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STUDIES IN TETRAHYDROFURAN SYNTHESIS. COMPLETE β-LACTONE FORMATION IN THE BROMOLACTONIZATION OF A 2,4-DISUBSTITUTED β,γ-UNSATURATED CARBOXYLIC ACID

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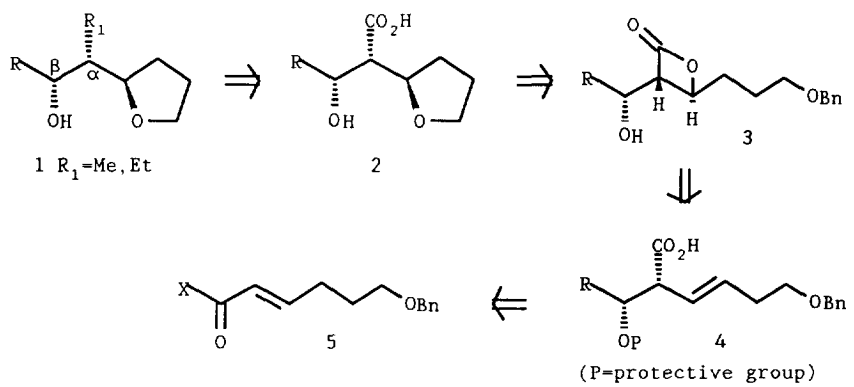
Abstract: A dienolate aldol/bromolactonization sequence has been used to demonstrate a new stereocontrolled route to protected α-(1-hydroxyalkyl) 2-oxetanones, and thus specifically functionalized tetrahydrofurans.

In the course of our work on the pamamycin polyether antibiotics,[1] efforts have largely focused on the development of an efficient synthetic protocol for assembling appendaged tetrahydrofurans **1** using a Cα-Cβ coupling strategy.[2] Hydroxy acids **2** represent viable precursors, as the carboxylic acid moiety could be readily converted to both methyl and ethyl groups.[3] Moreover, we have previously shown that these structures are formed stereospecifically from 2-oxetanones **3** *via* Lewis acid mediated intramolecular β-cleavage.[2] Unsaturated acids **4** were viewed as potential precursors, which could presumably be cyclized to structures **3** *via* halolactonization/reductive dehalogenation.[4] In turn, the acyclic precursors **4** would be prepared stereoselectively by directed aldol reaction of a dienolate derived from a conjugated carboxylic acid derivative **5**. Significantly, this aldol addition would, in effect, represent the Cα-Cβ coupling step in our strategy.

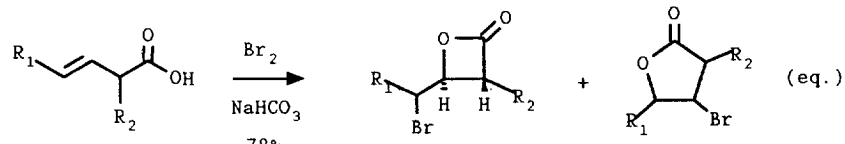
Scheme I



1 R_1=Me,Et 2 3 4 5

(P=protective group)

Under kinetically controlled conditions, halolactonizations of 2-substituted 3-butenoic acids have been reported to favor complete formation of β-lactones, with impressive trans selectivity.[4,5] In systems where the alkene moiety of the β,γ-unsaturated carboxylic acid is non-terminal, however, 1:1 mixtures of β- and γ-lactones are common[6] (see eq.). This lack of regioselectivity has impeded the widespread use of the halolactonization reaction in the synthesis of four-membered oxygen heterocycles. Galatsis,[7] for example, recently reported the selective synthesis of oxetanes upon iodolactonization of a variety of homoallylic alcohols. However, it was noted that tetrahydrofuran formation by 5-endo cyclization is the exclusive mode when the alkene is non-terminal, an observation shared by others working in related areas.[8]



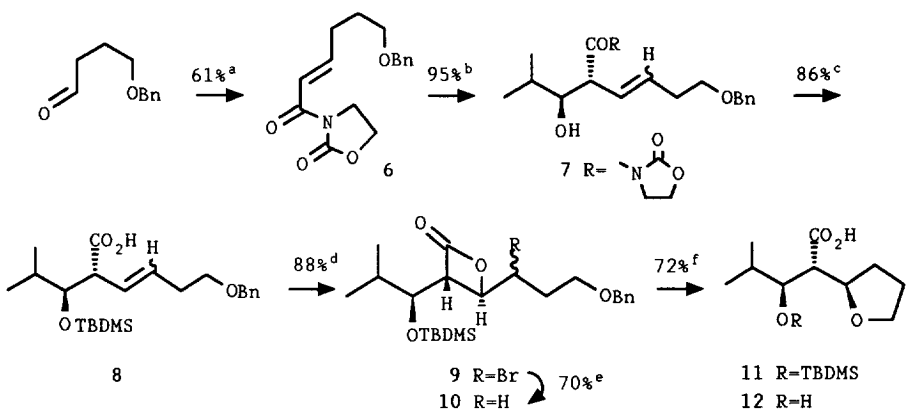
(R_1=Et, R_2=*i*-Pr) ~ 1 : 1[9]

Despite these reports, we reasoned that if the α-alkoxyalkyl substituent on the acid **4** were sufficiently bulky, the kinetically favored 4-exo cyclization would be promoted, relative to the 5-endo process,[10] by the Thorpe-Ingold effect.[11]

The preparation of a suitable substrate for halolactonization was our first objective. Initially, for the sake of ease of analysis, diastereomeric purity of our substrate was more important than specific stereochemistry. To date, the best documented examples of directed α-aldol reactions of dienolates have involved the use of crotonate imides.[12] Dibutylboron dienolates generated from these derivatives have been shown to add to aldehydes with excellent syn-selectivity.[12] Indeed, imide **6**, prepared from 4-benzyloxybutanal in four steps, was converted to alcohols **7**[13] with 95% diastereoselectivity by this method (Scheme II). Following chromatographic purification, alcohol protection and subsequent hydrolysis then provided the acids **8** without any disturbance to the double bonds.[12b] Bromolactonization of acids **8** gave a mixture of two compounds in a ratio of 2.5:1, as determined by ^{1}H NMR. With no evidence for γ-lactone formation by IR analysis, it appeared that this mixture consisted of bromo isomers **9** only. Our assignment was confirmed by conversion of this inseparable mixture to the single, pure diastereomer **10** by reductive debromination. Treatment of 2-oxetanone **10** with 2 equivalents of titanium tetrachloride provided the tetrahydrofuran **11** in 80% yield, which could be deprotected to the hydroxy acid **12** upon exposure to HF. Serendipitously, it was discovered that an extra equivalent of the Lewis acid effected

simultaneous tetrahydrofuran ring formation and alcohol deprotection to give the hydroxy acid **12** directly from **10**.

Scheme II

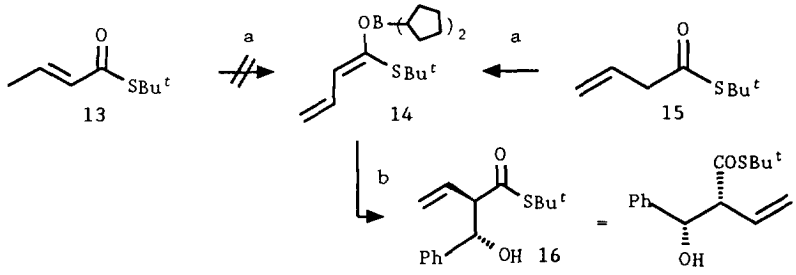


[a](i) $(EtO)_2POCH_2CO_2Et$, NaH; (ii) LiOH, MeOH-THF-H_2O; (iii) $(COCl)_2$, CH_2Cl_2, cat. DMF; (iv) 2-oxazolidone, *n*-BuLi, THF, -78°C; [b](i) Bu_2BOTf, CH_2Cl_2, Et_3N; (ii) Me_2CHCHO, -78°C; (iii) H_2O_2, pH 7; [c](i) TBDMSOTf, 2,6-lutidine, -78°C (94%); (ii) LiOOH, THF-H_2O (91%); [d]Br_2, Et_2O, $NaHCO_3$, 0°C; [e]Bu_3SnH, AIBN, CH_2Cl_2, hν, -78°C; [f]$TiCl_4$ (3 equiv.), CH_2Cl_2, 0°C.

Our general scheme realized, all that remained was to demonstrate anti-selectivity in the aldol reaction, as this would provide access to tetrahydrofurans **2**, and thus **1**, by an analogous route. For this, we turned to thioesters (Scheme III). Anti-selective additions of dicyclobutylboron enolates of tert-butyl thiolates to aldehydes are well documented.[14] Moreover, tert-butyl thiolates can be hydrolyzed to carboxylic acids under mild conditions.[15] However, to the best of our knowledge, neither the formation nor the aldol reactivity of the E(O)-boron dienolate **14** had been reported. Thioester **13** was prepared from crotonyl chloride using the method of Masamune.[16] However, attempts to generate boron dienolate **14** by γ-deprotonation proved unsuccessful. Eventually, the required dienolate was generated from deconjugated thioester **15**, prepared from vinylacetic acid.[17] To our delight, addition to this of benzaldehyde gave hydroxythioester **16** in 76% overall yield (6:1 anti:syn).

This reaction of thioester **15** will form the basis of our routes to tetrahydrofurans **1** and, thus, key pamamycin fragments. Anti diastereoselectivity could be increased using 3-(3-ethyl)pentyl thiolate[18] instead of t-butyl, while employment of a chiral boron triflate would allow the reaction to proceed enantioselectively.[18] As for the bromolactonization of β,γ-unsaturated carboxylic acids, further work is needed. However, we believe that a general strategy for directing 4-exo cyclizations in the halolactonization reaction has been demonstrated.

Scheme III



[a]Dicyclopentylboron triflate, *i*-Pr_2EtN; [b]PhCHO, -78°C

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