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Cyclohexyl Spiro-Fused α-Hydroxy Tetronic Acid Derivatives From Vitamin C

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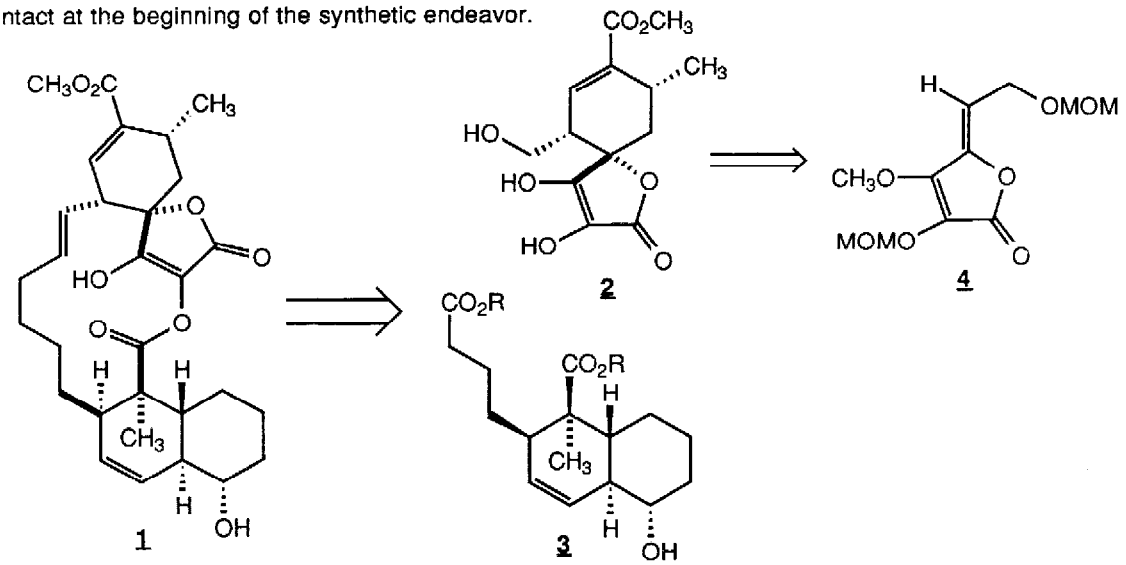
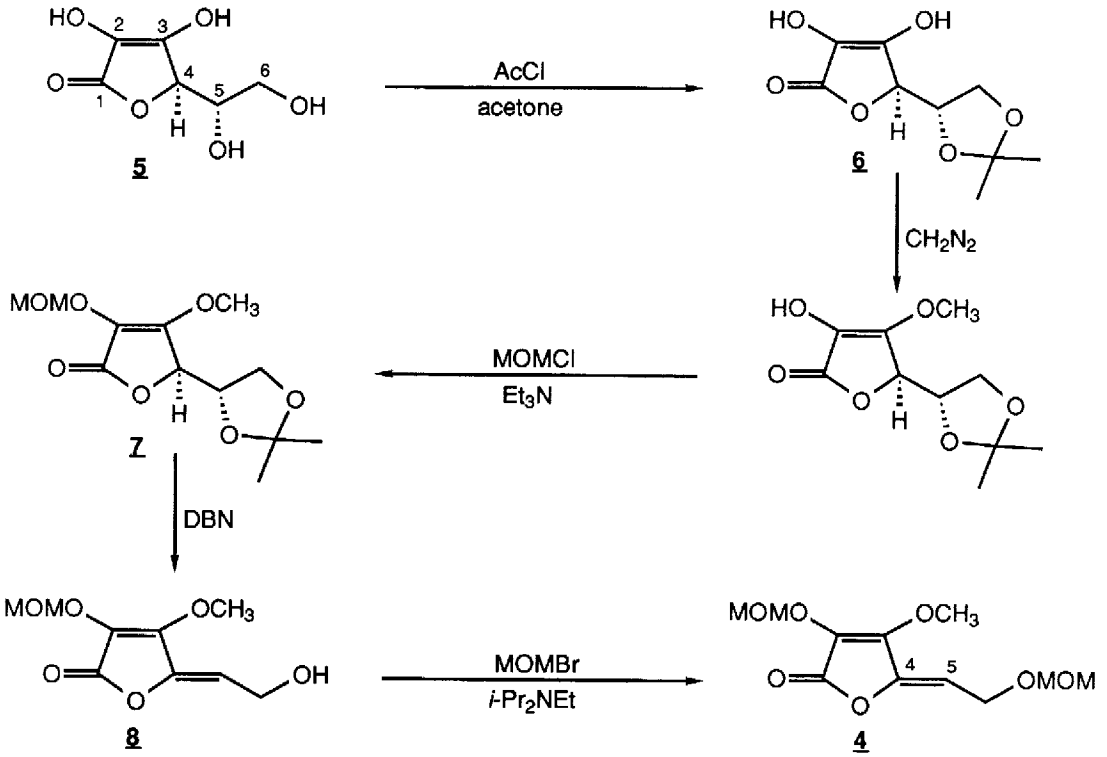
Abstract: The reaction of dienophile **4**, prepared from L-ascorbic acid in 5 steps, with various dienes to prepare cyclohexyl spiro-fused α-hydroxy tetronic acid derivatives is reported.

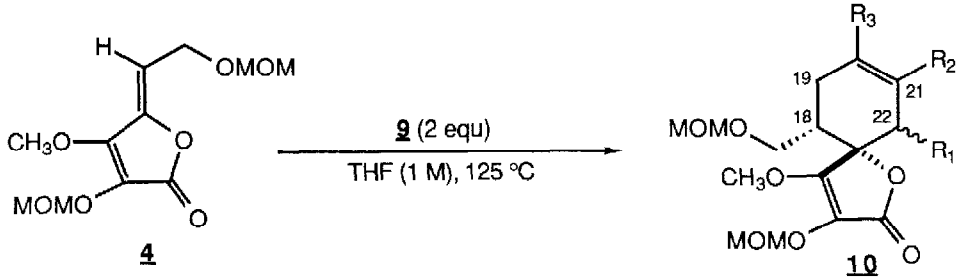
Chlorothricolide methyl ester, **1**, the aglycone of the antibiotic chlorothricin, has traditionally been retrosynthetically dissected into two nearly equal portions, **2** (top half) and **3** (bottom half).[1] Previous reports directed towards the bottom half of the macrocycle have culminated in the preparation of various versions of the *trans*-decalin ring system.[2] The carbocyclic skeleton of **2** has been assembled by Schmidt using the addition of a lithiated acrylate species to a substituted cyclohexanone.[3] Ireland has also fashioned an intermediate towards the top half of **1** by the intramolecular cyclization of an ester enolate with a cyclic anhydride.[4] Herein, we report the construction of various cyclohexyl spiro-fused α-hydroxy tetronic acid derivatives towards **2** by the [4+2] cycloaddition between ascorbic acid derived dienophile **4** and assorted dienes. This route differs from the aforementioned synthetic efforts in that the α-hydroxy tetronic acid functionality is intact at the beginning of the synthetic endeavor.

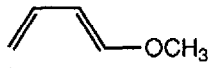
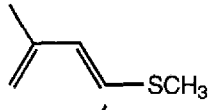
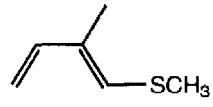
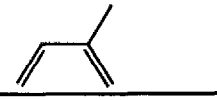


Vitamin C contains the α-hydroxy tetronic acid nucleus required in the natural product and functionality strategically oriented for conversion into dienophile **4**. Treatment of L-ascorbic acid, **5**, with catalytic acetyl chloride (0.25 equ.) in acetone (1.4 M, RT, 4.5 h) gave acetonide **6** in 80% yield.[5] Exposure of **6** to diazomethane (N-methyl-N-nitrosourea/KOH, 0.25 M MeOH, -20 °C, 97% yield) followed by reaction with MOMCl (1.3 equ.) and Et_3N (1.5 equ.) in THF (0.2 M, RT, 2 h, 97% yield) gave protected **7**.[6] Next, the C-4,5-exocyclic methylene was introduced by treatment of **7** with DBN (1.1 equ., 0.4 M THF, RT, 18 h, 67% yield) to afford **8** as a single olefinic isomer.[6,7] The stereochemistry about carbons 4 and 5 in **7** dictates an antiperiplanar elimination of the 5,6-O-isopropyl group leading only to the Z-configuration of the exocyclic double bond. Protection of the remaining alcohol as its methoxy methyl ether with MOMBr (2 equ.) and diisopropyl ethyl amine (2.5 equ.) in methylene chloride (1 M, RT, 18 h, 86% yield) finished the assembly of **4**.[8]

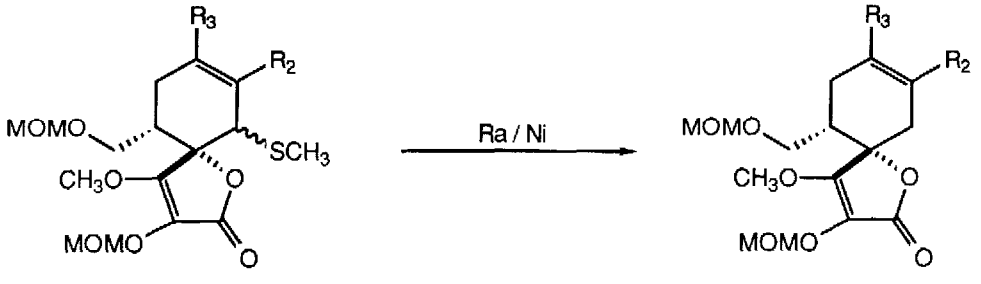


Having successfully prepared **4**, we embarked upon a study of its behavior in Diels-Alder reactions (Table).[9] Dienophile **4** was reacted with 1-methoxy-1,3-butadiene (2 equ.), **9a**, in THF (1 M) at 125 °C for 7 days and found to give spiro-adduct **10a** in 54% yield.[6,10] The position of the methoxy group on the cyclohexene ring of **10a** demonstrates the electron withdrawing effect of the α-hydroxy tetronic acid functionality in **4** on the C-4,5 double bond. The cycloaddition reaction, however, displayed no exo-endo orientation preference of the diene with respect to the dienophile as evidenced by a 1:1 mixture of stereoisomers at the methyl ether functionality.[11]



	diene (**9**)	reaction time	product (**10**)	yield (%)
a		7 d	$R_1 = OCH_3$, $R_2 = R_3 = H$	54
b		12 d	$R_1 = SCH_3$, $R_2 = H$, $R_3 = CH_3$	76
c		3 d	$R_1 = SCH_3$, $R_2 = CH_3$, $R_3 = H$	77
d		4 d	$R_1 = R_2 = H$, $R_3 = CH_3$	30

Treatment of **4** with thiomethyl substituted dienes **9b** and **9c** afforded [4+2] cycloaddition products **10b** and **10c**.[6,10] Again, the products from these reactions were equal mixtures of stereoisomers at the thio allylic position.[11] Exposure of **10b** or **10c** to Raney-Nickel in EtOH (0.03 M, reflux, 4 h) gave the corresponding desulfurized spiro-adducts, **11** (74% yield) and **12** (88% yield), as single stereoisomers, thus demonstrating the integrety of the C-4,5 exocyclic methylene of **4** in the Diels-Alder reaction.[6] Further experimentation showed that reaction of dienophile **4** with isoprene, **9d**, gave only geometric isomer **10d** rather than the commonly expected regiochemical mixtures.[12] The application of this methodology to the preparation of the top half of chlorothricolide is currently in progress.



10b $R_2 = H$, $R_3 = CH_3$
10c $R_2 = CH_3$, $R_3 = H$

11 $R_2 = H$, $R_3 = CH_3$
12 $R_2 = CH_3$, $R_3 = H$

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5. Jung, M. E.; Shaw, T. J. *J. Am. Chem. Soc.* **1980**, *102*, 6304.

6. All new compounds were characterized by IR, ^{1}H-NMR, ^{13}C-NMR and MS. Satisfactory combustion analyses were obtained for compounds **10a**, **10b**, **10c**, **10d**, **11** and **12**.

7. Eitelman, S.; Hall, R.; Jordaan, A. *J. C. S. Chem. Commun.* **1976**, 923.

8. Dienophile **4**: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 5.41 (t, 1H, J=7.1 Hz), 5.14 (s, 2H), 4.56 (s,2H), 4.24 (d, 2H, J=7.1 Hz), 4.12 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H). ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 164.9, 150.3, 143.4, 122.2, 105.7, 97.8, 96.6, 60.9, 59.8, 58.0, 55.6. IR ($CHCl_3$): λ 1774, 1659 cm^{-1}. Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.63; H, 6.22.

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10. Regiochemistry of the Diels-Alder adducts was assigned based on 300 MHz decoupled ^{1}H-NMR. The C18 methine proton (compound **10**) was found to be coupled to the adjacent C19 methylene rather than the C22 allylic proton. In the case of **10d**, 2D COSY ^{1}H-NMR was utilized to determine that the C21 olefin proton was adjacent to the C22 methylene and not the C19 methylene which is coupled to the C18 methine proton.

11 The 1:1 mixture of diastereomers was inseparable by liquid chromatography.

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