Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-O-(3,4,6-tri-O-acetyl-α-D-galactopyranosyl)-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (46) and Methyl O-α-L-Rhamnopyranosyl-(1→2)-O-α-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (47). A solution of the fully protected trisaccharide **45** (1 g, 0.86 mmol) in MeOH (50 mL) was hydrogenolyzed, as described above. A portion of the crude product was eluted from a column of silica gel (solvent F) to give **46** (0.17 g, 0.173 mmol): mp 210–211 °C (from ethanol), $[\alpha]_D$ +175° (*c* 0.6); FABMS *m/z* 982 $(M + 1)^+$, 1004 $(M + Na)^+$, 1020 $(M + K)^+$.

Anal. Calcd for $C_{48}H_{55}NO_{21}$ (981.92): C, 58.70; H, 5.64; N, 1.42. Found: C, 58.74; H, 5.70; N, 1.39.

The rest of the material was deacylated, as described above for the preparation of **15**. The crude product was eluted from a column of silica gel (solvent E) to afford, after freeze-drying, **47** (0.32 g, 0.59 mmol, total yield based on **45**, 88%) as a white hygroscopic solid: $[\alpha]_D$ +98° (*c* 0.7, H_2O); FABMS *m/z* 544 $(M + 1)^+$, 566 $(M + Na)^+$, 582 $(M + K)^+$.

Methyl O-(2,3,4-Tri-O-benzoyl-α-L-rhamnopyranosyl)-(1→3)-O-(2,4-di-O-benzoyl-α-L-rhamnopyranosyl)-(1→2)-O-(3,4,6-tri-O-acetyl-α-D-galactopyranosyl)-(1→3)-2-acetamido-4,6-di-O-benzyl-2-deoxy-α-D-glucopyranoside (51). Compound **17** (1.138 g, 1 mmol), **31** (0.416 g, 1 mmol), 2,4,6-trimethylpyridine (0.15 mL, 1.13 mmol), and $AgClO_4$ (0.08 M, 14 mL, 1.12 mmol) were allowed to react as described for the preparation of **35** (b). After conventional processing, as described above, the crude product was chromatographed (solvent B) to isolate two substances that showed chromatographic mobility closest to but faster than **31**. The material eluted first showed spectral data consistent with its being the β-linked substance **53** (14 mg, 0.9%): FABMS *m/z* 1516 $(M + 1)^+$.

Eluted next was the target tetrasaccharide **51** (0.52 g, 34.3%): $[\alpha]_D$ +158° (*c* 0.9); FABMS *m/z* 1516 $(M + 1)^+$, 1538 $(M + Na)^+$, 1555 $(M + K)^+$.

Anal. Calcd for $C_{82}H_{85}NO_{27}$ (1516.51): C, 64.93; H, 5.64; N, 0.92. Found: C, 65.22; H, 5.77; N, 0.87.

Methyl O-α-L-Rhamnopyranosyl-(1→3)-O-α-L-rhamnopyranosyl-(1→2)-O-α-D-galactopyranosyl-(1→3)-2-acetamido-2-deoxy-α-D-glucopyranoside (52). A solution of **51** (0.42 g) in 2-methoxyethanol (50 mL) was stirred in a hydrogen atmosphere at rt for 16 h. The mixture was processed as before, and to the solution of the crude product in MeOH (50 mL) was added M sodium methoxide in MeOH until the solution was strongly alkaline to litmus. After 16 h at 50 °C and conventional processing, the crude product was chromatographed (solvent E). Solutions of the purified material were made successively in MeOH and H_2O, and each of the solutions was filtered through a syringe membrane filter (pore size, 0.2 μm). After freeze-drying, compound **52** was obtained (168 mg, 88%) as a white, hygroscopic solid, $[\alpha]_D$ +52° (*c* 1.4, H_2O); FABMS *m/z* 690 $(M + 1)^+$, 712 $(M + Na)^+$, 770 $(M + K)^+$.

Supplementary Material Available: ^{13}C-NMR spectra of compounds **23**, **37**, **44**, **47**, and **52** and Tables SI, SII (extension of Tables III and IV, containing complete sets of ^1H- and ^{13}C-NMR chemical shifts for compounds **1–17**, **19–23**, **25**, **27–31**, **33–40**, and **42–53**), and SIII (containing ^1H-NMR coupling constants) (18 pages). Ordering information is given on any current masthead page.

Notes

Unprecedented Tandem Michael–Ene Reaction of 2-Formylcyclohexa-2,5-dienone and Subsequent Unusual Autoxidation

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Intramolecular ene reactions of unsaturated carbonyl compounds have been widely used in the synthesis of an enormous variety of monocyclic, bicyclic, and bridged compounds.[1,2] The carbonyl group serves either as the enophile or, via its enol tautomer, as the ene unit. The pronounced enolic character of β-dicarbonyl compounds allows ene cyclization at temperatures as low as 200 °C.[3] We report herein an unprecedented one-pot heteroannulation through the tandem Michael–ene reaction of 2-formyl-4,4-dimethylcyclohexa-2,5-dien-1-one (**1**)[4] with propargyl alcohol.

A toluene solution of **1** and an excess of propargyl alcohol (10 equiv) was heated in a sealed tube for 4 h at 160–165 °C. Silica gel column chromatographic purification of crude products gave nonpolar liquid product **4** (67%), in addition to the dipropargyl acetal of **1** (10%). In the ^1H-NMR spectrum of **4**, the signal at 2.12 (3 H, six-line multiplet) indicates the presence of a methyl group situated on the β-carbon atom of an α,β-enone. The multiplicity of this signal is due to long-range coupling between H-8 and H-2, in addition to expected homoallylic coupling[5] between H-8 and H-7a. The signals for geminally coupling C-2 methylene protons appear at δ 4.75 (ddq, 1 H, *J* = 1.4, 4.3, 14.8 Hz) and 4.64 (ddq, 1 H, *J* = 1.2, 6.2, 14.8 Hz). The observed multiplicity of these signals confirms the coupling between H-2 and H-8. The signal for H-7a appears at δ 4.90 as a nine-line multiplet, which is due to the long-range homoallylic coupling between H-7a

Scheme I

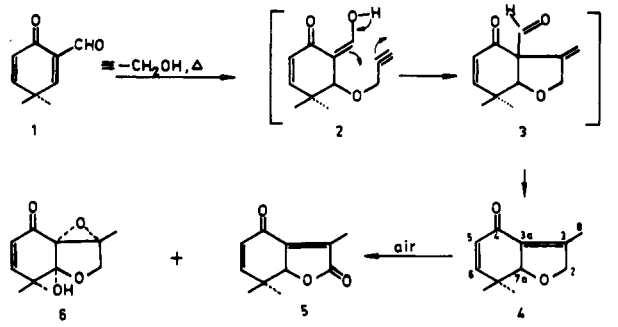

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Table I. ^{13}C NMR Chemical Shifts of Benzofurans 4–6

no.	4	5	6
2	79.24	173.02	71.88
3	145.64	133.10	73.67
3a	127.60	147.87	68.78
4	185.87	183.82	189.56
5	129.08	129.06	127.07
6	156.57	158.29	159.42
7	39.99	40.16	43.35
7a	91.72	85.39	106.74
7-Me_2	20.20	19.99	20.69
	25.60	26.19	26.49
3-Me	10.81	9.61	11.33

and H-8 as well as coupling across 4σ- bonds[6] between H-7a and H-2. The formation of 4 can be rationalized as shown in Scheme I.

Compound 1 first undergoes a Michael-type addition reaction with propargyl alcohol to give the enol intermediate 2 which then readily cyclizes to the intermediate 3 through intramolecular ene reaction. An excess of propargyl alcohol present in the reaction mixture facilitates the elimination of the formyl group from 3 with isomerization of the exocyclic double bond to yield product 4.

Liquid 4, on exposure to the air for 4–5 days, was converted to a solid mixture of essentially two compounds. Silica gel column chromatographic separation of this mixture yielded crystalline compounds 5 (40%, mp 146–47 °C) and 6 (32%, mp 135–36 °C). The IR spectrum of 5 exhibits bands at 1755 and 1670 cm^{-1} suggesting the presence of an α,β-unsaturated γ-lactone, in addition to a conjugated keto group. The ^1H-NMR spectrum shows signals at δ 2.21 (d, 3 H, J = 2.4 Hz, H-8) and δ 4.97 (q, 1 H, J = 2.4 Hz, H-7a) indicating the presence of long-range homoallylic coupling between H-8 and H-7a. The IR spectrum of 6 shows the presence of a hydroxy group (3430 cm^{-1}) in addition to that of an α,β-enone (1670 cm^{-1}). In the ^1H-NMR spectrum of 6, the signal for H-8 appears at δ 1.56 (s, 3 H), whereas two signals at δ 3.84 and 4.20 (d, 1 H each, J = 10.5 Hz) arise from geminally coupled methylene protons at C-2. Thus, H-2 and H-8 resonate at considerably higher field in 6 as compared to those in 4, thereby indicating the absence of a double bond between C-3 and C-3a. In the ^{13}C-NMR spectrum of 6, the signal for C-7a appears at δ 106.74 (s), a characteristic of a hemiketal carbon.[7] The signals at δ 73.67 (s) and 68.78 (s) for C-3 and C-3a, respectively, indicate the presence of an epoxide moiety. The signal at δ 71.88 (t) is easily assigned to C-2. The structure of this compound was finally confirmed by single-crystal X-ray analysis.[8]

2,5-Dihydrofuran derivatives are known to undergo autoxidation to the corresponding γ-lactones.[9] However, to the best of our knowledge, this is the first report where, in addition to the γ-lactone 5, the corresponding epoxy alcohol derivative 6 was also obtained. A possible mechanism for autoxidation of 4 to compounds 5 and 6 may involve the formation of intermediate hydroperoxides at C-2 and C-7a, respectively.

Thus, the above findings constitute the first report of heteroannulation through tandem Michael–ene reactions and the facile autooxidation of the 2,5-dihydrofuran derivative thus formed. In view of the natural occurrence[10] of a large number of terpenic dihydrofurans, γ-lactones, and epoxytetrahydrofuranols, the above findings assume greater significance and will have future applications in the synthesis of analogous natural products and other heterocycles.

Experimental Section

1. 3,7,7-Trimethyl-4-oxo-2,4,7,7a-tetrahydrobenzofuran (4). A solution of formyl dienone 1 (300 mg, 2 mmol) and propargyl alcohol (2 mL, 1.9 g, 34 mmol) in toluene (5 mL) was heated in a sealed tube at 160–165 °C for 4 h. After cooling, the solvent and propargyl alcohol were removed in vacuo and the residue was chromatographed on silica gel (petroleum ether–ethyl acetate (9:1)) to give two fractions. The nonpolar fraction was characterized as benzofuran derivative 4 (238 mg, 67%), a colorless liquid. IR ν_{max} (neat): 2950, 1680, 1650, 1270, 1020, 830 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (1 H, d, J = 10.0 Hz, H-6), 5.94 (1 H, d, J = 10.0 Hz, H-5), 4.90 (1 H, m, H-7a), 4.75 (1 H, ddq, J = 1.4, 4.3, 14.8 Hz, H-2), 4.64 (1 H, ddq, J = 1.2, 6.2, 14.8 Hz, H-2), 2.12 (3 H, m, CH_3 at C-3), 0.99 and 1.24 (3 H each, s, 2xCH_3 at C-7). ^{13}C NMR (75.4 MHz, $CDCl_3$) Table I. MS: m/e 178 (M^+). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.36; H, 8.03.

The polar fraction was identified as a 2-formyl-4,4-dimethylcyclohexa-2,5-dienone dipropargyl acetal (49 mg, 10%), a viscous liquid. IR ν_{max} (neat): 3310, 2920, 2260, 1660, 1230, 900 cm^{-1}. ^1H NMR (60 MHz, $CDCl_3$): δ 7.0 (2 H, m, H-3 and H-5), 6.22 (1 H, d, J = 10 Hz, H-6), 5.72 (1 H, s, OCHO), 4.3 (4 H, d, J = 3 Hz, 2xOCH_2), 2.45 (2 H, t, J = 3 Hz), 1.25 (6 H, s, 2xCH_3). MS: m/e 244 (M^+).

2. Autoxidation of Benzofuran 4. Benzofuran 4 (100 mg, 0.56 mmol) was placed in an unstoppered Pyrex round-bottom flask (25 mL) and exposed to atmospheric air and daylight on a laboratory table for 5 days without stirring, by which time it became fully solidified. This solid material was chromatographed on silica gel (petroleum ether–ethyl acetate (7:3)) to furnish two fractions. The less polar fraction was characterized as 3,7,7-trimethyl-4-oxo-2,4,7,7a-tetrahydrobenzofuran-2-one (5) (44 mg, 40%), mp 146–147 °C (recrystallized from benzene). IR: ν_{max} (Nujol) 2930, 1770, 1760, 1680, 1650, 1460, 1370, 1010, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.82 (1 H, d, J = 10.1 Hz, H-6), 6.16 (1 H, d, J = 10.1 Hz, H-5), 4.97 (1 H, q, J = 2.4 Hz, H-7a), 2.21 (3 H, d, J = 2.4 Hz, CH_3 at C-3), 0.93 and 1.43 (3 H each, s, 2xCH_3 at C-7). ^{13}C NMR (75.4 MHz, $CDCl_3$) Table I. MS: m/e 192 (M^+). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.76; H, 6.25. Found: C, 69.05; H, 6.34.

The polar fraction was characterized as 3,7,7-trimethyl-3,3a-epoxy-4-oxo-2,3,3a,4,7,7a-hexahydrobenzofuran (6) (38 mg, 32%) mp 135–136 °C. A monoclinic crystal, obtained from recrystallization from mixture of petroleum ether and $CHCl_3$, was used for single-crystal X-ray analysis. IR ν_{max} (Nujol): 3430, 2920, 1670, 1460, 1100, 1040, 820 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.88 (1 H, d, J = 10.2 Hz, H-6), 6.13 (1 H, d, J = 10.2 Hz, H-5), 4.20 and 3.84 (1 H each, d, J = 10.4 Hz, H-2), 3.11 (1 H, s, D_2O exchangeable), 1.56 (3 H, s, CH_3 at C-3), 1.30 and 1.18 (3 H each, s, 2xCH_3 at C-7). ^{13}C NMR (75.4 MHz, $CDCl_3$) Table I. MS: m/e 210 (M^+). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 63.07; H, 6.82.

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Registry No. 1, 30758-46-4; 1 dipropargyl acetal, 138433-40-6; 4, 136830-63-2; 5, 138433-39-3; 6, 138513-41-4; propargyl alcohol, 107-19-7.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds 4–6 and the X-ray structure of 6 (8 pages). Ordering information is given on any current masthead page.

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