SYNTHESIS OF POTENTIAL TRANSITION STATE INHIBITORS OF SUCCINYL CoA:TETRAHYDRODIPICOLINATE *N*-SUCCINYL-TRANSFERASE†

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Abstract- The preparation of 2-hydroxytetrahydropyran-2,6-dicarboxylic acid (6S-**1**), 2-hydroxytetrahydrofuran-2,5-dicarboxylic acid (**17**), and 3,3-difluoro-2-hydroxytetrahydropyran-2,6-dicarboxylic acid (**26**), three transition state analogs of hydrated tetrahydrodipicolinic acid (THDPA) and a depsipeptide derivative (**11**) of 6S-**1** is described.

Because *meso*-2,6-diaminopimelic acid (DAP) has a pivotal role in bacterial cell wall biosynthesis and function, and is also the precursor to the essential amino acid lysine,[1] much interest has been generated in regulating or inhibiting the DAP biosynthetic pathway.[1-3] Succinyl-CoA:tetrahydrodipicolinate *N*-succinyl-transferase is a key enzyme in the biosynthesis of diaminopimelic acid and lysine in bacteria, blue-green algae, and higher plants where it catalyzes the *N*-succinylation of tetrahydrodipicolinic acid (THDPA) by succinyl-coenzyme A to afford L-2-succinylamino-6-oxopimelic acid. A number of cyclic and acyclic analogs of tetrahydrodipicolinic acid have been evaluated as potential inhibitors of succinyl transferase.[3] This led to the discovery[3] that 2-hydroxytetrahydropyran-2,6-dicarboxylic acid (**1**) is a potent competitive inhibitor ($K_{i(app)}$ = 58nM compared to a $K_{m(app)}$ for the substrate, THDPA, of 20μM) of the succinyl-transferase enzyme and it was proposed[3] that **1** is a transition state analog of the hydrated intermediate derived from THDPA. However, as determined by disc diffusion assay, **1** was devoid of antibacterial activity against any of the strains tested. It was suggested that this was probably due to lack of transport and that efficient portage delivery of this compound should provide a potent antibiotic.[3] Nmr studies show that the pyran (**1**) exists in solution as a mixture[3] of the open and closed forms. Furthermore, as tested, **1** was also racemic, and both the

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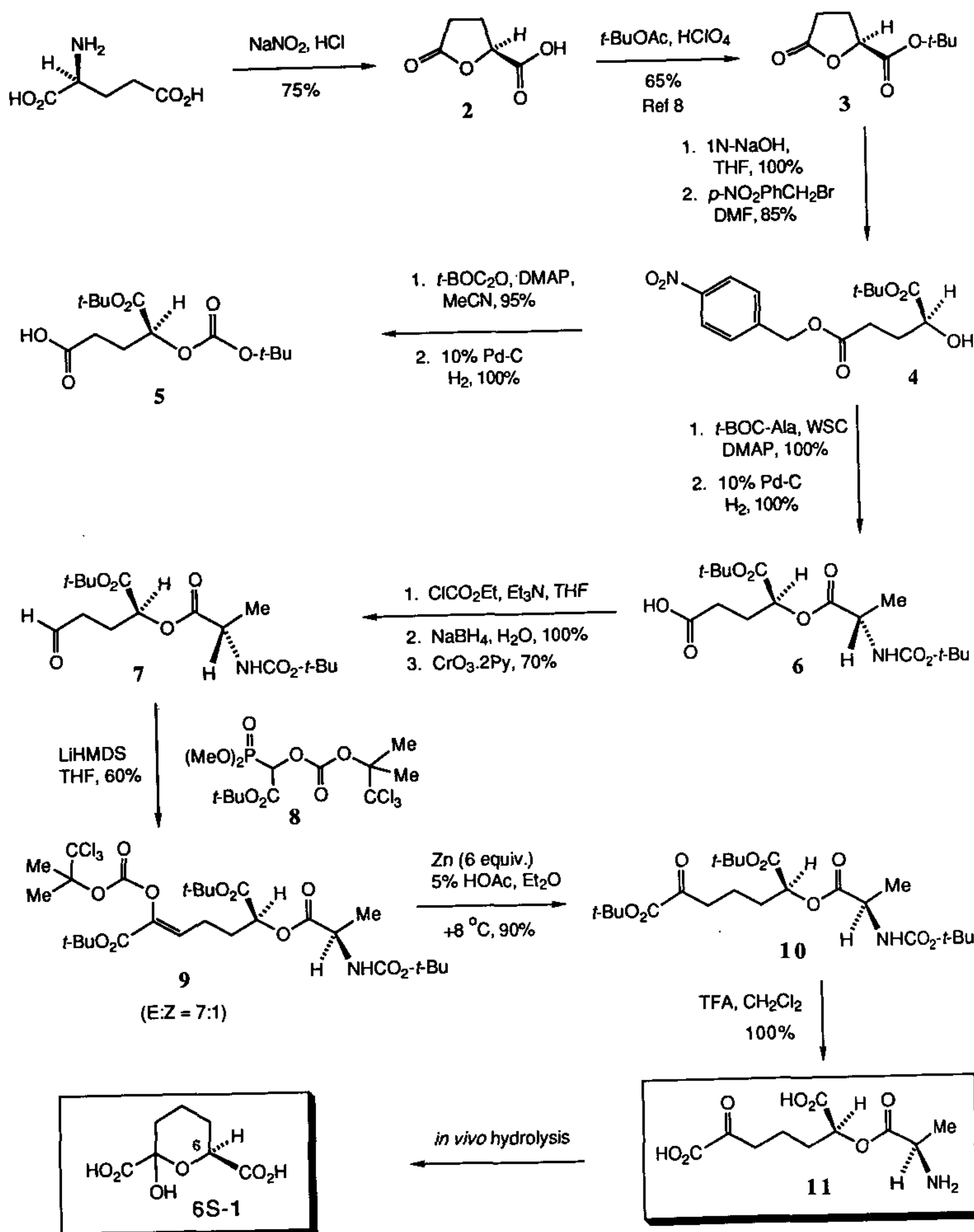
proposed[3] stereochemical model for the succinylation of THDPA, and the chirality of THDPA, imply that there should be a stereochemical requirement for the S configuration at C-6 of **1**. Hence we were interested in carrying out a synthesis of 6S-**1** as well as preparing the depsipeptide derivative (**11**), which would be capable of being transported into the cell. In this communication we describe the synthesis of the depsipeptide (**11**), as well as the furan analog (**17**), and the difluorinated pyran (**26**). These latter two analogs were targeted because they should preferably exist in the cyclized form.

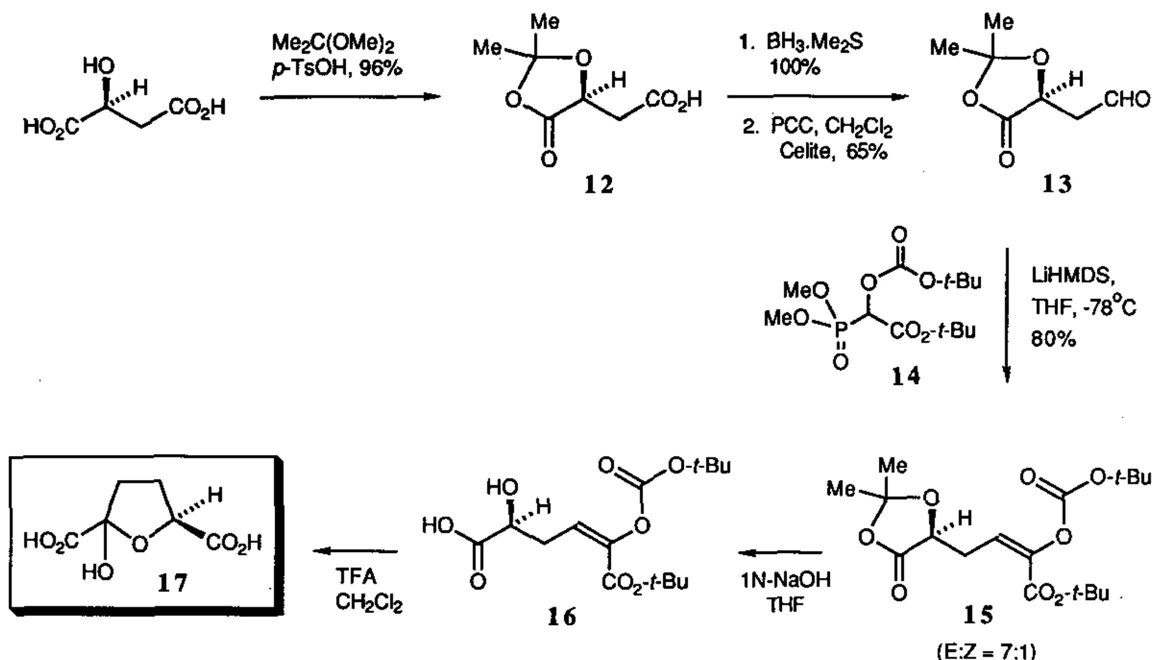
Conceptually, the approach we describe to both **1** and **17** uses a C_5 or C_4 precursor from the chiral pool to set the configuration at C-6 and introduces the pyruval functionality *via* a Horner-Wadsworth-Emmons reaction with a protected, oxygenated phosphonate. In the case of the racemic fluorinated pyran (**26**), the fluorinated pyruval end was constructed from a commercially available difluorinated precursor and, in a reversal of roles, the oxygenated phosphonate was used to introduce the C-6 hydroxyl containing region.

As depicted in Scheme 1, L-glutamic acid was readily converted to the differentially protected diester alcohol (**4**). This was coupled to *t*-BOC-protected L-alanine, employing the water soluble carbodiimide (WSC)[4] for activation, and then hydrogenolyzed to quantitatively afford the alanine-ester acid (**6**). The acid (**6**) was then converted to the aldehyde (**7**), *via* the corresponding alcohol in a routine two-step reduction-oxidation sequence. The aldehyde (**7**) underwent facile Horner-Wadsworth-Emmons reaction with the trichloro-*t*-butyloxycarbonyl (TCBOC) protected[5,6] oxygenated phosphonate (**8**) to afford the enol ester (**9**) in an E:Z ratio of 7:1. Reductive elimination of the TCBOC protecting group with zinc dust, in a dilute solution of acetic acid in ether,[6,7] unmasked the pyruval ester function to give **10**. Removal of the remaining protecting groups with trifluoroacetic acid (TFA) led to the desired depsipeptide of 6S-**1**, namely **11**. Biological data indicates that **11** is indeed transported into the bacterial cell and then cleaved to afford 6S-**1**.

Scheme 2 outlines the synthesis of the analogous hydroxyfuran dicarboxylic acid (**17**). The known[9] acetonide (**12**) of S-malic acid was readily converted in two steps to the corresponding aldehyde (**13**) which was then submitted to a Horner-Wadsworth-Emmons reaction, this time with the *t*-butyloxycarbonyl (BOC) protected[5,6] oxygenated phosphonate (**14**) to afford the enol ester (**15**)(E:Z = 7:1). In this instance we found that it was cleaner to first remove the acetonide by base hydrolysis, and then deprotect the resulting hydroxy acid (**16**) with TFA to obtain the desired furan (**17**). Nmr analysis indicated that this was a mixture of the two possible anomeric ring-closed structures (ratio of 3:2) along with a minor amount (less than 10%) of the open-chain isomer. It should be noted that 6S-**1** can be prepared from the acid (**5**) by application of the chemistry described in both Schemes 1 and 2.

Scheme 1

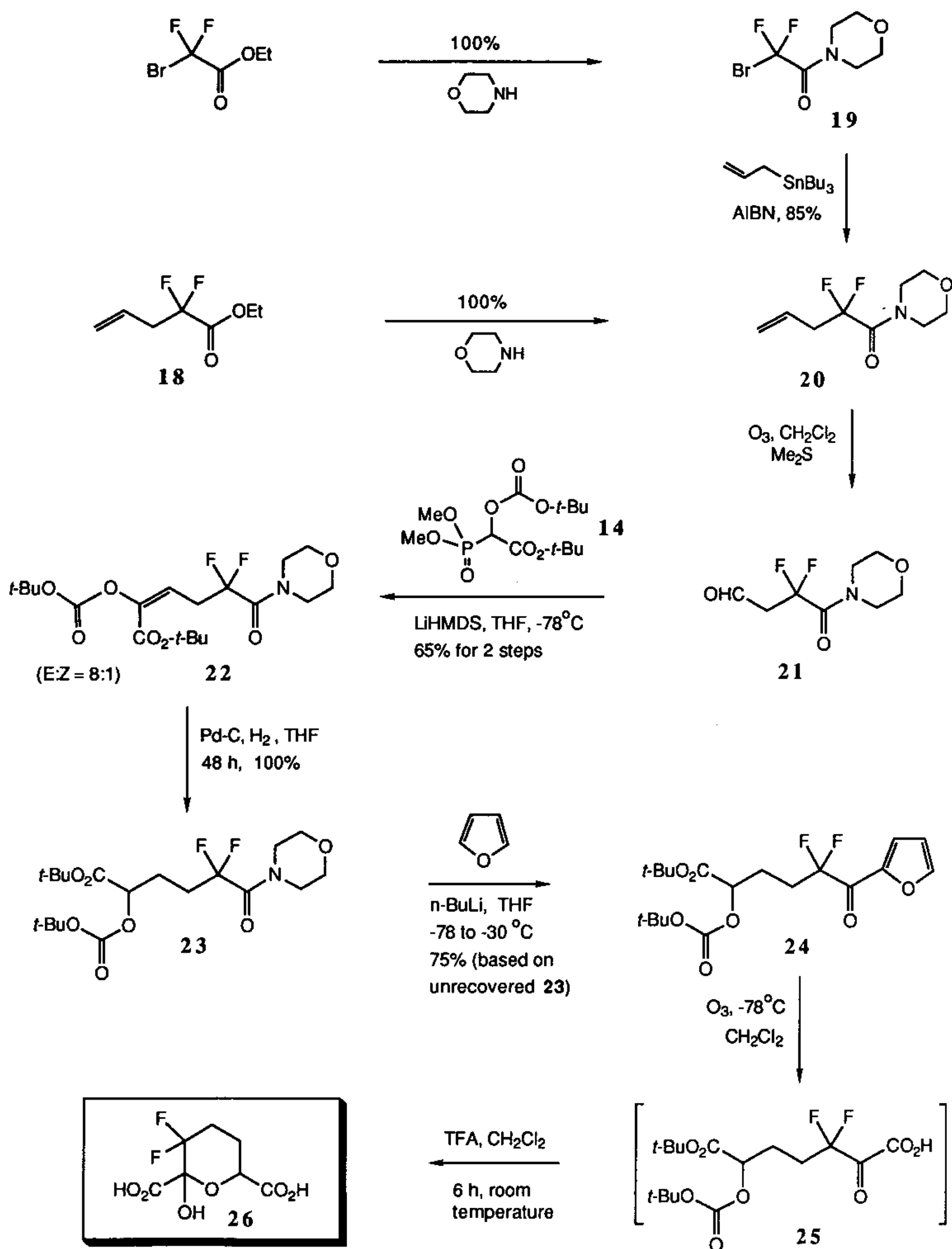




Scheme 3 describes the synthesis of **26**, the corresponding difluoro analog of **1**. The key difluorinated-C_4 intermediate (**21**) was prepared by ozonolysis of the difluoro-C_5-olefin (**20**), which could be made either by reaction of morpholine with the known[10] ester (**18**) or by allylation of the morpholinoamide (**19**). The morpholinoamide moiety in **21** was introduced in place of the corresponding ethyl ester because of problems we encountered with the corresponding difluoroester function in subsequent steps (bis addition of anions, etc.). Horner-Wadsworth-Emmons reaction of **21** with the *t*-butyloxycarbonyl (BOC) protected[5,6] oxygenated phosphonate (**14**) afforded the enol ester (**22**)(E:Z = 8:1), which was converted to the protected hydroxyester (**23**) by palladium catalyzed hydrogenation. This hydrogenation was rather slow, presumably due to problems of steric hindrance, and required a higher catalyst to substrate ratio than normal. Reaction of **23** with 2-lithiofuran gave **24**, which was oxidatively cleaved with ozone to afford the difluoropyruval compound (**25**). Deprotection of **25** with TFA gave the difluorohydroxypyran dicarboxylic acid (**26**). ^{1}H- and ^{19}F-nmr analysis of **26** indicated that there was no open chain material and that the ring closed material existed as a single isomer, but unfortunately the spectral data did not permit the determination of the relative configuration of that isomer.

The biological data on these four compounds will be reported in detail elsewhere.

Scheme 3



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4. Abbreviations: WSC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimde hydrochloride; DMAP = dimethylaminopyridine; (t-BOC)$_2$O = di-*tert*-butyl dicarbonate; PCC = pyridinium chlorochromate; LiHMDS = lithium hexamethyldisilazane.
5. The trichloro-*t*-butyloxycarbonyl (TCBOC) protected oxygenated phosphonate (**8**) was made from di-*t*-butyl tartrate in an analogous manner to that described for the methyl ester[6] (see references 4 and 7 of reference 6). The *t*-butyloxycarbonyl (BOC) protected oxygenated phosphonate (**14**) was made by the same route except that the hydroxyl function was protected as the *t*-butyl carbonate [(*t*-BOC)$_2$O, DMAP].
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7. We found that this reductive elimination step is very substrate dependent and care must be taken with respect to the time, temperature, and number of equivalents of zinc used to avoid further reduction to the corresponding hydroxy ester. This problem could be circumvented by the use of the phosphonate (**14**) which would allow for the simultaneous removal of all the protecting groups.
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