α-ALLYLATION OF β-TETRONIC ACIDS AND CHIRALITY TRANSFER *VIA* THE 4-OXYGENATED 2(5*H*)-FURANONE SYSTEM

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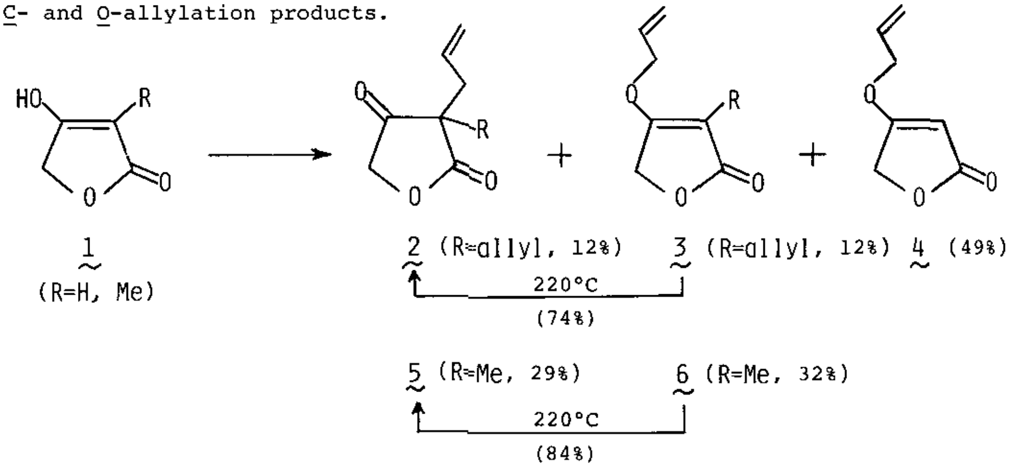
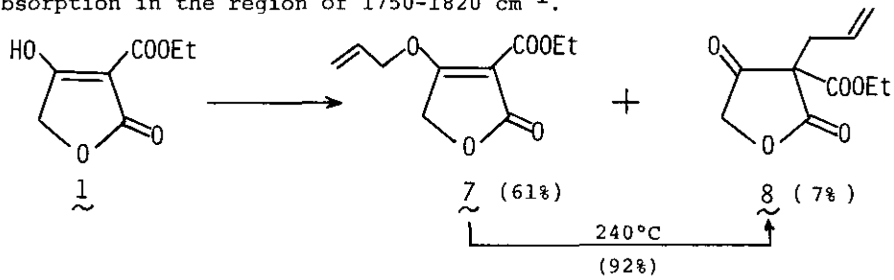
Abstract- α-Allylation of the β-tetronate system was accomplished by direct attack of allyl halide on C-3 of the system in the presence of potassium carbonate in *N*,*N*-dimethylformamide or the Claisen rearrangement of allyl tetronates concomitantly formed in the preceding direct allylation. The chirality of natural L-amino acids was transferred into the β-tetronic acid system at the α-position *via* initial incorporation into the γ-position and subsequent α-allylation by application of analogous sequence of reactions.

Although substituted tetronic acids have received much attention as starting materials for several classes of natural products,[1] the selective *C*-alkylation essential for the modification of the system as synthetic strategy has been reported only to a small extent.[2] In our continuous studies on the 4-hydroxy-2(5*H*)-furanone system associated with the synthetic design of biologically active compounds, we examined the effective α-allylation of β-tetronic acids (**1**; R=H,[3a] Me,[1f] COOEt[3b]).
Direct allylation of **1** (R=H or Me) was effected by action of allyl bromide in *N*,*N*-dimethylformamide (DMF) at 80°C in the presence of potassium carbonate (K_2CO_3) to give *C*- and *O*-allylation products.



Allyl α-allyl- or α-methyltetronate (**3** or **6**) was transformed into 2,4(3*H*,5*H*)-furandione (**2** or **5**) in 74% or 84% yield by the Claisen rearrangement on heating at 220°C. Allylation of α-ethoxycarbonyl-β-tetronic acid (**1**; R=COOEt), on the other hand, gave *O*- and *C*-allylation product (**7** and **8**) in relatively low yield under the same conditions as above. When the allylation was conducted under sonication in hexamethylphosphoric triamide (HMPA) in the presence of silver oxide (Ag_2O), *O*- and *C*-allylation product (**7** and **8**) were obtained in 61% and 7% yield, respectively. The *O*-allylation product **7** was transformed into **8** in 92% yield by the Claisen rearrangement on heating at 240°C. The 2,4(3*H*,5*H*)-furandiones **2**, **5**, and **8** display a characteristic ir absorption in the region of 1750-1820 cm^{-1}.[4]



1

7 (61%)

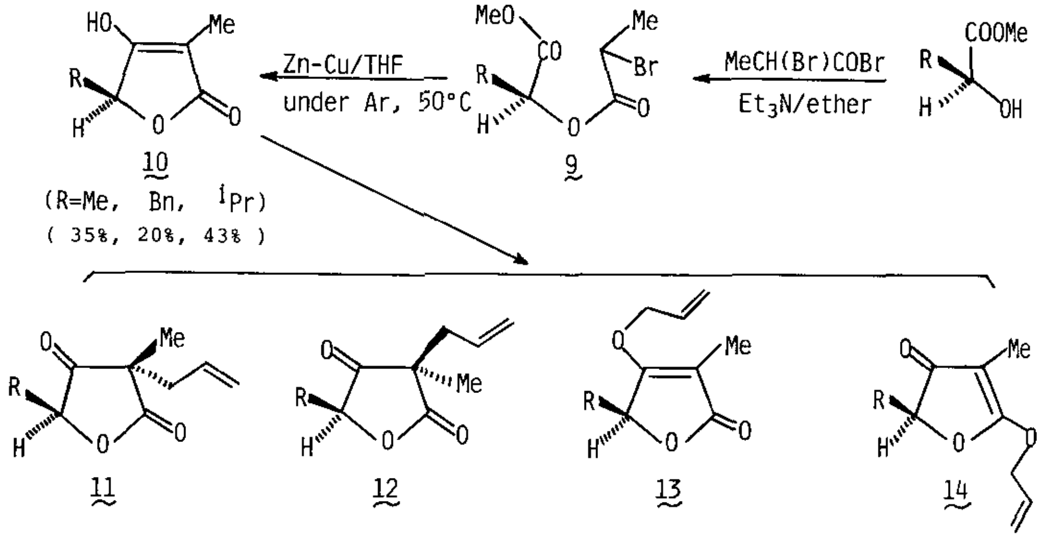
8 (7%)

240°C
(92%)

We extended the above allylation procedure to chiral tetronic acids in order to examine the transfer of chirality of natural L-amino acids into their α-position, and realized considerable diastereoselectivity in α-allylation.

To date, a number of methods to produce quaternary carbons in an efficient and enantioselective manner from 'deracemizing alkylations' of tertiary carbon centers have been developed,[5] and the method using chiral γ-lactones[6] or γ-lactam[7] has also been reported. We examined the introduction of chirality into the α-carbon of the β-tetronic acid system *via* its initial incorporation into the γ-position followed by application of the reaction sequence investigated above. The preparation of the starting chiral tetronic acids was first investigated.

Although a number of synthetic routes to substituted tetronic acids have been developed,[4a,8] few of these are practically general, simple, and applicable to the synthesis of 'chiral' tetronic acids. Of the methods reported, the preparation of α,γ-disubstituted tetronic acids and α,α-disubstituted 2,4(3*H*,5*H*)-furandiones by use of the Reformatsky reaction of a silylated cyanohydrin with an α-bromo ester[9] was attractive as ones of general utility for our purpose. We examined the 'intramolecular' Reformatsky-fashioned ring closure of α-bromo diesters (**9**). The optically active diesters were readily prepared by reaction of α-bromoacyl bromide with α-hydroxy esters which were derived from the diazotization of natural L-amino acids.

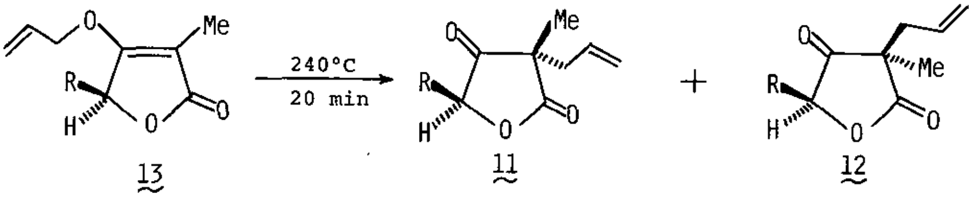


(R=Me, Bn, ^{i}Pr)
(35%, 20%, 43%)

	11	12	13	14
R=Me	29%	8%	42%	2.5%
R=Bn	30%	5%	39%	2.4%
R=^{i}Pr	42%	2%	39%	1.3%

(isolated yield)

The 'intramolecular' Reformatsky reaction of 9 was achieved in the presence of activated zinc[10] in tetrahydrofuran (THF) to give the desired tetronic acids (10) in 20-43% yield. The allylation of 10 (R=Me, Bn, ^{i}Pr) was conducted in HMPA in the presence of Ag_2O under sonication below 10°C to give four allylation products. The stereochemistry of the diastereoisomers 11 (R=^{i}Pr) and 12 (R=^{i}Pr) was assigned on the basis of the nuclear Overhauser enhancement and exchange spectroscopy (NOESY) experiment,[11] and the nuclear Overhauser effect (NOE) was observed between the dimethyl in isopropyl moiety at C-5 and C_3-methyl for 11 and lacked for 12, while it was evident between the dimethyl and C_3-allyl methylene for 12 and lacked for 11.

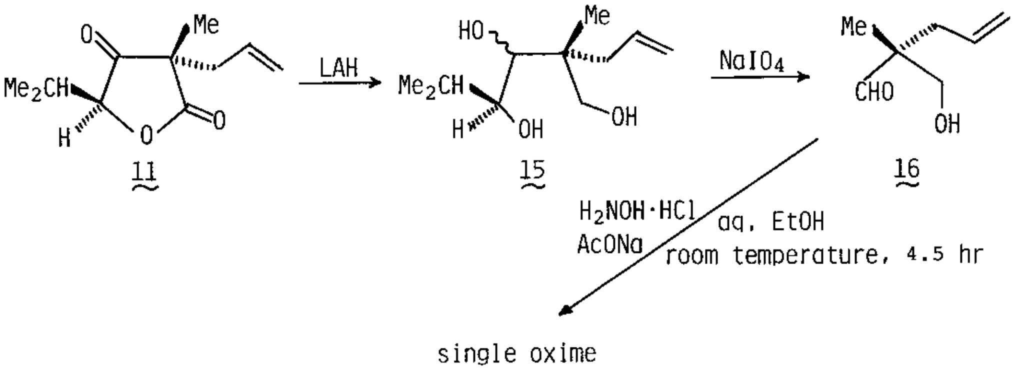


	11	12
R=Me	56%	14%
Bn	56%	18%
iPr	58%	7%

(isolated yield)

When the reaction was conducted in DMF in the presence of K_2CO_3, the product resulted in some racemization at the γ-position as evidenced by monitoring the optical rotation.[12] The Claisen rearrangement of the allyl tetronate 13 was effected by heating at 240°C for 20 min to give 2,4(3*H*,5*H*)-furandiones 11 and 12 in 64-70% total yield. Stereoselectivity of the rearrangement was lower than the preceding direct allylation.

The major isomer 11 ($R={}^{i}Pr$) from both the direct allylation and the Claisen rearrangement was then transformed into a 'chiron' bearing an asymmetric quaternary carbon. The lithium aluminum hydride (LAH) reduction of 11 ($R={}^{i}Pr$) gave a highly crystallizable triol (15),[13] oxidative cleavage of which at the 1,2-glycol moiety with sodium metaperiodate gave a hydroxy aldehyde (16)[14] in 70% yield from 11. The properties of its oxime are as follows: A colorless viscous oil; $[\alpha]_D^{16.5}$ +0.93° (c=2.70, $CHCl_3$); ^1H-nmr(500 MHz, $CDCl_3$) δ: 1.08(3H, s), 2.22 & 2.25(each 1H, each ddd, *J*=7.2, 2.5, 1.1 Hz), 2.42(1H, br, exchangeable with D_2O), 3.55 & 3.61(each 1H, each d, *J*=11.2 Hz), 5.11(1H, dm, *J*=16.5 Hz), 5.12(1H, dm, *J*=10.5 Hz), 5.79(1H, ddt, *J*=16.5, 10.5, 7.2 Hz), 7.36(1H, s), 7.45(1H, br, exchangeable with D_2O); ir($CHCl_3$) cm^{-1}: 3280, 2900, 1638, 1036, 990, 919.



All new compounds described above gave satisfactory spectroscopic and combustion data.

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11. ^{1}H-Nmr spectra (both 1D and 2D) were taken on a JEOL JNM-GSX 500 spectrometer for the *ca.* 0.75% solution in $CDCl_3$ with tetramethylsilane as an internal standard.

12. Specific rotations of the sample of **11** are shown below:

11 (R=Me) : $[\alpha]_D^{21.5}$ $-41.8°$ (c=1.10, $CHCl_3$) (method with Ag_2O)
$[\alpha]_D^{22}$ $-41.9°$ (c=0.86, $CHCl_3$) (method by the Claisen Rearr.)
$[\alpha]_D^{21.5}$ $-37.3°$ (c=1.10, $CHCl_3$) (method with K_2CO_3)
11 (R=Bn) : $[\alpha]_D^{21}$ $-103.8°$ (c=1.06, $CHCl_3$) (method with Ag_2O)
$[\alpha]_D^{21}$ $-105.0°$ (c=1.0, $CHCl_3$) (method by the Claisen rearr.)
$[\alpha]_D^{21}$ $-82.1°$ (c=1.12, $CHCl_3$) (method with K_2CO_3)
11 (R=iPr): $[\alpha]_D^{21}$ $-106.7°$ (c=1.27, $CHCl_3$) (method with Ag_2O)
$[\alpha]_D^{20}$ $-106.4°$ (c=2.34, $CHCl_3$) (method by the Claisen rearr.)
$[\alpha]_D^{20}$ $-102.4°$ (c=2.065, $CHCl_3$) (method with K_2CO_3)

The value obtained from the run by K_2CO_3 catalysis indicates some contamination by the antipode resulting from the epimerization of **12**.

13. A mixture of one-sided ratio of stereoisomers. Single recrystallization from benzene gave a pure sample, mp 96-97°C, of the major isomer.

14. A less stable colorless oil. Ir($CHCl_3$) cm^{-1}: 3565, 3400, 3080, 2920, 2860, 2700, 1720, 1640, 1460, 1373, 1038, 999, 920. ^{1}H-Nmr(270 MHz, $CDCl_3$) δ: 1.10 (3H, s), 1.91(1H, t, *J*=6.0 Hz, exchangeable with D_2O), 2.29 & 2.35(each 1H, each ddt-like, *J*=14.2, 7.5, 1.0 Hz), 3.63 & 3.72(each 1H, each dd, *J*=11.6, 6.0 Hz), 5.14(1H, dm, *J*=9.7 Hz), 5.15(1H, dm, *J*=17.5 Hz), 5.77(1H, ddt, *J*=17.5, 9.7, 7.5 Hz), 9.58(1H, s).

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