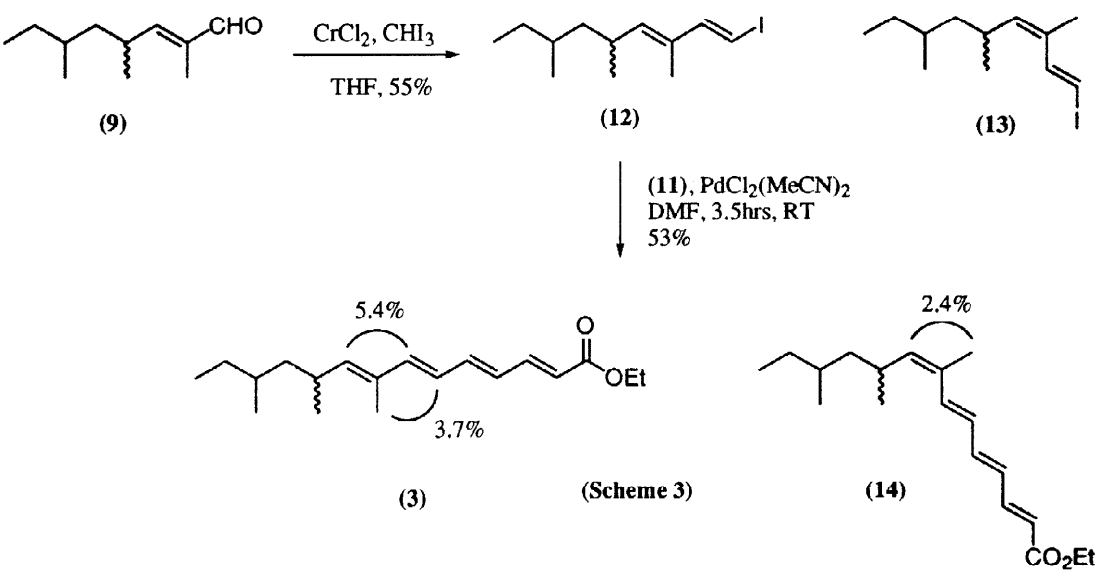
Synthesis of both diastereomers of the C9-C25 fragment of L755,807.

As part of our strategy towards the synthesis of L-755,807 we required the C9-C25 side-chain fragment. In order to gain valuable evidence into the side-chain stereochemistry we again prepared both diastereomers in order to compare the ^{13}C NMR data with those of the natural product. Our strategy towards the *(E,E,E,E)*-tetraene (**3**) involved a palladium mediated coupling of the vinyl iodide (**12**) with the stannane (**11**). The stannane (**11**) was easily prepared from the known ester (**10**)[8] in 40% yield over three steps while the desired vinyl iodide was prepared by a Takai homologation[9] of the unsaturated aldehyde (**9**) (1.5:1 mixture of *syn/anti*). Interestingly, attempts to purify the iodide (**12**) by column chromatography led to an unexpected partial isomerisation to give (**13**) ((**12**)/(**13**) = 5/1).



(**Scheme 2**)

Consequently, the crude iodide (**12**) was used without further purification and reacted with the stannane (**11**) and $PdCl_2(MeCN)_2$ in DMF to give the desired tetraene as a 5:1 mixture of double bond isomers (**3**):(**14**) as determined by nOe experiments.



(**Scheme 3**)

Evidence for the relative stereochemistry of the side-chain

With both the diastereomers of the model triene (2) and the C9-C25 fragment (3) in hand we turned our attention to the assessment of the accuracy of their predicted theoretical ^{13}C NMR. There is relatively good agreement between the actual and the theoretical ^{13}C values for the model trienes (2a) and (2s) although the predicted value for C24 is the most inaccurate of the three, table 1. However, the relative sense of the prediction of all of the corresponding carbons is correct (i.e. the theoretical considerations correctly predict that the carbons C21 and C24 will be at a lower ppm in the *anti* isomer than in the *syn* isomer). These results show that the use of MM3/SOS-DFPT/IGLO calculations for determining the stereochemistry of acyclic 1,3-dimethylated hydrocarbon fragments is a potentially useful tool in natural product elucidation. Comparison of the ^{13}C NMR data of both diastereomers of the model (2) and C9-C25 fragment (3) (run in CD_2Cl_2) with that of the natural product can be seen in Table 1. The shift data for the *syn* isomers is relatively close in agreement with that of the natural product (within 0.1-0.2 ppm) while substantial differences are observed with the *anti* isomers (0.2-1.3 ppm). This spectroscopic data provides evidence that the relative configuration of the methyl groups in the side-chain of L-755,807 is *syn* and is in good agreement with the conclusions reached by theoretical considerations.[2]

Table 1

Predicted and observed ^{13}C NMR shifts of the side-chain of L-755,807

Carbon[a]	*Anti* (2a) Observed (Predicted)[b,c]	*Syn* (2s) Observed (Predicted)[b,c]	*Anti* (3a)[c]	*Syn* (3s)[c]	L-755,807
C21	29.5 (29.3)	**30.4** (30.9)	29.5	**30.3**	30.4
C23	19.5 (19.6)	**19.1** (19.2)	19.4	**19.0**	19.2
C24	20.8 (19.7)	**21.6** (20.4)	20.5	**21.3**	21.4

[a] L-755,807 numbering. [b]Predicted using MM3/SOS-DFPT/IGLO ref 2. [c] ^{13}C NMR spectra run in CD_2Cl_2 at 100MH

Acknowledgements

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