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LETTERS

STUDIES RELATED TO THE ABSOLUTE CONFIGURATION OF CYCLOCINAMIDE A: TOTAL SYNTHESIS OF 4(*R*),11(*R*)-CYCLOCINAMIDE A

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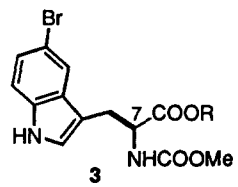
corresponding methyl ester **3** (R = Me)[3] *via* a two-step sequence. Hydrolysis [1.0 N NaOH, MeOH] of the methyl ester followed by esterification[4] with 9-fluorenylmethanol [DCC (*N,N'*-dicyclohexylcarbodiimide), CH_2Cl_2] provided fluorenylmethyl ester **3** (R = Fm) in 98% overall yield. The synthesis of *N*-BOC-*O*-benzoyl-(*R*)-isoserine **4** *via* a six-step sequence originated with (*R*)-malic acid employing the protocol of Milewska and Polonski[5] developed for the conversion of (*S*)-malic acid into (*S*)-isoserine. (*R*)-Malic acid was converted [$(CH_2O)_x$, $CHCl_3$, TsOH, reflux] in quantitative yield into dioxolone **5** which was subsequently transformed *via* a Curtius reaction [(a) $SOCl_2$, reflux; (b) NaN_3, acetone, H_2O, -20 °C; (c) *t*-BuOH, reflux] into the *N*-BOC-dioxolone **6** in 41% overall yield. Cleavage [1.0 N NaOH, MeOH] of the dioxolone followed by benzoylation [BzCl, pyr, 0 °C] provided (71%) the (*R*)-isoserine fragment **4**. The fully protected, activated (*S*)-asparagine residue **7** is commercially available.[6] The (*R*)-2,3-diaminopropanoic acid fragment **8** was prepared from N_α-BOC-(*R*)-asparagine *via* a Hoffman rearrangement.[7] Thus, treatment of N_α-BOC-(*R*)-asparagine with iodosobenzene diacetate in *n*-propanol:methyl acetate:water (8:5:1) [0 °C (1h) → 50 °C (2h)] and subsequent exposure of the resulting amine to *N*-(9-fluorenylmethoxycarbonyloxy)succinimide[8] in aqueous acetone afforded the fully protected (*R*)-2,3-diaminopropanoic acid moiety **8** in 75% overall yield.



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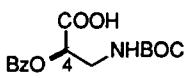

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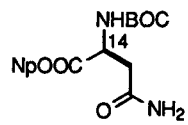

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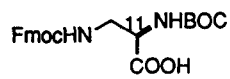

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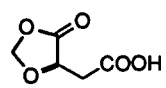

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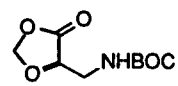

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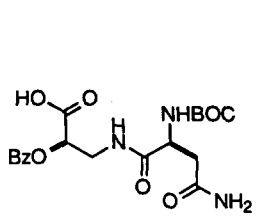
With the requisite amino acid fragments in hand, assembly of the linear tetrapeptide **11** was undertaken. It was anticipated that tetrapeptide **11**, needed for construction of the tetracyclic peptidic core **12** of 4(*R*),11(*R*)-cyclocinamide A (**2**), could be assembled by conventional BOP [(1*H*-benzotriazol-1-yloxy)tris(dimethylamino)-phosphonium hexafluorophosphate] promoted coupling protocols.[9] In an effort to minimize protecting group manipulations, the *O*-benzoyl-(*R*)-isoserine, derived from fragment **4**, was coupled with the commercially available (*S*)-asparagine moiety **7**.[6] Thus, the *N*-BOC protected (*R*)-isoserine **4** was deprotected [30% TFA in CH_2Cl_2] and the resulting crude trifluoroacetate salt was treated [HOBt (1-hydroxybenzotriazole), DIEA (*N,N*-diisopropylethylamine), DMF] with the activated 4-nitrophenyl ester **7** of N_α-BOC-(*S*)-asparagine giving rise to dipeptide **9** as a single diastereomer in 65% overall yield. Removal [TMSI, $CHCl_3$, reflux] of the methyl carbamate protecting group in **3** provided the corresponding fluorenylmethyl ester of (*S*)-5-bromotryptophan which, upon coupling [BOP, HOBt, DIEA, DMF] with dipeptide **9**, afforded tripeptide **10** in 57% overall yield. Cleavage [30% TFA in CH_2Cl_2] of the *N*-BOC group in tripeptide **10** gave rise to the corresponding trifluoroacetate salt which was dissolved in DMF and coupled [BOP, HOBT, DIEA] with the differentially protected (*R*)-2,3-diaminopropanoic acid **8** giving rise to tetrapeptide **11** in 76% yield.



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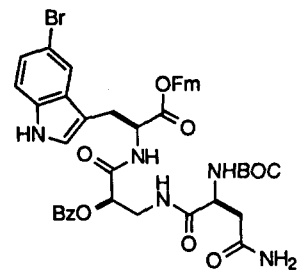

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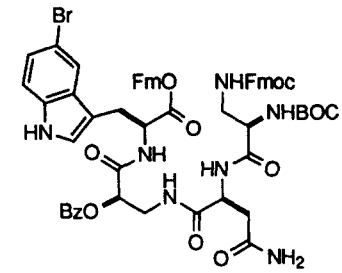

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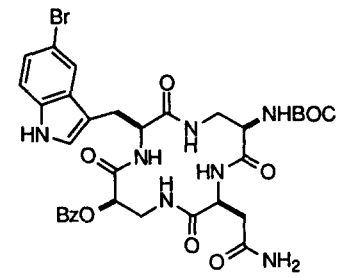
With the linear tetrapeptide **11** in hand, the ring closure reaction to form the core of 4(*R*),11(*R*)-cyclocinamide A (**2**) was examined. Simultaneous deprotection [20% TEA in CH_2Cl_2, DMF, 2h] of the termini of tetrapeptide **11** provided, after evaporation of the volatile components *in vacuo*, a solid residue which, upon dissolution in DMF and treatment with *N,N*-diisopropylethylamine and pentafluorophenyldiphenylphosphinate,[10] afforded in 62% overall yield the cyclized tetrapeptide core **12** of **2**.



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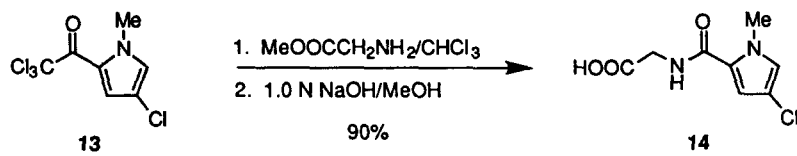
Prior to completing the total synthesis of **2**, a synthesis of the glycine derived fragment **14** needed to be developed. This was accomplished *via* a two-step protocol. Condensation of methyl glycinate with 1-methyl-2-trichloroacetyl-4-chloropyrrole (**13**)[11] and subsequent hydrolysis of the methyl ester provided dipeptide fragment **14** in 90% overall yield.



13 14

Completion of the total synthesis of 4(*R*),11(*R*)-cyclocinamide A (**2**) necessitated cleavage of the BOC group on the nitrogen at C(11) in **12** followed by coupling with the dipeptide side chain **14**. Thus, cleavage (30% TFA in CH_2Cl_2) of the BOC group on the cyclic tetrapeptide core **12** provided the crude trifluoroacetate salt which was dissolved in *N,N*-dimethylformamide and coupled [BOP, HOBT, DIEA] with dipeptide **14**. Deprotection of the C(4) hydroxyl group in the coupled material employing 1% sodium hydroxide in methanol gave rise to 4(*R*),11(*R*)-cyclocinamide A (**2**) in 41% overall yield. A comparison of the ^1H NMR spectrum (500 MHz, MeOH-

d4) of **2** with that of natural cyclocinamide A provided by Professor Crews revealed that the spectra were similar, but not identical. Biogenetic considerations would suggest that the absolute configuration at C(4) and C(11) are both *S*. Efforts are underway to prepare the remaining diastereomers [4(*S*),7(*S*),11(*S*),14(*S*); 4(*S*),7(*S*),11(*R*),14(*S*) and 4(*R*),7(*S*),11(*S*),14(*S*)] of cyclocinamide A.

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