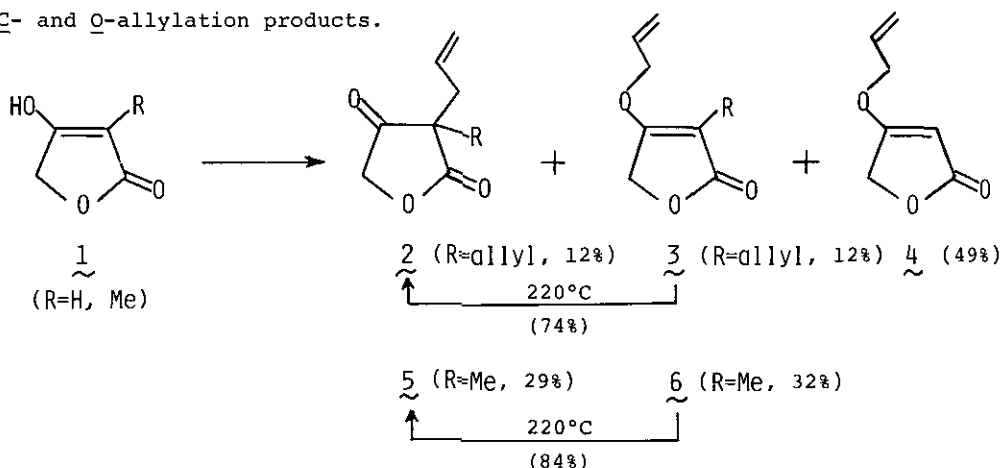


α-ALLYLATION OF β-TETRONIC ACIDS AND CHIRALITY TRANSFER VIA THE 4-OXYGENATED 2(5H)-FURANONE SYSTEM

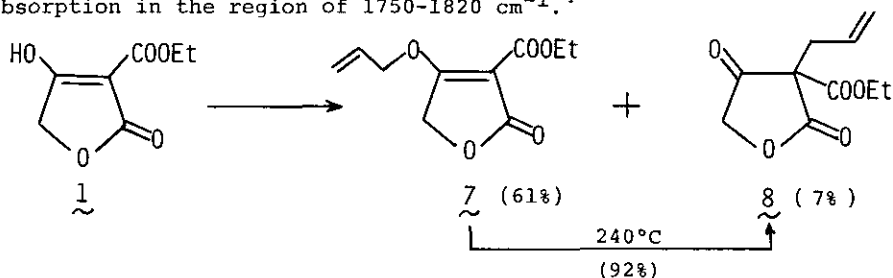
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Abstract- α -Allylation of the β -tetronate system was accomplished by direct attack of allyl halide on C-3 of the system in the presence of potassium carbonate in *N,N*-dimethylformamide or the Claisen rearrangement of allyl tetronates concomitantly 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(5H)-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 (K₂CO₃) to give C- and O-allylation products.



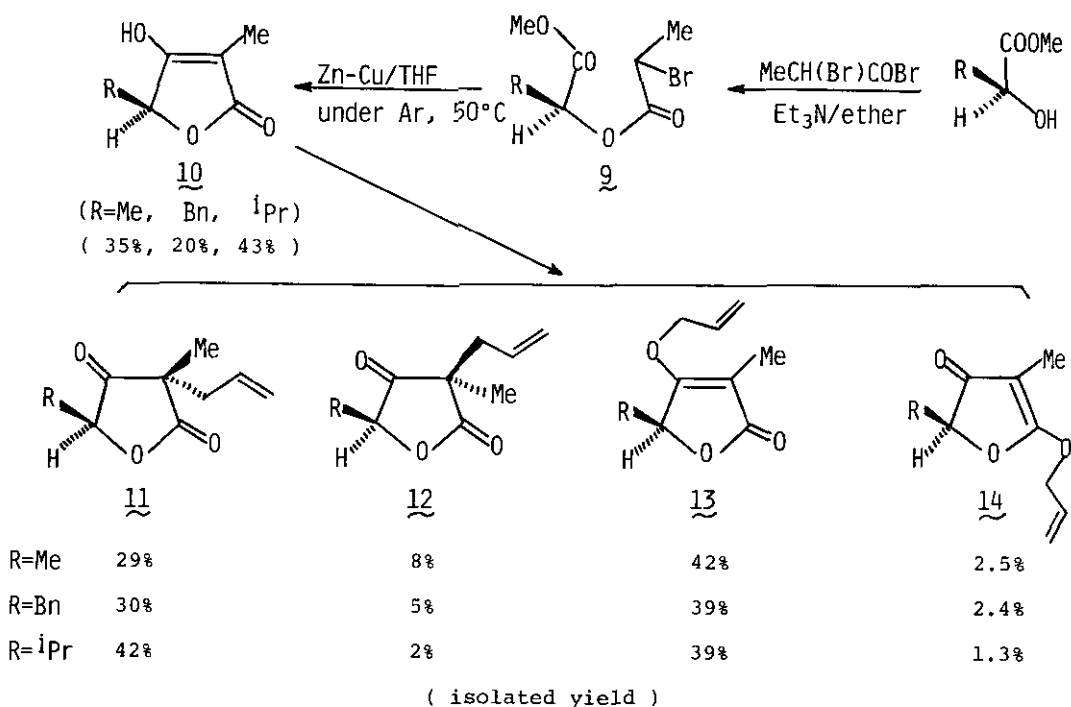
Allyl α -allyl- or α -methyltetronate (3 or 6) was transformed into 2,4(3H,5H)-furan-dione (2 or 5) in 74% or 84% yield by the Claisen rearrangement on heating at 220°C. Allylation of α -ethoxycarbonyl- β -tetronic acid (1; R=COOEt), on the other hand, gave O- and C-allylation product (7 and 8) in relatively 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 (Ag₂O), 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(3H,5H)-furan-diones 2, 5, and 8 display a characteristic ir absorption in the region of 1750-1820 cm⁻¹.⁴



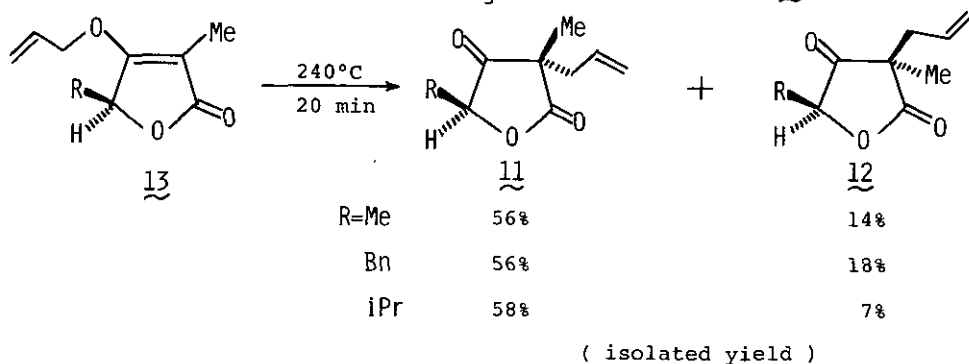
We extended the above allylation procedure to chiral tetronic acids in order to examine the transfer of chirality of natural L-amino acids into their α -position, and realized considerable diastereoselectivity in α -allylation.

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 -lactones⁶ or γ -lactam⁷ 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(3H,5H)-furan-diones by use of the Reformatsky reaction of a silylated cyanohydrin with an α -bromo ester⁹ 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.

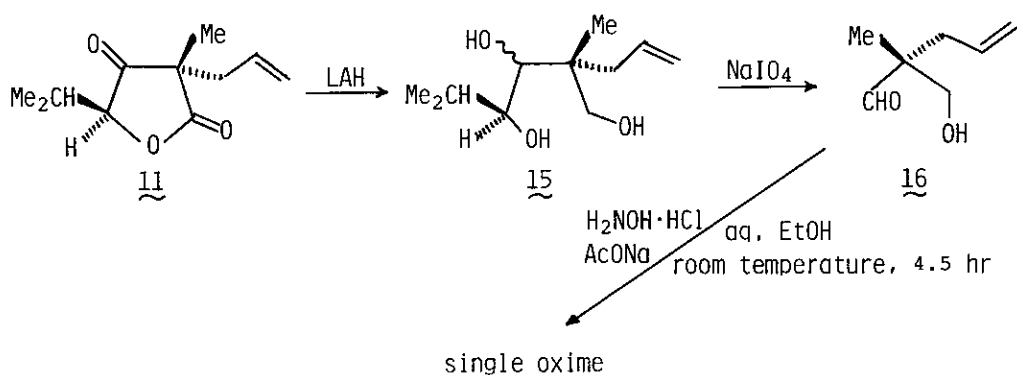


The 'intramolecular' Reformatsky reaction of 9 was achieved in the presence of activated zinc¹⁰ in tetrahydrofuran (THF) to give the desired tetronic acids (10) in 20-43% yield. The allylation of 10 (R=Me, Bn, *i*Pr) was conducted in HMPA in the presence of Ag_2O under sonication below 10°C to give four 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 C₃-methyl for 11 and lacked for 12, while it was evident between the dimethyl and C₃-allyl methylene for 12 and lacked for 11.



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(3H,5H)-furanones 11 and 12 in 64-70% total yield. Stereoselectivity of the rearrangement was lower than the preceding direct allylation.

The major isomer 11 ($R=iPr$) 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 ($R=iPr$) 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; $[\alpha]_D^{16.5} +0.93^\circ$ ($c=2.70$, $CHCl_3$); 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. $^1\text{H-Nmr}$ 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:
- | | | | | |
|---------------------|------------------------------|----------------|-----------------------------|----------------------------------------|
| <u>11</u> (R=Me) : | $[\alpha]_{\text{D}}^{21.5}$ | -41.8° | (c=1.10, CHCl_3) | (method with Ag_2O) |
| | $[\alpha]_{\text{D}}^{22}$ | -41.9° | (c=0.86, CHCl_3) | (method by the Claisen Rearr.) |
| | $[\alpha]_{\text{D}}^{21.5}$ | -37.3° | (c=1.10, CHCl_3) | (method with K_2CO_3) |
| <u>11</u> (R=Bn) : | $[\alpha]_{\text{D}}^{21}$ | -103.8° | (c=1.06, CHCl_3) | (method with Ag_2O) |
| | $[\alpha]_{\text{D}}^{21}$ | -105.0° | (c=1.0, CHCl_3) | (method by the Claisen rearr.) |
| | $[\alpha]_{\text{D}}^{21}$ | -82.1° | (c=1.12, CHCl_3) | (method with K_2CO_3) |
| <u>11</u> (R=iPr) : | $[\alpha]_{\text{D}}^{21}$ | -106.7° | (c=1.27, CHCl_3) | (method with Ag_2O) |
| | $[\alpha]_{\text{D}}^{20}$ | -106.4° | (c=2.34, CHCl_3) | (method by the Claisen rearr.) |
| | $[\alpha]_{\text{D}}^{20}$ | -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 $96-97^\circ\text{C}$, of the major isomer.
14. A less stable colorless oil. $\text{Ir}(\text{CHCl}_3) \text{ cm}^{-1}$: 3565, 3400, 3080, 2920, 2860, 2700, 1720, 1640, 1460, 1373, 1038, 999, 920. $^1\text{H-Nmr}$ (270 MHz, CDCl_3) δ : 1.10 (3H, s), 1.91(1H, t, $\underline{J}=6.0$ Hz, exchangeable with D_2O), 2.29 & 2.35 (each 1H, each ddt-like, $\underline{J}=14.2, 7.5, 1.0$ Hz), 3.63 & 3.72 (each 1H, each dd, $\underline{J}=11.6, 6.0$ Hz), 5.14(1H, dm, $\underline{J}=9.7$ Hz), 5.15(1H, dm, $\underline{J}=17.5$ Hz), 5.77(1H, ddt, $\underline{J}=17.5, 9.7, 7.5$ Hz), 9.58(1H, s).

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