and L-fucose, $[\alpha]_D$ -75° (c = 10, H_2O), treated in the identical fashion. Results obtained were as follows: For pseudopterosin F (2), $[\alpha]_D$ -17.5° (c = 1.7, H_2O), for pseudopterosin G (3), $[\alpha]_D$ = -20.5° (c = 0.7, H_2O), for pseudopterosin K (4), $[\alpha]_D$ -11.5° (c = 1.0, H_2O).

Single-Crystal X-ray Diffraction Analysis of Pseudopterosin F (2). Pseudopterosin F crystallized as clear prisms, and a specimen roughly 0.4 mm on an edge was selected for further analysis. Preliminary X-ray photographs showed monoclinic symmetry, and accurate lattice constants of a = 11.816 (3), b = 10.294 (4), and c = 21.255 (4) Å, and β = 107.6 (2)°, were determined from diffractometer measured 2θ values. Systematic extinctions, optical activity, and crystal density indicated space group $P2_1$ with two molecules of composition $C_{25}H_{36}O_6 \cdot 2H_2O$ in the asymmetric unit (Z = 4). All unique diffraction maxima with $2\theta > 114°$ were collected on a computer-controlled four-circle diffractometer using graphite monochromated Cu Kα radiation (1.5418 Å) and 1° ω scans. All 3392 independent reflections collected in this manner were used in subsequent calculations. The structure was solved with some difficulty using direct methods and was refined using blocked full-matrix least-squares with anisotrophic heavy atoms and fixed isotropic hydrogens to a conventional crystallographic discrepency index of 6.8%. Additional crystallographic information is available in the supplementary material.

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Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for pseudopterosin F (2) and carbon NMR spectra for pseudopterosins (1-8) (16 pages). Ordering information is given on any current masthead page.

A New Synthesis of Aryl Mono *C*-Glycosyl Derivatives of Dialdehyde Sugars

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A new synthesis of mono *C*-glycosyl derivatives of dialdehyde sugars using a Michael addition/aldol condensation sequence has been developed. It is complementary to previously reported methods for the production of *C*-glycosyl compounds. The synthesis involves the Michael addition reaction of an enol silyl ether with acetylbenzoquinone followed by an aldol condensation and subsequent aromatization of the resulting hydroxy ketone. The aldol condensation proceeds only under select conditions and affords the unstable ketols 7 and 15.

Recently, the preparation of *C*-glycosyl compounds has become a very active area. New synthetic methods have been developed for the appendage of aliphatic and aromatic groups onto carbohydrates and for the de novo synthesis of *C*-glycosyl compounds.[1] The synthetic objectives have been either naturally occurring *C*-glycosyl compounds or more complex natural products for which the *C*-glycosyl compound was employed as a synthetic intermediate. Notable synthetic advances include the elegant extensions of the Ferrier reaction by Danishefsky,[2] Fraser-Reid,[3] and others,[4] the preparation of aryl *C*-glycosyl compounds from activated carbohydrates by Kozikowski,[5] Cai,[6] and Schmidt,[7] and the useful modifications of *C*-glycosyl compounds by Horton.[8] Our own contributions have centered around the stereoselective reductions of carbohydrate hemiketals.[9]

We recently reported a direct synthesis of nanaomycin A which proceeded in excellent overall yield.[10] The focal

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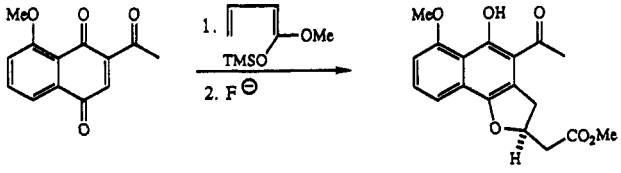
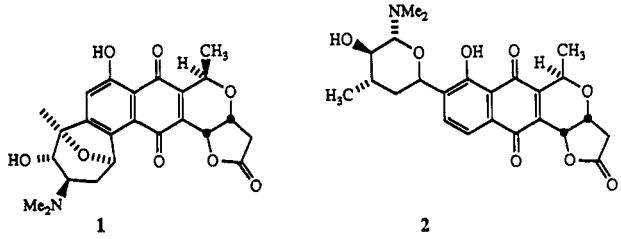
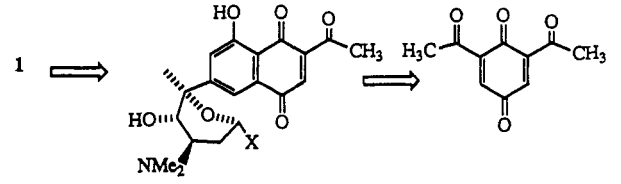
point of our synthesis was a Diels–Alder reaction followed by a retro-Claisen rearrangement. This sequence nicely



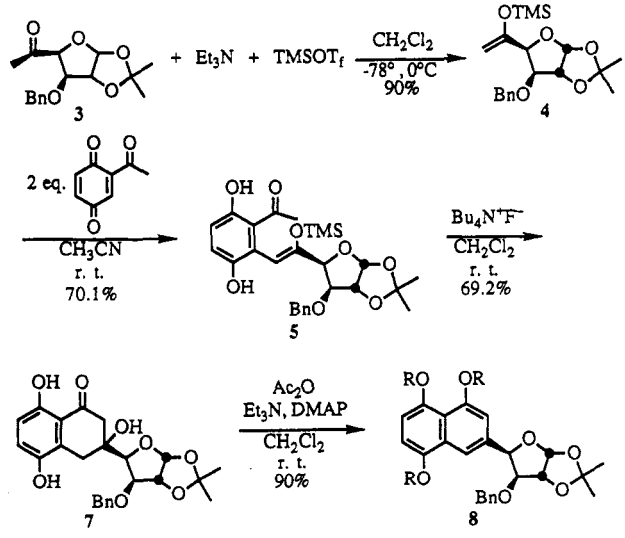
affixed the pyranacetic acid unit present in nanaomycin A. In the context of extending our Diels–Alder/retro-Claisen strategy to more complex pyranonaphthoquinones such as SCH 38519 (1)[11] and medermycin (2),[12] we recognized the need for a synthesis of aryl C-glycosyl compounds based on a Michael addition/aldol sequence. This se-



quence would provide an aryl C-glycosyl compound with the phenol group meta to the C-glycosyl linkage. In contrast, the synthetic approaches developed by Kozikowski, Cai, Schmidt, and Casiraghi would produce the C-glycosyl compound with a phenol in the ortho or para position. If such a sequence could be realized, a retrosynthetic analysis for compound 1 might be devised as shown below.



In order to test this question, we reacted the enol silyl ether of 3[13] with acetylbenzoquinone, expecting to obtain a diketone. The product we actually isolated in 70% yield was enol silyl ether 5.



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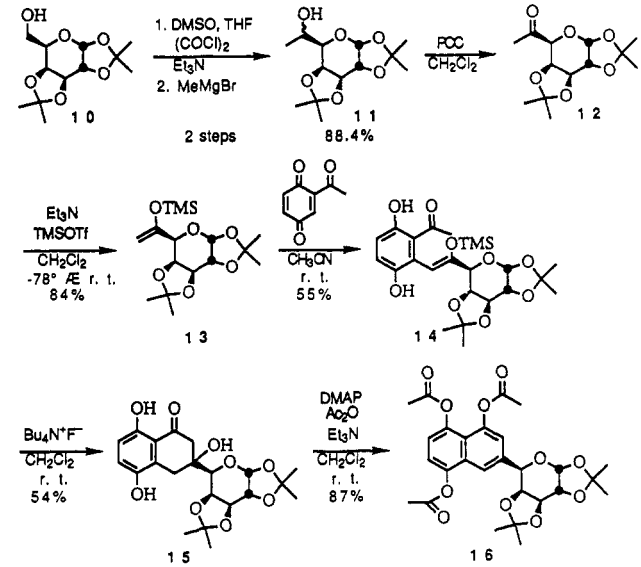
Surprisingly, all attempts to cyclize 5 to naphthol 8 (R = H) led to the recovery of 5 (tBuOK in THF or DMF, 25 °C) or to the decomposition of 5 (tBuOK in DMF, 60 °C; NaOMe/MeOH, 25 °C). However, the deprotection of the enol silyl ether 5 with commercially available tetrabutylammonium fluoride in methylene chloride unexpectedly produced the hydroxy ketone 7 in 62% yield. We had anticipated that the hydroxy ketone would rapidly dehydrate to form the aromatic ring. The structure of 7 was supported by ^{13}C NMR resonances at δ 201.69 and 156.15. The proton NMR exhibited three AB quartets for the three methylene groups in 7. This reaction has been repeated three times with yields ranging from 55% to 62%. The reaction of hydroxy ketone 7 with acetic anhydride, triethylamine, and 4-(dimethylamino)pyridine (DMAP) afforded triacetate 8 in 90% yield.

The conversion of ketone 3 into triacetate 8 demonstrated that the Michael addition/aldol sequence was a viable one for the generation of C-glycosyl compounds. In compound 1 there are two bonds from the carbohydrate unit to the naphthoquinone ring. In the hope of achieving the second linkage on a model system which more closely resembled a precursor to 1, we prepared pyranose 12 from the readily available bis-acetonide 10 by a two-pot reaction.[14] The enol silyl ether was then generated by the reaction of 12 with triethylamine and trimethylsilyl triflate. Enol silyl ether 13 reacted with acetylbenzoquinone to afford a 55% isolated yield of adduct 14.

This compound was treated with tetrabutylammonium fluoride in methylene chloride to afford keto alcohol 15 in 54% yield. The naphthalene 16 was generated by reaction of 15 with acetic anhydride, triethylamine, and DMAP in 87% yield.

The cyclization of pyranose 16 was examined. Despite extensive variation of temperature, Lewis acid (PTSA/MeCN, 25 °C to 80 °C, $SnCl_4$, 0 °C, 25 °C; Amberlite IR-20/THF, 25 °C to 70 °C) and order of addition, no



cyclized products such as 17 were obtained. Attempts to selectively cleave the 1,2-acetonide (Ac_2O, AcOH, H_2SO_4) resulted in the decomposition of 16.

The methodology described herein offers an attractive new pathway for the synthesis of aromatic C-glycosyl compounds which would be difficult to prepare by previously reported methods. The three-step sequence of Michael addition, aldol condensation, and aromatization is compatible with a variety of functional groups on both

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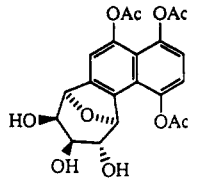

17

the carbohydrate portion and the quinone portion. The preparation of the requisite carbohydrate and quinone units for the total synthesis of 1 is in progress.

Experimental Section

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. H–EA refers to hexanes–ethyl acetate solvent mixtures for TLC and chromatography. The purity of all title compounds was determined to be >90% by proton NMR and/or elemental analysis.

5-*C*-Acetyl-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (12). To a stirred solution of oxalyl chloride (3.97 g, 31.3 mmol) in 50 mL of THF at −78 °C was added dimethyl sulfoxide (3.26 g, 41.7 mmol). The solution was stirred at −78 °C for 30 min. The diacetonide of galactose (5.43 g, 20.9 mmol) in 20 mL of THF was added. The solution was allowed to warm to 0 °C for 30 min and then cooled to −78 °C. Triethylamine (10.55 g, 104 mmol) was added, and the solution was allowed to slowly warm to 25 °C over 1 h. The solution was then cooled to −78 °C, and MeMgBr (3.0 M, 38.2 mL, 114 mmol) was added dropwise. After the reaction had stirred at −78 °C for 2 h, it was allowed to warm to 25 °C for 4 h. The solution then was cooled to −78 °C and quenched by the addition of 3 mL of EtOH followed by 20 mL of NH_4Cl/NH_4OH buffer. The reaction mixture was poured into 300 mL of NH_4Cl/NH_4OH buffer and extracted twice with 300 mL of ether. The organic layer was dried over $MgSO_4$ and purified by silica gel chromatography with 1:1 H–EA. The purified alcohol 11 was dissolved in 150 mL of CH_2Cl_2. To this solution was added PCC (9.05 g, 42 mmol). The reaction was stirred for 36 h, diluted with ether, filtered, and purified by silica gel chromatograpy with 2:1 H–EA to provide 5.02 g (88% yield) of ketone **12**: ^1H NMR ($CDCl_3$) δ 5.645 (d, 1 H, J = 5.1 Hz), 4.639 (dd, 1 H, J = 2.4, 8.7 Hz), 4.557 (dd, 1 H, J = 2.1, 7.5 Hz), 4.363 (dd, 1 H, J = 2.4, 5.1 Hz), 4.168 (d, 1 H, J = 2.1 Hz), 2.259 (s, 3 H), 1.505 (s, 3 H), 1.448 (s, 3 H), 1.342 (s, 3 H), 1.313 (s, 3 H); IR (neat) 1722, 1303, 1258, 1078, 1009, 922, 775 cm^{-1}; MS m/e 272, 257, 229, 199, 171, 155, 141, 111, 97, 85, 71; HRMS m/e for $C_{13}H_{26}O_6$ calcd 272.125 99, measured 272.125 82; TLC (1:1 H–EA) R_f = 0.40.

5-*C*-(1-((Trimethylsilyl)oxy)ethenyl)-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (13). To a solution of **12** (0.650 g, 2.39 mmol) and Et_3N (0.315 g, 3.11 mmol) in 5 mL of CH_2Cl_2 at 0 °C was added trimethylsilyl triflate (0.55 mL, 2.86 mmol). The solution was allowed to warm to 25 °C over 4 h. The solution was diluted with CH_2Cl_2 and poured into a brine/ammonium chloride solution. The brine was extracted twice with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. The resulting oil (84% yield) was unstable and was taken directly on to the next step.

General Procedure for the Enol Silyl Ether Additions to Acetylbenzoquinone. To a solution of acetylbenzoquinone (2 equiv) in acetonitrile (0.25 M) at 25 °C was added the enol silyl ether (1 equiv) dissolved in MeCN. The reaction was allowed to stir at 25 °C for 8 h. The solvent was removed in vacuo. The residue was dissolved in ether an washed with saturated $Na_2S_2O_3$. The ether layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by silica gel chromatography with 5:1 H–EA to afford the pure product.

5-*C*-(2-(2-Acetyl-3,6-dihydroxyphenyl)-1-((trimethylsilyl)oxy)ethenyl)-1,2-*O*-(1-methylethylidene)-3-(phenylmethoxy)-L-threofuranose (5): ^1H NMR ($CDCl_3$) δ 12.185 (s, 1 H), 7.349 (s, 5 H), 6.974 (d, 1 H, J = 9 Hz), 6.775 (d, 1 H, J = 9 Hz), 5.991 (d, 1 H, J = 3.6 Hz), 4.728 (d, 1 H, J = 9.3 Hz), 4.630 (d, 1 H, J = 3.6 Hz), 4.548 (d, 1 H, J = 10.8 Hz), 4.544 (d, 1 H, J = 3.3 Hz), 4.106 (d, 1 H, J = 3.3 Hz), 3.893 (d, 1 H, J = 17.7 Hz), 3.121 (d, 1 H, J = 17.7 Hz), 1.549 (s, 3 H), 1.341 (s, 3 H), 0.069 (s, 9 H); IR (oil) 1639, 1464, 1620, 1209, 1126, 982, 937 cm^{-1}; MS m/e 514, 424, 265, 237, 204, 147, 91, 73; HRMS m/e for $C_{27}H_{34}O_8Si$ calcd 514.202 31, measured 514.201 05; ^{13}C NMR ($CDCl_3$) δ 204.114, 157.862, 149.569, 137.470, 128.441, 127.987, 127.758, 126.123, 118.317, 117.335, 112.035, 112.006, 110.205, 105.699, 82.921, 82.651, 81.969, 73.017, 43.554, 31.083, 26.943, 26.374, 1.461; TLC (5:1 H–EA) R_f = 0.48.

5-*C*-(2-(2-Acetyl-3,6-dihydroxyphenyl)-1-((trimethylsilyl)oxy)ethenyl)-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (14): ^1H NMR ($CDCl_3$) δ 12.200 (s, 1 H), 6.994 (d, 1 H, J = 8.7 Hz), 6.779 (d, 1 H, J = 9.0 Hz), 5.523 (d, 1 H, J = 4.8 Hz), 4.678 (dd, 1 H, J = 2.1, 8.1 Hz), 4.477 (dd, 1 H, J = 1.8, 8.1 Hz), 4.340 (dd, 1 H, J = 2.1, 4.8 Hz), 4.042 (d, 1 H, J = 1.8 Hz), 3.989 (s, 1 H), 1.602 (s, 3 H), 1.502 (s, 3 H), 1.393 (s, 3 H), 1.335 (s, 3 H), 0.153 (s, 9 H); IR (oil) 3030, 1634, 1450, 1254, 1051, 933, 845 cm^{-1}; MS m/e 494, 479, 421, 265, 237, 204, 164, 73, 59; HRMS m/e for $C_{24}H_{34}O_9Si$ calcd 494.197 22, measured 494.196 75; ^{13}C NMR ($CDCl_3$) δ 204.013, 157.744, 150.119, 126.145, 118.314, 117.420, 117.115, 110.453, 108.139, 108.933, 108.762, 96.581, 70.894, 70.485, 69.818, 43.422, 31.031, 26.071, 25.817, 24.892, 24.149, 1.482; TLC (5:1 H–EA) R_f = 0.33.

General Procedure for the Aldol Condensation. To a solution of ketone (1 equiv) in CH_2Cl_2 (0.1 M) was added tetrabutylammonium fluoride (1.0 M in THF, 1 equiv). The solution was stirred at 25 °C for 8 h. The solution was concentrated in vacuo. The product was purifed by chromatography on silica gel with 1:1 H–EA.

5-*C*-(1,2,3,4-Tetrahydro-2,5,8-trihydroxy-4-oxo-2-naphthyl)-1,2-*O*-(1-methylethylidene)-3-(phenylmethoxy)-L-threofuranose (7): ^1H NMR ($CDCl_3$) δ 11.682 (s, 1 H), 7.387 (m, 5 H), 6.819 (d, 1 H, J = 8.7 Hz), 6.625 (d, 1 H, J = 8.7 Hz), 6.082 (d, 1 H, J = 3.9 Hz), 4.757 (d, 1 H, J = 11.4 Hz), 4.690 (d, 1 H, J = 3.9 Hz), 4.551 (d, 1 H, J = 11.4 Hz), 4.211 (d, 1 H, J = 3.3 Hz), 4.010 (d, 1 H, J = 3.3 Hz), 3.500 (dd, 1 H, J = 1.8 Hz), 2.809 (d, 1 H, J = 1.8 Hz), 2.750 (s, 1 H), 2.702 (d, 1 H, J = 1.8 Hz), 1.472 (s, 3 H), 1.353 (s, 3 H); IR (oil) 3460, 2970, 2830, 1637, 1485, 1446, 1298, 1113, 870, 707 cm^{-1}; MS m/e 442, 333, 275, 229, 192, 129, 113, 91, 69; HRMS m/e for $C_{24}H_{26}O_8$ calcd 442.162 78, measured 442.162 50; ^{13}C NMR ($CDCl_3$) δ 201.690, 156.151, 145.723, 135.442, 128.985, 128.878, 128.380, 125.153, 124.972, 115.874, 115.620, 112.006, 101.835, 82.777, 82.118, 81.365, 73.733, 72.252, 47.555, 33.207, 26.742, 26.186; TLC (1:1 H–EA) R_f = 0.49.

5-*C*-(1,2,3,4-Tetrahydro-2,5,8-trihydroxy-4-oxo-2-naphthyl)-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (15): ^1H NMR ($CDCl_3$) δ 11.737 (s, 1 H), 6.934 (d, 1 H, J = 8.7 Hz), 6.679 (d, 1 H, J = 9.0 Hz), 5.648 (d, 1 H, J = 4.8 Hz), 4.629 (dd, 1 H, J = 2.1, 8.1 Hz), 4.506 (dd, 1 H, J = 2.1, 8.1 Hz), 4.333 (dd, 1 H, J = 2.1, 4.8 Hz), 4.046 (s, 1 H), 3.669 (s, 1 H), 3.159 (s, 2 H), 3.027 (s, 2 H), 1.510 (s, 3 H), 1.381 (s, 3 H), 1.280 (s, 3 H), 1.124 (s, 3 H); IR (oil) 3508, 3221, 1639, 1591, 1462, 1375, 1167, 771 cm^{-1}; MS m/e 422, 407, 364, 346, 288, 204, 193, 176, 150, 71, 59; HRMS m/e for $C_{21}H_{26}O_9$ calcd 422.157 69, measured 422.157 38; ^{13}C NMR ($CDCl_3$) δ 202.625, 156.109, 146.046, 125.404, 115.795, 115.569, 110.057, 108.884, 96.587, 74.879, 71.345, 70.934, 70.342, 68.900, 48.143, 31.999, 25.805, 25.682, 24.834, 23.966; TLC (2:1 H–EA) R_f = 0.55. This compound was a yellow solid with mp 195–196 °C.

General Procedure for Aromatization. To a solution of aldol (1 equiv) in CH_2Cl_2 (0.1 M) was added Et_3N (10 equiv), acetic anhydride (8 equiv), and a small crystal of DMAP. The reaction was stirred for 8 h. The solution was diluted with CH_2Cl_2 and poured into brine. The brine was extracted twice with CH_2Cl_2. The organic layer was dried and concentrated in vacuo. The product was purified by silica gel chromatography with 1:1 H–EA.

5-*C*-(4,5,8-Triacetoxy-2-naphthyl)-1,2-*O*-(1-methylethylidene)-3-(phenylmethoxy)-L-threofuranose (8): ^1H NMR ($CDCl_3$) δ 7.808 (s, 1 H), 7.276 (d, 1 H, J = 8.4 Hz), 7.142 (m, 5 H), 6.894 (d, 1 H, J = 6.9 Hz, 6.888 (d, 1 H, J = 7.8 Hz), 6.140 (d, 1 H, J = 3.6 Hz), 5.360 (d, 1 H, J = 3.0 Hz), 4.723 (d, 1 H, J = 3.9 Hz), 4.262 (d, 1 H, J = 12 Hz), 4.162 (d, 1 H, J = 12 Hz), 4.066 (d, 1 H, J = 3.0 Hz), 2.430 (s, 3 H), 2.400 (s, 3 H), 2.366 ns, 3 H), 1.569 (s, 3 H), 1.379 (s, 3 H); IR (oil) 3032, 2924, 2854, 1761, 1614, 1464, 1375, 1202, 951, 1078, 1022, 887, 744, 698 cm^{-1}; MS: m/e 550, 508, 466, 442, 424, 257, 204, 91; HRMS m/e for $C_{30}H_{30}O_{10}$ calcd 550.183 91, measured 550.184 98; TLC (1:1 H–EA) R_f = 0.46.

Anal. Calcd for $C_{30}H_{30}O_{10}$: C, 65.49; H, 5.50. Found: C, 65.48; H, 5.58. This compound was a white solid with mp 153–154 °C.

5-*C*-(4,5,8-Triacetoxy-2-naphthyl)-1,2:3,4-bis-*O*-(1-methylethylidene)-L-arabinopyranose (16): ^{1}H NMR ($CDCl_3$) δ 7.327 (s, 1 H), 7.270 (d, 1 H, J = 9.0 Hz), 7.255 (s, 1 H), 7.084 (d, 1 H, J = 8.1 Hz), 5.730 (d, 1 H, J = 4.8 Hz), 4.997 (s, 1 H), 4.731 (dd, 1 H, J = 2.1, 7.8 Hz), 4.476 (d, 1 H, J = 7.8 Hz), 4.420 (dd, 1 H, J = 2.1, 4.8 Hz), 2.441 (s, 3 H), 2.374 (s, 6 H), 1.581 (s, 3 H), 1.434 (s, 3 H), 1.332 (s, 3 H), 1.276 (s, 3 H); IR (oil) 1763, 1614, 1460 cm^{-1}; MS m/e 530, 488, 446, 404, 346, 204, 113,85, 59; HRMS m/e for $C_{27}H_{30}O_{11}$ calcd 530.178 82, measured 530.178 85; TLC (1:1 H-EA) R_f = 0.42. Anal. Calcd for $C_{27}H_{30}O_{11}$: C, 61.17; H, 5.70. Found: C, 61.16; H, 5.84. This compound was a white solid with mp 234–235 °C.

C-Allylation of L-Ascorbic Acid under Palladium(0) Catalysis

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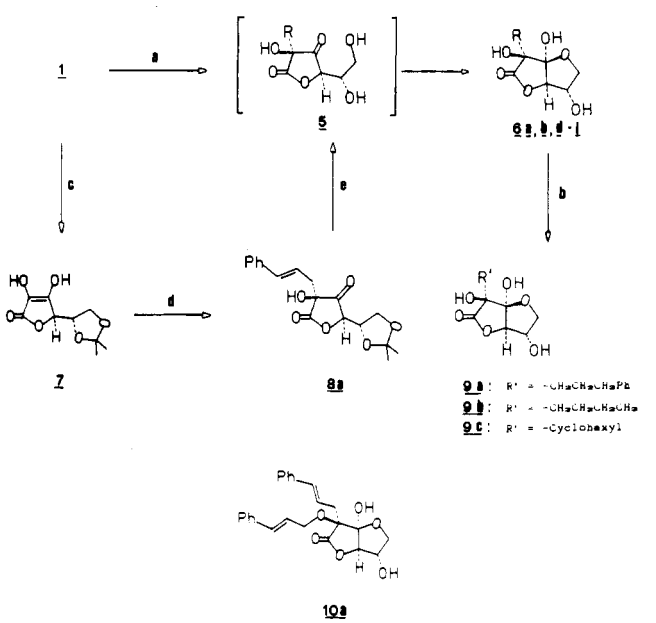
L-Ascorbic acid (1) is efficiently allylated at C-2 with primary and secondary allylic substrates by using palladium(0) catalysis. Hydrogenation of the resulting allylated compounds **6** affords L-ascorbic acid derivatives with saturated chains at C-2.

Some attention has been directed to the chemistry of L-ascorbic acid (vitamin C) (1) with the aim of preparing derivatives with biological activity but resistant to air oxidation.[1] However, despite the enormous biological and industrial importance of L-ascorbic acid, its chemistry has not been developed as it could be thought due to its inherent difficulties. Thus, in relation with reactivity at the active oxygen atoms some confusion has arisen concerning the site of alkylation, and in the review by Tolbert et al.[1] published in 1975 it has been stated that "ascorbic acids derivatized at the 2-O position have often been called 3-O derivatives, and early work should be critically evaluated". Recently the problem of noncrystallographic differentiation of O-2 and O-3 acyl derivatives of L-ascorbic acid has been approached.[2] Moreover, no general methods to alkylate L-ascorbic acid at C-2 have been reported.

L-Ascorbic acid is a fully enolic and strongly acidic β-dicarbonyl compound with a pK_a value of 4.85 in ethanol–water.[3] It is well known that compounds sharing these features present great difficulties for alkylation at the activated carbon atom under kinetically controlled conditions, the oxygen atoms being the preferred sites for reaction. To the best of our knowledge only two reports dealing with direct C-alkylations of L-ascorbic acid have appeared in the chemical literature. Thus, Jackson and Jones[4a] reported the reaction of sodium L-ascorbate with benzyl chloride to afford mixtures of benzylated products at C-2 and O-3. More recently Poss et al. have described the C-alkylation of potassium L-ascorbate with some allylic and propargylic halides.[4b]

Many familiar carbon–carbon bond formation processes such as the aldol and the Michael reactions occur under thermodynamic control, thus eluding the carbon–oxygen bond formation which is the kinetically favored alternative. Therefore, it is not surprising that some recently reported reactions of L-ascorbic acid forming a carbon–carbon bond at C-2 can be cataloged as aldol[5a,b] or Michael reactions.

Scheme I[a]



[a] (a) See Table I; (b) H_2/10% Pd-C/EtOH; (c) MeCOCl/acetone; (d) **4a**/Pd(acac)$_2$/PPh$_3$/THF/reflux, 15 h; (e) 2 N HCl/MeOH.

In the last case the Michael acceptor can be a conventional one[6a–d] or of the quinone methide type,[7a,b] one particular case being the reactions leading to ascorbigens.[8a–c]

Additional evidence of the recently renewed interest on the chemistry of L-ascorbic acid is provided by the paper by Kato et al. on the synthesis of 2-*O*-alkylascorbic acids for testing as scavengers of active oxygen species[9] and by

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