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Towards an Asymmetric Synthesis of ADDA Conjugates

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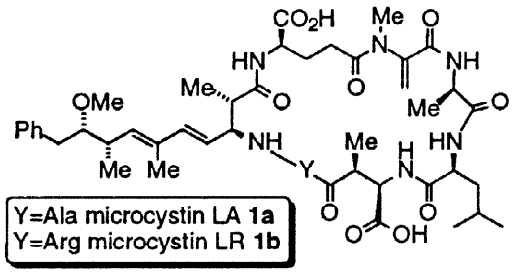
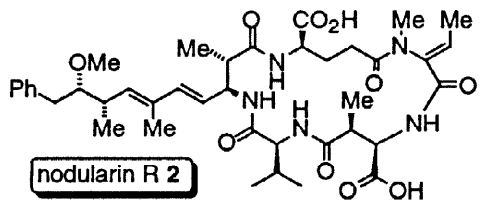
Abstract: In order to develop a general synthesis of ADDA containing peptides, an asymmetric synthesis of the β-lactam **4** and initial investigations into its opening with aminoesters is described.

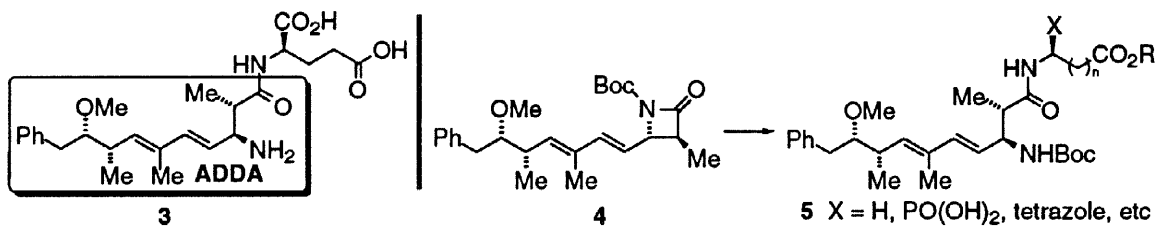
The microcystin (e.g. microcystin LA **1a** and LR **1b**) and nodularin (e.g nodularin R **2**) families of cyclic peptides are secondary metabolites isolated from various strains of blue-green algae. Biological testing has shown that these peptides cause acute hepatotoxicosis in mammals through inhibition of serine/threonine protein phosphatases PP1 and PP2A and promote tumours in animal models.[2]





Over 40 microcystins and nodularins have been isolated and their biological activity assessed leading to the conclusion that the ADDA-glutamic acid residue **3** is essential for potent biological activity.[2-4] In support of this, the crystal structure of mammalian PP1 complexed with microcystin LR **1b** showed that the carboxy group of glutamic acid and the carbonyl of ADDA play key roles in the enzyme-peptide association.[5] Nevertheless, the assumed importance of the ADDA-Glu residue **3** is based solely on SAR data from natural microcystin and nodularins. No systematic study of the effect of replacing (i) the glutamic acid residue with other aminoacids or (ii) the glutamic acid carboxyl with a bioisostere has been reported. Expanding the SAR data beyond that obtained from the natural series of peptides would enhance the understanding of the nature of the interaction of these peptides with protein phosphorylases.

This paper describes the synthesis of lactam **4** and initial investigations into its application to the synthesis of dipeptides **5**, analogues of the ADDA-Glu dipeptide **3** (scheme 1).[6]



3 **4** **5** X = H, $PO(OH)_2$, tetrazole, etc

Scheme 1

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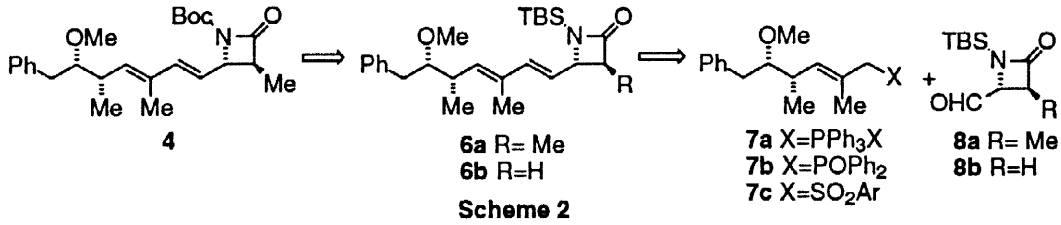
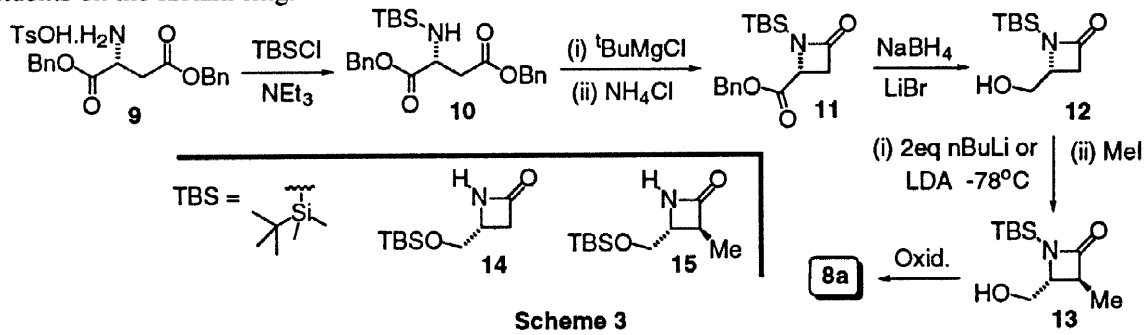
The retrosynthesis of the lactam **4** (scheme 2) leads to the *N-tert*-butyldimethylsilyl (TBS) lactam **6a**, for which we considered two potential routes. The first involves condensing the aldehyde **8a** with **7**. Alternatively, reaction of aldehyde **8b**[7] with **7** would give the lactam **6b** which on methylation gives lactam **6a**. The results of the more convergent first route are described here.



Scheme 2

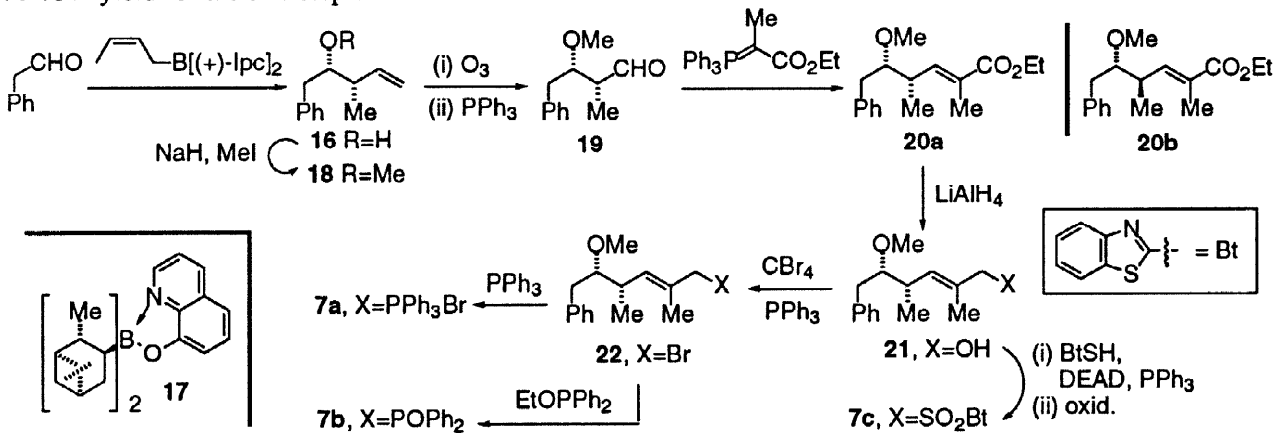
The synthesis of aldehyde **8a** is shown below (Scheme 3). The *para*-toluenesulfonic acid salt of (*D*)-dibenzylaspartate **9**[8] was treated with TBSCl in the presence of 2 equivalents of Et_3N to give *N*-TBS (*D*)-dibenzylaspartate **10**[9] in >90% yield. *N*-TBS dibenzylaspartate **10** is sufficiently stable in solution to allow the liberated $Et_3N.HCl$ to be removed by aqueous workup. The neat liquid, however, was relatively unstable to prolonged storage or extensive manipulation and was used immediately. *Ent*-**10** has previously been prepared in a two step process from the salt *ent*-**9** by liberation of the free amine and subsequent reaction with *N-tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide.[9] Reaction of *N*-TBS dibenzylaspartate **10** with ^tBuMgCl proceeded smoothly to give the benzyl ester **11** in addition to an equivalent of benzyl alcohol.[9] This crude material was treated with $NaBH_4$ in the presence of LiBr to give the alcohol **12** after silica gel chromatography.[10] $Ca(BH_4)_2$ has been recommended[11] for the reduction of (±)-**11** and related compounds in order to suppress migration of the TBS group from nitrogen to oxygen, however, only trace amounts of the lactam **14**[12] were obtained from the more convenient $NaBH_4$/LiBr reduction procedure. Reaction of 30-70 mmol of salt **9** delivered a 50-60% yield of alcohol **12** in a process requiring only the final product to be purified. Reaction of the alcohol **12** with two equivalents of *n*-BuLi or LDA at -78°C followed by addition of methyl iodide (1 equiv.) and quenching the reaction at -78°C gave the alcohol **13** stereospecifically. Although the reaction did not proceed beyond 70% conversion, the starting material could be easily separated from the product by chromatography and recycled. The isolated yield of the *trans*-methylated product **13** was 50-55% on a multigram scale. Attempts to perform the reaction at temperatures greater than -78°C resulted in increasing amounts of the lactams **14** and **15** being isolated as a result of N-O silyl migration. Both Dess-Martin periodinane[13] and Swern[7,14] oxidation procedures delivered the aldehyde **8a** in 90% yield. The H2-H3 coupling constant of 2.8 Hz obtained from the ^1H n.m.r. spectrum of **8a** confirmed the *trans*-orientation of the substituents on the lactam ring.



Scheme 3

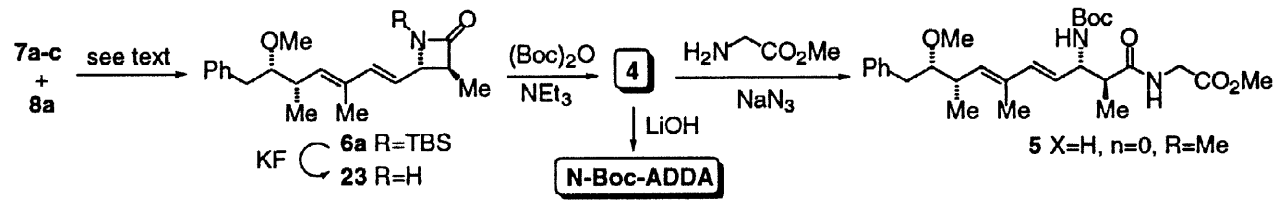
The synthesis of the coupling partners **7a-c** is illustrated in Scheme 4. The synthesis of the phosphonium salt **7a** has been described previously and applied to the synthesis of ADDA derivatives[15a-c,e], however, the

syntheses required many chromatographic purification steps and expensive reagents. Efforts were directed to streamlining its synthesis. Brown crotylation of phenylacetaldehyde and workup with 8-**hydroxyquinoline**[16] gave the *syn*-homoallylic alcohol **16**. ^{1}H n.m.r analysis confirmed both the diastereo-and **enantioselectivity for** this reaction to be >95%.[17] The workup procedure permitted the pinene derived chiral auxiliary to be removed as the solid complex **17**, allowing the alcohol **16** to be isolated in the filtrate of the workup solution. The alcohol **16** was directly methylated to give the alkene **18**. The efficacy of the Brown crotylation combined with the 8-hydroxyquinoline workup and simple short path distillation of the alkene **18** allowed the conversion of phenylacetaldehyde to the alkene **18** to be conducted on a 80 mmol scale in 85-90% yield. Ozonolytic cleavage of the alkene **18** and reductive workup gave the aldehyde **19**[15b-f,i] which was reacted without purification with (carbethoxyethylidene)triphenylphosphorane to give the αβ-unsaturated ester **20a**[15b-d] in 80-85% yield after short path distillation. ^{1}H n.m.r analysis indicated that the *E*:*Z* ratio was >20:1, but that it was contaminated with ~5% of the C4 epimer **20b**. The $LiAlH_4$ reduction[15d] of ester **20a** and workup with $Na_2SO_4.10H_2O$ gave the alcohol **21**[15a-e] in quantitative yield. Conversion of the alcohol to the bromide **22**[15a-c,e] (65-70% yield) and reaction with PPh_3 gave the phosphonium salt **7a**.[15a-c,e] Alternatively, reaction of the bromide with $EtOPPh_2$ gave the phosphine oxide **7b** in 70-75% yield.[18] Mitsunobu reaction of the alcohol **21** and 2-mercaptobenzothiazole (BtSH) followed by oxidation of the intermediate sulfide gave the sulfone **7c** in 70-75% yield for the two steps.[19]



Scheme 4

The couplings of **7a-c** and the aldehyde **8a** were studied extensively (Scheme 5). Deprotonation of the phosphonium salt **7a** and addition of aldehyde **8a** gave the lactam **6a** in 25% with an *E*:*Z* ratio of ~1:1. The condensation of the phosphine oxide **7b** and the aldehyde **8a** under a variety of conditions gave only the *E*-isomer, however the yield of lactam **6** was poor (10-15%). The yield and *E*:*Z* ratio of the diene from the condensation of sulfone **7c** with aldehyde **8a** in THF varied with the nature of the base used to deprotonate the

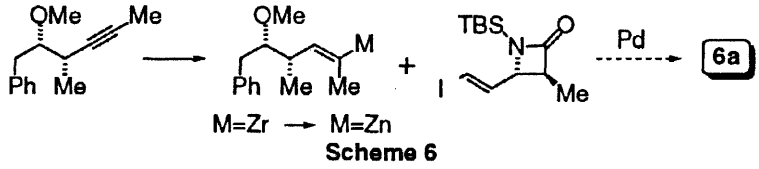


Scheme 5

sulfone. To aid purification, the crude products were treated with KF to give the lactam **23** as the isolated product. Examination of the products isolated in this fashion indicated that KHMDS was the base of choice

delivering lactam **23** in 40-45% with an ~3:1 *E*:*Z* ratio. Reactions using NaHMDS were highly *E*-selective (*E*:*Z* ratio ~4:1) however the yield was inferior (20-25%). Use of LiHMDS as base gave the poorest *E*:*Z* ratio of ~2:1. **Reaction of the lactam 23 with $(Boc)_2O$ gave the** N-Boc lactam **4**[20] in 90-95% yield **which on reaction with glycine methyl ester in the presence** of NaN_3[6,21] **gave the dipeptide 5 (X=H, n=0, R=Me) in 76% yield. The identity of the *N*-Boc lactam 4 was confirmed** by conversion to *N*-Boc-ADDA[15c,f,h,i] using Greico's procedure.[22]

The reaction of the *N*-Boc lactam **4** with other aminoacids (Scheme 1) and improving the yield of *N*-TBS lactam **6a** using the diene synthesis recently described by Panek[15i,23] (Scheme 6) are being investigated.



Scheme 6

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4. Microcystins related to microcystin LR **1b** in which the C-9 methoxy group of the ADDA residue is replaced with hydroxy or acetoxy show slightly reduced toxicity in laboratory animal tests. Microcystins or nodularins in which the C-6,7 double bond of the ADDA residue has been isomerised to the *Z*-isomer are essentially non-toxic in the same animal study. See ref. 2 and references cited therein.
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