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CALYCULINS. ASYMMETRIC SYNTHESIS OF THE C_{26}-C_{32} FRAGMENT.

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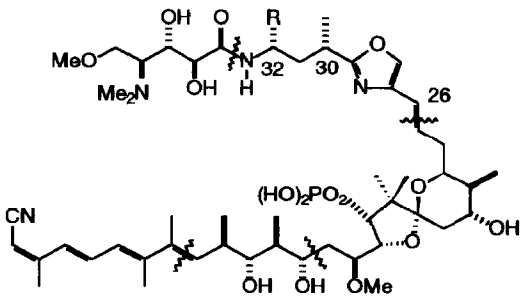
Abstract: *An efficient and highly stereocontrolled method for the construction of the natural syn stereochemistry at C_{30} and C_{32} in the calyculin C oxazole fragment has been devised starting from alanine. The title fragment itself is accessible in seven steps from N-BOC-alaninal.*

Calyculins A and C are the main components in the extract from the marine sponge *Discodermia calyx* isolated by Fusetani and co-workers.[1] The organism itself and the calyculins are potently cytotoxic against both sea urchin eggs and leukaemia cell lines P388 and L1210. The IC_{50} values of calyculins A and C are below 1 ng/mL.[2] It has been suggested that the main reason for the high cytotoxicity lies in the ability of calyculins to inhibit protein phosphatases 1 and 2A. Since protein phosphatases play a central role in cellular signalling processes, calyculins have rapidly gained an important position in the research on intracellular processes.[3,4]



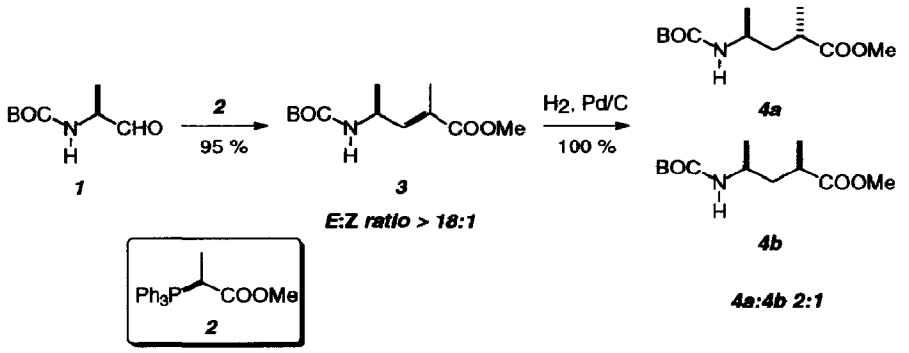
R = H Calyculin A
R = Me Calyculin C

The structure of calyculin A was determined by X-ray diffraction,[1] and the structures of the other calyculins were deduced on the basis of spectroscopic comparisons with that of calyculin A.[2,3] The configuration of the C_{32} methyl group of calyculin C was deduced from nOe experiments.[2] The absolute stereochemistry of calyculin A was ascertained only in 1991, when Shioiri *et al.* compared a synthetic C_{33}-C_{37} amino acid fragment with the one obtained by hydrolysis of the natural product by Fusetani.[5,6] Calyculin A has yielded to synthesis by two groups: Evans and co-workers reported the

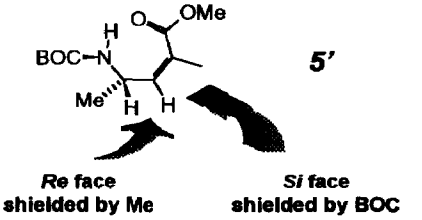
first total synthesis of the enantiomer of calyculin A in 1992,[7] and Masamune *et al.* reported the first total synthesis of the natural enantiomer in early 1994.[8] Several other groups, including ours, have also been involved in the game.[9,10]

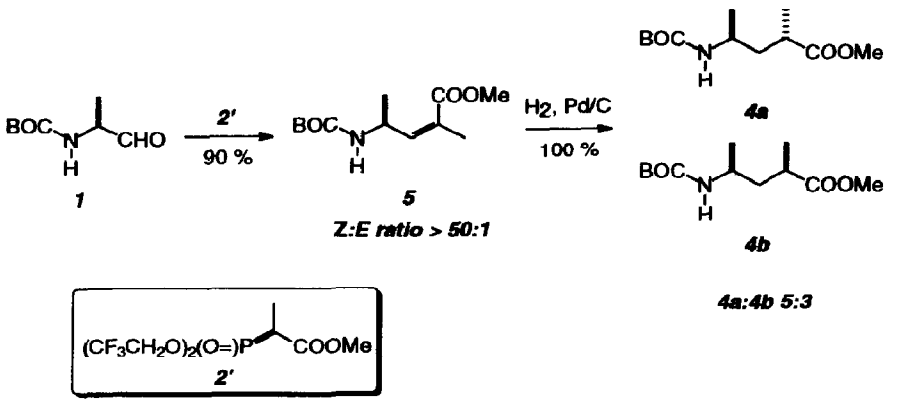
We have elected as our primary target calyculin C, partly to confirm synthetically the configuration at C_{32}, partly to be able to generate a synthesis of isomers of calyculins also. In this paper, we present an expedient synthesis of [2*R*, 4*S*]-4-((*tert*-butoxycarbonyl)amino]2-methylpentanoid acid ***8***, the requisite amino acid for constructing the oxazole bearing fragment C_{26}-C_{32} starting from alanine. The synthesis described herein is shown starting from natural L-alanine which leads to chirality enantiomeric to natural calyculin C at C_{30} and C_{32}.

Our synthesis began with the amino aldehyde ***1***, prepared in 62 % overall yield in three steps from L-alanine by a route slightly modified from the literature methods.[11,12] Olefination with the phosphorane ***2*** gave the *E*-enoate ***3*** (mp 79 °C, lit[13] mp 79-80 °C) in 95 % yield with an *E*:*Z* ratio (NMR) >18:1. Attempted catalytic asymmetric hydrogenation with the Pfaltz-type[14] bisoxazoline, semicorrin or pyridyloxazoline ligands and cobalt(II)/$NaBH_4$ proved to be unsuccessful. We therefore attempted direct hydrogenation over Pd/C, and obtained, in a quantitative yield, a 2:1 mixture of the *anti*- and *syn* isomers ***4a*** and ***4b*** (The structure of ***4a*** was confirmed by X-ray analysis of the derived free acid).[15] The slight predominance of the *anti*-isomer could be rationalised by 1,3-allylic strain[16] and this prompted us to attempt the synthesis through the *Z*-enoate ***5***.

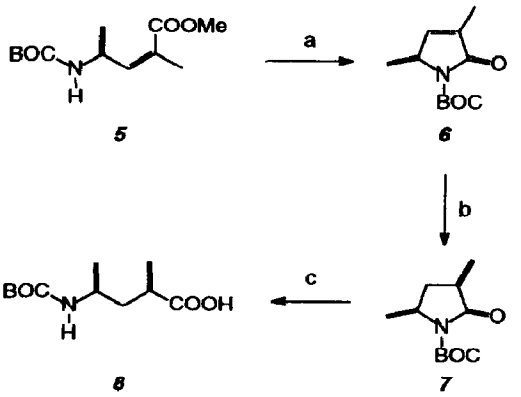


The *Z*-enoate ***5*** (mp. 48-51 °C; $[\alpha]_D$ = +62.8 °, *c* = 1.00, MeOH) was prepared from ***1*** through a Still-Gennari version of the Horner-Emmons-Wadsworth reaction with the bis(trifluoroethyl) phosphonate ***2'*** in 90 % isolated yield.[17] To our surprise, catalytic hydrogenation of ***5*** gave practically the same isomer ratio (5:3) with the undesired *anti*-isomer predominating. This unexpected result can be rationalised by a γ-turn type of conformation ***5'*** of the *Z*-enoate, possibly driven by a dipolar interaction between the NH and ester groups.





The successful route to the desired *syn*-isomer was found when we noticed that the unsaturated *Z*-ester ***5*** was easily converted to the corresponding γ-lactam ***6*** upon treatment with BOC_2O, DMAP, CH_3CN (85 %, mp 66-67 °C, $[\alpha]_D$ = +109.6 °, *c* = 1.00, MeOH)[18] and hydrogenated to the pyrrolidone derivative ***7*** (Pd/C, 99 %, *syn:anti* 10:1, oil, $[\alpha]_D$ = +51.5 °, *c* = 1.00, MeOH). Hydrolysis of the lactam with LiOH in THF/H_2O gave the acid ***8*** (mp 75-76 °C, $[\alpha]_D$ = -5.9 °, *c* = 1.00, MeOH) in quantitative yield.



REAGENTS: (a) BOC_2O, DMAP, CH_2Cl_2, 85 %; (b) H_2, Pd/C, 99 %, 10:1 *syn:anti*; (c) LiOH, THF, H_2O, 100 %.

The final stages for the construction of the oxazole ring system was achieved by methods reported by Evans.[7] Thus, amidation with serine methyl ester, utilising the mixed carbonic anhydride methodology, gave the corresponding amide in 85 % yield. Conversion to the oxazoline with thionyl chloride proceeded uneventfully to provide the oxazoline in 59 % isolated yield as a single isomer (NMR). Finally, oxidation of the oxazoline to the oxazole was obtained with the recently described $CuBr_2$-DBU-hexamethylenetetramine method.[19]

Our synthesis of the C_{26}-C_{32} fragment of calyculin C is short (seven steps from the known alaninal derivative ***1***), efficient, and capable of scaling-up. The optimisation of the final steps, especially the construction of the oxazole ring, will be reported in the full paper in due course.

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