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HIGHLY DIASTEREOSELECTIVE ALKYLATION REACTIONS OF VINYLOGOUS URETHANES DERIVED FROM SIMPLE TETRONIC ACIDS

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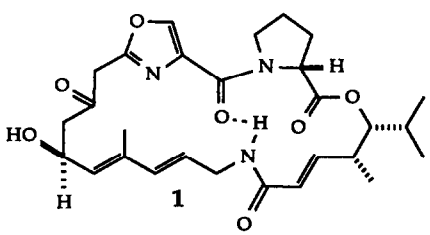
Summary: The lithium enolates generated from the tetronic acid derived vinylogous urethanes 3 and 4 have been found to undergo alkylation reactions with a variety of electrophiles to give products with predictable stereochemistry accompanied by very high diastereoselectivity.

As part of an effort to construct the natural products virginiamycin M_2 (1) and erythronolide A *seco*-acid (2), we examined the alkylation behavior of the lithium enolates derived from vinylogous urethanes **3** and **4**.[1] The results of this investigation reveal that these reactions occur with excellent regio- and diastereoselectivity, that they are quite general, and that a variety of alkylating agents can be utilized.



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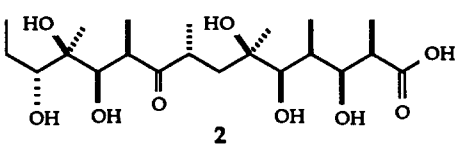

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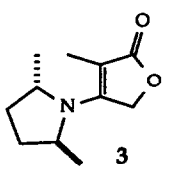

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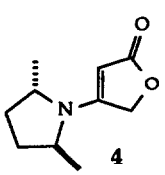

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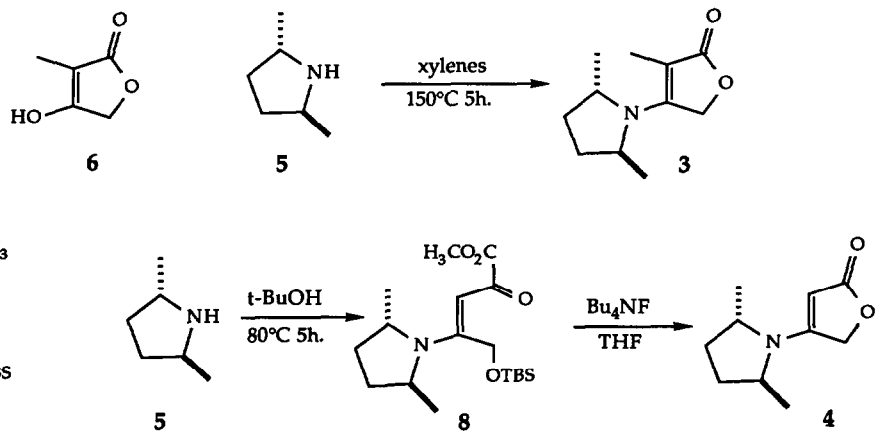
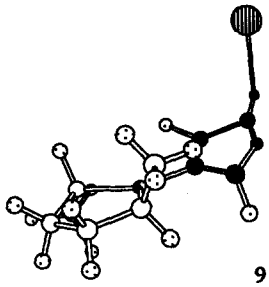
PREPARATION OF THE VINYLOGOUS URETHANES 3 AND 4: Surprisingly, these substances had to be prepared by different routes in order to optimally utilize the chiral auxiliary *trans*-2,5-dimethylpyrrolidine (**5**).[2] Thus, reaction of **5** with the tetronic acid **6**[3] (one equivalent each) in xylenes at 150°C, 5h (Ace-Thred® pressure tube) affords **3** (oil)[4] in 73% yield, after chromatography, $[\alpha]_D$ -126 (c=3.7 CH_2Cl_2). Compound **4**, on the other hand, was prepared by reacting **5** with the acetylenic ester **7** in refluxing *t*-butyl alcohol, 5 h, to afford, in essentially quantitative yield, the vinylogous urethane ester **8**. Treatment of **8** with tetra-*n*-butylammonium fluoride in THF at 0°C to 22°C gave the vinylogous urethane lactone **4**, mp 126-128°C after crystallization[4] in 94% overall yield, $[\alpha]_D$ +4.76 (c=2.5 CH_2Cl_2).



ALKYLATION OF THE VINYLOGOUS URETHANES 3 AND 4: The lithium enolates **9** or **10** could be generated by deprotonation of either **4** or **3**, respectively, in THF solution using *t*-butyllithium (-78°C 30 min). The alkylating agent was then added at -78°C, allowed to react at this temperature for 30 min, and the reaction worked up in the usual fashion. It was our anticipation that **9** and **10**, represented below would undergo alkylation at C-4 of the enolate predominately from the *Re* face. The regioselectivity of these reactions was demonstrated by ^1H NMR analysis (300 MHz) while the diastereoselectivity was found to be best analyzed by HPLC. The absolute stereochemistry of these adducts follows from a single crystal X-ray analysis of compound **12** (Figure 1). Chemical yields, ratios of products, optical rotations, and method of analysis are listed in Table I for each enolate system.



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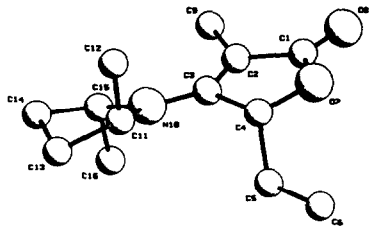

Figure 1

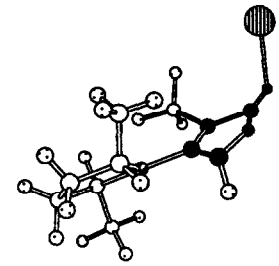

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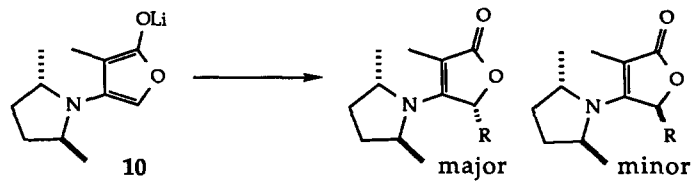
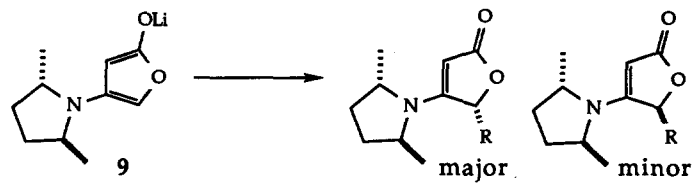
Table I



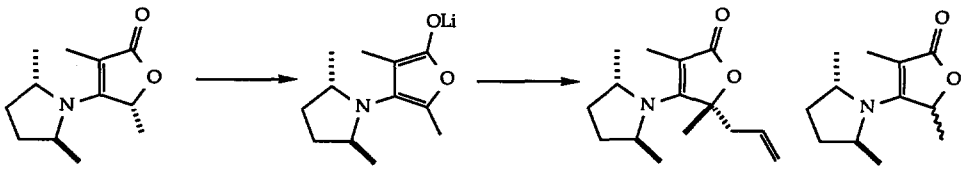
R-X	Compound #	% Major isomer	Optical rotation	% Minor isomer	% Chemical yield
methyl-I	**11**	98%	-333 (c = 2.0 CH_2Cl_2)	2%	86%[5]
ethyl-I	**12**	99%	-252 (c = 2.1 CH_2Cl_2)	1%	74%[5]
allyl-Br	**13**	99%	-170 (c = 2.5 CH_2Cl_2)	1%	89%[5]
benzyl-Br	**14**	99%	-114 (c = 2.0 CH_2Cl_2)	1%	91%[5]



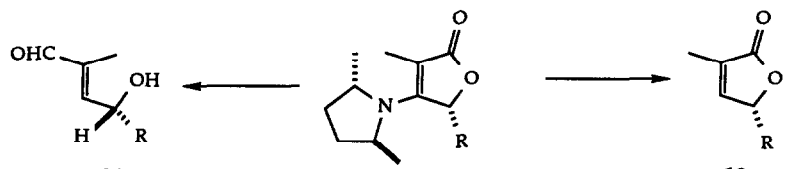
R-X	Compound #	% Major isomer	Optical rotation	% Minor isomer	%Chemical yield
methyl-I	**15**	97%	-111 (c = 0.7 CH_2Cl_2)	3%	88%[5]
ethyl-I	**16**	98%	-53.6 (c = 1.0 CH_2Cl_2)	2%	78%[5]
allyl-Br	**17**	98%	-37.7 (c = 1.8 CH_2Cl_2)	2%	86%[5]
benzyl-Br	**18**	97%	none	3%	95%[6]

Deprotonation of the adducts **11** through **18** can be accomplished using *t*-butyllithium in THF solution at -78°C. These C-4 substituted enolates can be alkylated and chemical yields in the

60% range (not optimized) have been realized–one example is shown below. It is interesting to note the remaining 40% of the reaction mixture is starting material, but with the C-4 alkyl substituent now a 1:1 epimeric mixture.[7]



Like their six-membered-ring analogues,[8] these butyrolactone derived vinylogous urethanes undergo dissolving metal reductions followed by elimination of the amine residue to give either butenolides of type **19** or 4-hydroxy unsaturated aldehydes of type **20**.



20 **19**

Ackowledgment. Financial support from the NIH and the Merck Corporation are gratefully acknowledged.

REFERENCES AND FOOTNOTES

1. Holker, J. S. E.; Fell, S. C. M.; Heaps, J *J. Chem. Soc. Chem. Commun.* **1979**, 81, had established, at the time we started this work, that the pyrrolidine analogue of **3** regioselectively alkylated at C-4. No information was available on the alkylation behavior of systems similar to **4** that lack a C-2 substituent.

2. Schlessinger, R. H.; Iwanowicz, E. J. *Tetrahedron Lett.* **1987**, *28*, 2083-2086.

3. The protocol described by Zimmer, H.; Schmidt, D. G. *Synthetic Commun.* **1981**, *11*, 385-390 was followed in this instance starting from 2-methyl ethylacetoacetate.

4. The vinylogous urethane lactones **3** and **4** both contain ca. 1.2% of the *cis*-2,5-dimethylpyrrolidine isomer–the result of contamination in the *trans*-2,5-dimethylpyrrolidine used for their preparation. Authentic **3** and **4** carrying the *cis*-2,5-dimethylpyrrolidine ring (hydrogenation of 2,5-dimethylpyrrole) were prepared. Alkylations of these compounds, as described for the *trans*-dimethyl pyrrolidine species, **3** and **4** were carried out for purposes of NMR and HPLC comparison.

5. Yields reported are for chromatographed, and where possible, crystallized, materials, chemical ratios were determined by HPLC analysis.

6. The chemical yield and isomer ratio in this instance was evaluated by ^{1}H NMR (300 MHz). This substance could not be chromatographed or crystallized, and therefore the yield must be considered crude.

7. The diastereofacialselectivity shown by enolates **9** and **10** on alkylation is reasonable considering the relationship of the chiral auxiliary to the reactive nucleophilic center. It is not surprising however, that protonation of these enolates under the conditions used (NH_4Cl/H_2O) is non-stereoselective.

8. Schlessinger, R. H.; Iwanowicz, E. J.; Springer, J. P. *J. Org. Chem.* **1986**, *51*, 3070.

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