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SYNTHESIS OF (2S,3S,8S,9S)-ADDA FROM D-GLUCOSE

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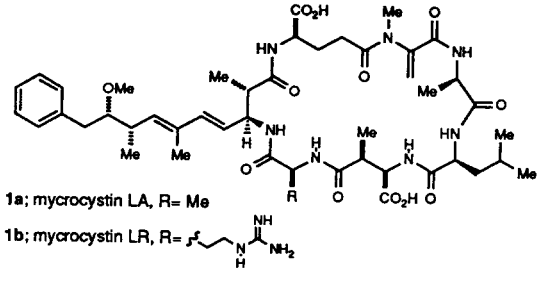
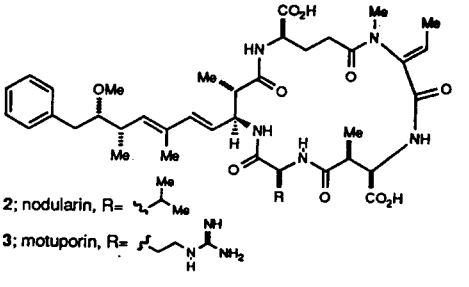
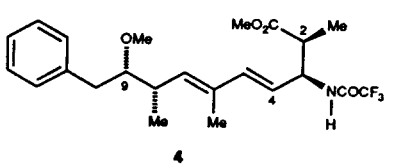
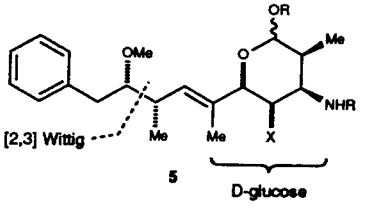
Summary: *The N-trifluoroacetyl derivative of the novel β-amino acid (2S,3S,8S,9S)-Adda methyl ester 4 has been prepared from the D-glucose derived oxazoline 7. A key step in the construction of 4 was the generation of the E,E decadienoate system via dissolving metal reduction of vicinal bis-mesylate 15.*

Studies of toxic blooms of freshwater cyanobacteria[1] have resulted in the isolation and characterization of the microcystins (**1**), a family of hepatotoxic heptapeptides containing the novel β-amino acid (2S,3S,8S,9S)-3-amino-10-phenyl-2,6,8-trimethyl-4,6-decadienoic acid (Adda).[2] Adda has been identified as a constituent amino acid of the structurally related pentapeptide toxins nodularin **2**, isolated from the cyanophyte *Nodularin spumigena*,[3] and motuporin **3**, a potent protein phosphatase 1 inhibitor isolated from the marine sponge *Theonella swinhoei*.[4] Interest in the ability of Adda-containing peptides to inhibit the activity of phosphatases[5] has focused attention on this novel amino acid, and several groups have recorded syntheses of Adda derivatives.[4b,6] These schemes share a common connective strategy, based on development of the decadienoate framework via Wittig or sulfone-based olefination reactions. In conjunction with our program to examine the use of carbohydrate templates for the development of highly-oxygenated acyclic targets,[7] we have examined a conceptually different approach to Adda based on the linear elaboration of key structural and stereochemical elements via the [2,3] Wittig rearrangement[8] of a carbohydrate-derived allylic ether. Herein we report the successful application of this strategy to the asymmetric synthesis of N-trifluoroacetyl Adda methyl ester **4** from D-glucose.



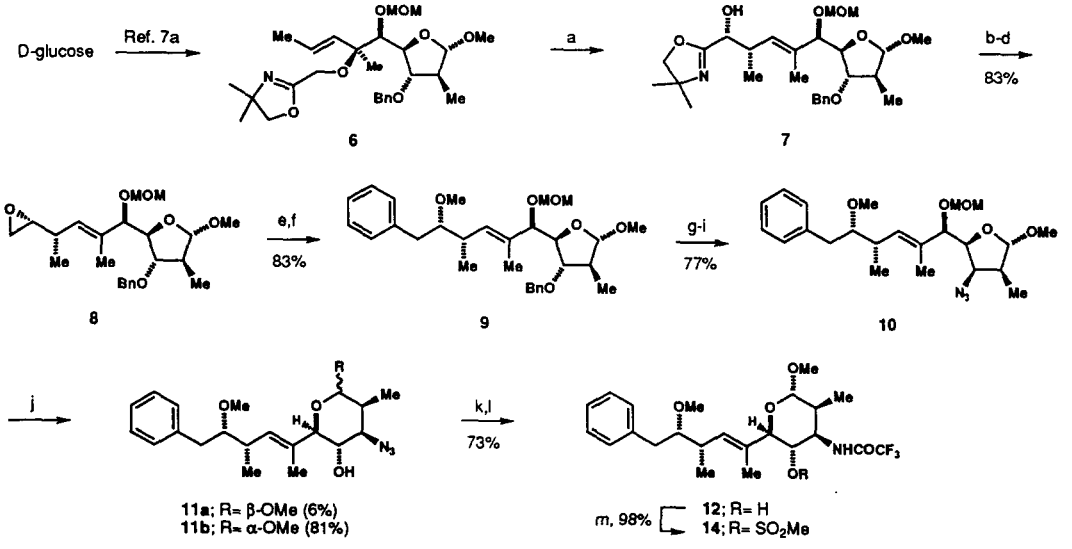






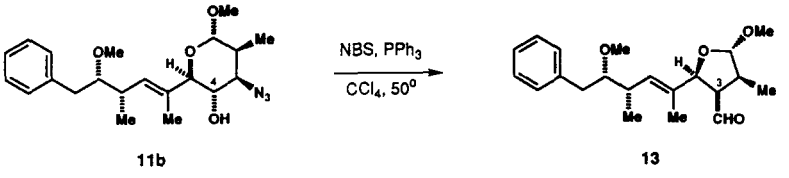
Our plan for constructuction of the decadienoate system of **4** was based on the expectation that the Vassela-type reductive dehalogenation of a suitably functionalized 4-halopyranose **5** would furnish the desired E,E diene geometry.[9] We anticipated that pyranose **5** would be readily available from oxazoline **7**, the product of [2,3] Wittig rearrangement of the D-glucose-derived tertiary ether **6** which was prepared during the course of recent model studies directed at the immunosuppressant rapamycin (Scheme 1).[7a] Reductive cleavage of the oxazoline system of **7** afforded the corresponding diol, which underwent regioselective tosylation followed by base-induced cyclization to furnish the epoxide **8**.[10] Introduction of the aryl subunit of Adda was accomplished by addition of phenyl Grignard reagent to **8**; O-methylation of the resulting alcohol yielded **9**, comprising the complete carbon framework of Adda.

Scheme 1



Reagents: (a) BuLi, THF, -78°; (b) TFA (1 eq), H_2O (1 eq), THF, then $LiAlH_4$; (c) TsCl, pyridine; (d) NaOH, MeOH; (e) PhMgBr, THF, -0°; (f) KH, MeI, DME; (g) H_2, $Pd(OH)_2$, MeOH; (h) Tf_2O, pyridine, CH_2Cl_2, -20°; (i) LiN_3, DMF; (j) HCl, MeOH, 50°; (k) $(CF_3CO)_2O$, pyridine; (l) H_2, Pd-C, EtOAc; (m) MsCl, pyridine.

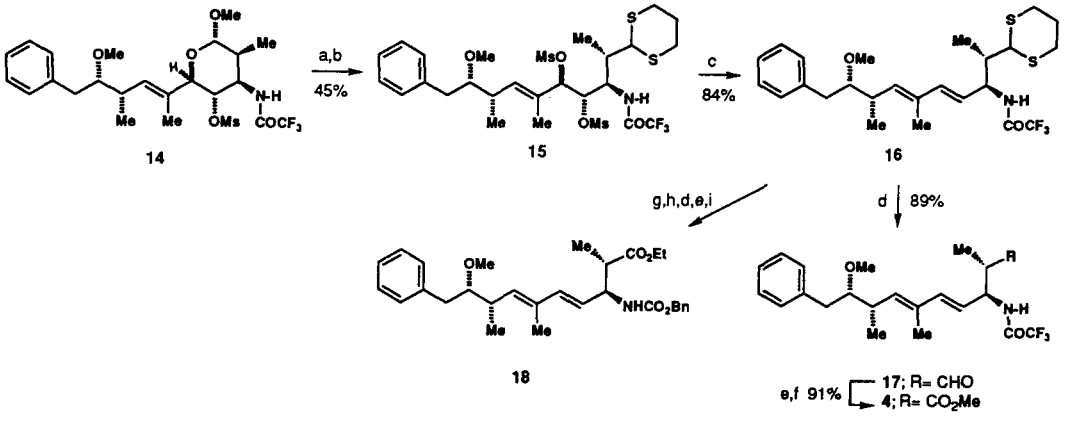
With the carbon skeleton and C8-C9 stereochemistry of **4** in place, we turned our attention to installation of the C3 nitrogen substituent and diene system of Adda. Deprotection of benzyl ether **9** afforded the corresponding alcohol, which was converted to the sensitive triflate and treated directly with lithium azide in DMF to yield azide **10**. Exposure of **10** to acidic methanol resulted in solvolytic cleavage of the methoxymethyl ether followed by a thermodynamically driven furanose-to-pyranose conversion. An equilibrium mixture of products was obtained, consisting predominantly of the anomeric pyranoses **11a** (6%) and **11b** (81%), accompanied by 9% of the corresponding furanose anomers (from deprotection of **10**). These furanose products and **11a** could be resubjected to the reaction conditions to afford additional **11b**. At this juncture, we attempted to introduce a halogen substituent at C4 in anticipation of the reductive halogenation which would generate the desired E,E diene system of **4**. Neither the mesylate nor the triflate derived from **11b** proved reactive with a variety of halogen nucleophiles, an observation we attribute to a combination of steric and inductive effects which mitigate nucleophilic attack in this system. An attempt to halogenate **11b** with triphenylphosphine and N-bromosuccinamide resulted an unprecedented rearrangement to the furanose aldehyde **13**, presumably via a pinacol-type mechanism involving [1,2] migration of the C4-C5 bond with concurrent loss of azide anion.[11,12]



11b 13

While the conversion of **11b** to **13** represents an intriguing parlay of carbohydrate stereochemistry, this reaction brought us no closer to our goal of preparing a C4-halogenated pyranose derivative **5**. In an effort to employ anchimeric activation of a C4 sulfonate,[13] alcohol **11b** was acylated and the azido group was reduced to the amine, accompanied by an acyl migration to nitrogen, to afford amide **12**. Unfortunately, we were once again unable to effect halogenation of **12** or the derived mesylate, **14**. Attempts to introduce halogen by nucleophilic displacement of the corresponding triflate led to complex product mixtures.

Scheme 2



14 15 16 18

Reagents: (a) BF_3-Et_2O, $HS(CH_2)_3SH$, CH_2Cl_2; (b) MsCl, pyridine; (c) Na, anthracene, THF, 0°; (d) $AgNO_3$, CH_3CN,H_2O; (e) CrO_3, H_2SO_4, H_2O; (f) CH_2N_2, Et_2O, 0°; (g) K_2CO_3, MeOH, H_2O; (h) $BnCO_2Cl$, NEt_3, CH_3CN; (i) K_2CO_3, EtI, DMF.

Frustrated in our attempts to procure a halogenated substrate **5** for Vasella reduction, we investigated an alternative approach to the Adda decadienoate system in which ring opening of the pyranose system would precede olefination. Of particular interest in this regard was a report describing the stereocontrolled formation of E alkenes from the dissolving metal reduction of vicinal sulfonates.[14] To examine the potential of this approach, we prepared the vicinal bis-mesylate **15** by Lewis acid catalyzed thioketalization of mesylate **14**, to give the acyclic dithiane derivative, followed by mesylation of the C5 alcohol. Upon exposure to a THF solution of Na-anthracene, bis-mesylate **15** was rapidly and stereoselctively transformed to the desired E,E diene **16**. Hydrolysis of the dithiane group yielded aldehyde **17**; final transformation to the N-trifluoroacetyl derivative of Adda methyl ester was accomplished by Jones oxidation and esterification with diazomethane to give **4** ($[a]_D^{20}$ +18.92°, c= 0.37, $CHCl_3$). Transformation of diene **16** to the known N-benzylcarbonyl ethyl ester, **18** ($[\alpha]_D^{20}$ -24.0°, c= 0.05, $CHCl_3$, lit.[6a] $[\alpha]_D^{26}$ -20.9, c= 1.37, $CHCl_3$), an Adda derivative prepared previously by Rinehart and co-workers,[15] confirmed that our synthesis of **4** had indeed succeeded in establishing the correct relative and absolute stereochemistry of Adda.

In summary, our synthesis of the N-trifluoroacetyl Adda ester **4** from the glucose-derived tertiary ether **6** demonstrates the potential of the [2,3] Wittig rearrangement launched from a carbohydrate-based stereochemical platform to rapidly establish the key structural and stereochemical elements of an extended acyclic system. The results of ongoing efforts to apply this strategy to the preparation of other biologically active compounds will be the subject of future reports from this laboratory.

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12. Such a mechanism is consistent with our stereochemical assignment for **13**, which is based on the H3-H4 coupling constant of 7.2 Hz indicative of a *cis* relationship between the C3 and C4 substituents. An alternative mechanism, involving [1,2] migration of the C2-C3 bond of **11b** with concomittant displacement of the C4 hydroxyl, would yield the C3 epimer of **13**. Studies aimed at defining the scope and mechanism of this unusual pyranose rearrangement are in progress.
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15. The 500 MHz NMR, IR and FAB low resolution mass spectra of **17** corresponded to spectra of authentic material kindly provided by Prof. Rinehart.

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