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An Approach to Erythronolide A Seco Acid via a Simple Tetronic Acid

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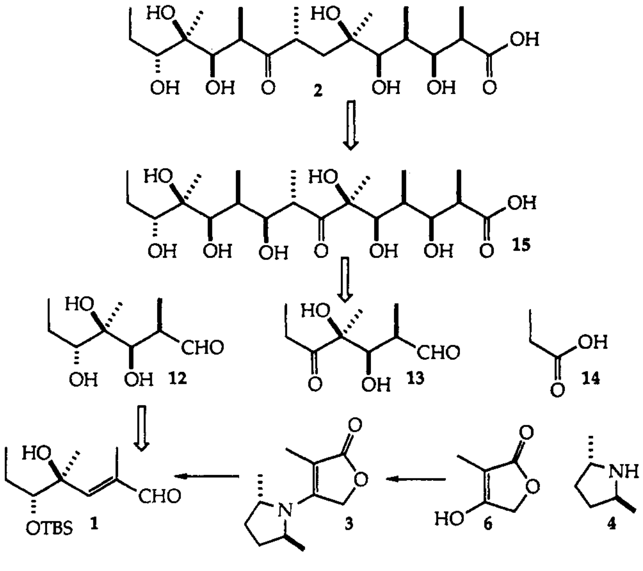
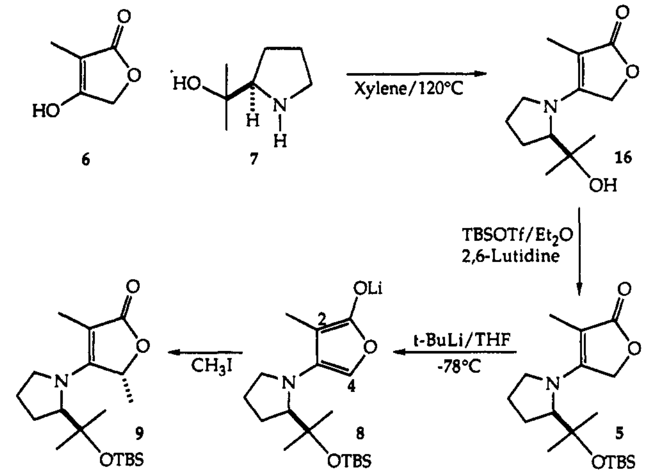
Summary: The unsaturated aldehyde **1**, a key intermediate in our approach to erythronolide A seco acid (**2**), has been prepared from the simple tetronic acid **6** by its seriatim transformations into the vinylogous urethanes **5**, **9**, and **11** concluding with reductive conversion of the latter into **1**.

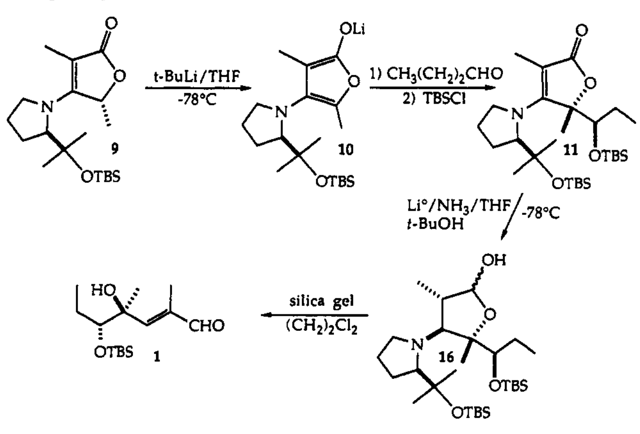
We have been engaged in attempts to develop a simple means of securing the aldehyde **1** in nonracemic form, since it plays a pivotal role in our approach (outlined below) to erythronolide A seco acid (**2**).[1] Indeed, we had secured a route to chiral **1** starting from the vinylogous urethane lactone (VUL) **3**,[2] but concluded that realizing sufficient quantities of **1** would be limited by our ability to prepare in large quantities the C_2 symmetric pyrrolidine derivative **4**.[3]



To circumvent this problem, we chose to examine the behavior of the VUL **5**, a substance prepared from the tetronic acid **6** and the readily available amino alcohol **7**.[4] The lithium enolates derived from vinylogous urethane lactones such as **3**, and less elaborate analogues, are known to react at C-4.[2,5] Calculations show this regioselectivity to result when the nitrogen lone pair interacts with the π-system of the lactone ring enolate enhancing the C-4 orbital coefficient.[6] This electronic circumstance requires the pyrrolidine ring of **3** to be relatively coplanar to the lactone ring enolate—hence, we held the hope that reactions of **5**, as its lithium enolate, might be highly diastereoselective, since the only reasonable geometric form to exhibit C-4 reactivity for this species would be that depicted in structure **8**.



Condensation of a mixture of **6** and **7** in xylenes (120 °C) followed by protection of the tertiary alcohol residue of the crude product with *tert*-butyldimethylsilyl trifluoromethane sulfonate gave the VUL **5** in 74% yield (two steps). Deprotonation of **5** using *tert*-butyl lithium in THF at −78 °C gave the enolate **8**, and this species upon alkylation with methyl iodide afforded **9** as a single diastereomer, $[\alpha]_D$ −183.8° (c = 0.85, CH_2Cl_2) (mp 89–90 °C), in 93% yield.[7] Treatment of **9** with *tert*-butyllithium in THF at −78 °C generated the enolate **10**,[8] which on treatment with propionaldehyde, followed by trapping of the resulting lithium adolate with *tert*-butyldimethylsilyl chloride, gave **11** as a single diastereomer, $[\alpha]_D$ −207.6° (c = 2.3, CH_2Cl_2), in 97% yield. **1**, as a single diastereomer, $[\alpha]_D$ 17.55 (c = 7.50, CH_2Cl_2), was obtained in 57% yield by a dissolving metal reduction of **11** followed by elimination of the β-amino lactol residue using silica gel suspended in $(CH_2)_2Cl_2$.[9]



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(1) For a detailed outline of this strategy together with the preparation of racemic 1, the proof of structure of 1, and subsequent transformations of it, see: Adams, A. D. PhD. Dissertation, University of Rochester, Rochester, NY, 1986.

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(6) Private communication from Professor Dennis Liotta. We thank Professor Liotta for these calculations.

(7) Full experimental details are available in the supplementary material.

(8) Protonation of this enolate affords an epimeric mixture of **9** at C-4. Similar behavior was observed for materials derived from the VUL **3**, ref 2.

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The unsaturated aldehyde 1, prepared from 5 by the protocol outlined above, was compared to that obtained from the optically active VUL 3. Both aldehyde samples were found to be idential with respect to optical rotation and the retention time using chiral stationary-phase HPLC analysis. Racemic 1 was prepared from the pyrrolidine analogue of 3, again by the same experimental protocol as used for the conversion of either 5 or 3.[1] This racemic substance was used as a standard for the HPLC evaluations of optical purity of 1 as obtained from either 5 or 3—in both of these cases the optical purity of 1 was greater than 99:1. Lastly, a single-crystal X-ray determination of 9 was carried out, and its structure demonstrated to be that as shown in 9.

Acknowledgment. Financial support from the NIH and the Merck Sharp and Dohme Corp. is gratefully acknowledged.

Supplementary Material Available: Experimental procedures, compound characterization data, and X-ray data (14 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(9) The low-yield step in this two reaction sequence is the amine elimination—a subject of further experimental effort.

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Cyclizations of 3,4-Pentadien-1-yllithium Reagents

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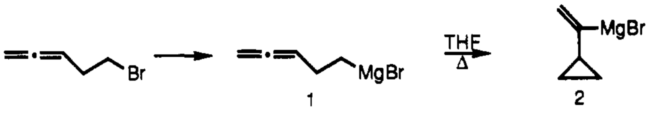
Summary: A number of 3,4-pentadien-1-yllithium reagents were obtained by metal–halogen exchange. Certain of these intermediates undergo facile cyclization to the isomeric 1-cyclobutenylmethyllithium derivatives.

Recent advances in the methodology for lithium–iodine exchange[1] have enabled the smooth formation and subsequent cyclization of a number of olefinic[2] and acetylenic[3] organolithium derivatives without interference from competing radical processes. Our long-standing interest in the utilization of the allene function as a site for intramolecular reactions of organometallic and radical intermediates[4-6] has prompted an examination of this potential route to allenic alkyllithiums.[7] We describe herein the chemistry of 3,4-pentadien-1-yllithium intermediates.[8] The only prior report in the literature on a homoallenyl main-group organometallic concerns the formation of the parent Grignard reagent 1 from the corresponding bromide in modest yield and the slow, but complete conversion of this species into its cyclopropyl isomer 2 upon heating in THF.[9] For comparison, the analogous 3-butenyllithium reagents interconvert with the isomeric cyclopropylcarbinyl species in a number of instances, although the acyclic form is ordinarily favored at equilibrium owing to the strain associated with the cyclopropyl ring in the cyclic isomer.[10]

Table I. **Reactions of Organolithium Reagents 4 and 6 with Electrophiles**

RI	t-BuLi equiv	E	additive	products[a] (%) 5	7	8
3a	1.6[b]	CHOHPh		92		
3a	2.05	$COHBu_2$	TMEDA		62	
3a	2.05	$SnPh_3$				59[c]
3a	2.05	CHOHPh	TMEDA		70[d]	30[d]
3a	2.05	CHOHPh	Ti(O-i-Pr)$_4$		68	
3b	1.6[b]	CHOHPh		82		
3b	2.05	$COHEt_2$			61	16
3b	2.05	CHOHPh	Ti(O-i-Pr)$_4$		82	
3c	2.05	CHOHPh		75		
3d	1.6[b]	TMS		80		
3e	2.05	$COHBu_2$			39	

[a] Isolated yields based on iodide. [b] Reaction not warmed to room temperature. [c] 4:1 mixture of 8:7 in crude product. [d] Not isolated, product ratio.



Fortunately, the rapid metal–halogen exchange induced by treating allenic iodides 3 with t-BuLi was not usually complicated by direct metalation of the allene function, which is also a facile process.[11] Thus, the parent iodide

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