Preparation and Reaction of Dilithio-2,4-oxazolidinedione with α-Halo Ketones. A Versatile Synthesis of 3-Hydroxy-2(5*H*)-furanones

Arie Zask

Medicinal Chemistry Department, Wyeth-Ayerst Research, CN 8000, Princeton, New Jersey 08543-8000

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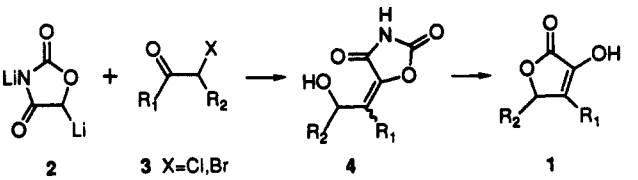
Furanones are important constituents of natural products[1] and useful synthetic intermediates[2] which have recently received much attention as synthetic targets.[3] Routes to 3-hydroxy-2(5*H*)-furanones (**1**), however,[4,5] have been limited primarily to condensations of pyruvic acid derivatives with carbonyl compounds.[5] A novel approach to 3-hydroxy-2(5*H*)-furanone construction is described in which dilithio-2,4-oxazolidinedione **2** is coupled with α-halo ketones **3** to produce intermediate allylic alcohols **4** which are hydrolyzed to the corresponding furanones **1** (Scheme I). In this synthesis, the furanone substitution is derived from the α-halo ketone groups R_1 and R_2 allowing access to a wide range of 4,5-substituted furanones.

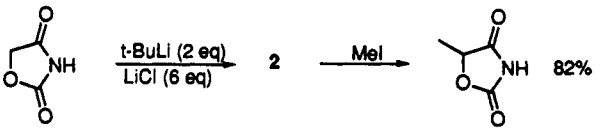
The dianion of 2,4-oxazolidinedione **2** has not been described in the literature, and initial attempts to prepare it by treating 2,4-oxazolidinedione with alkyllithium reagents failed, even in the presence of complexing solvents such as HMPA. Addition of the first equivalent of base produced a white precipitate, presumably the N-lithiated heterocycle, which was inert to further deprotonation. However, addition of lithium chloride[6] to 2,4-oxazolidinedione in THF allowed formation of clear solutions of dianion **2** upon treatment with *t*-BuLi as evidenced by the efficient synthesis of 5-methyl-2,4-oxazolidinedione upon addition of iodomethane (Scheme II).[7]

Treatment of dianion **2** with α-halo ketones **3** gave allylic alcohols **4a/4b**.[8] The olefin geometry obtained was dependent on the α-halo ketone substitution (Table I).

Scheme I



Scheme II



Scheme III

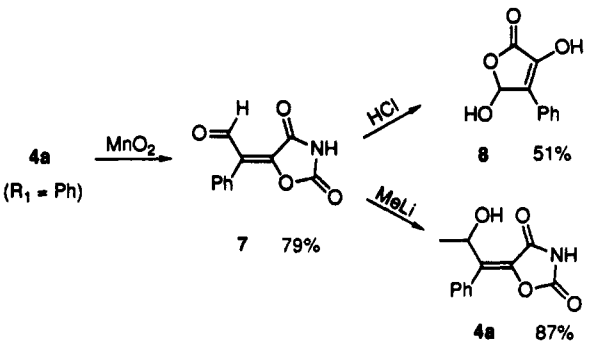
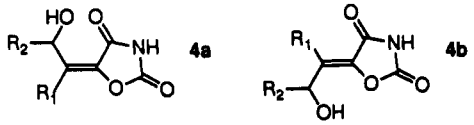


Table I. Preparation of Allylic Alcohols and 2(5*H*)-Furanones

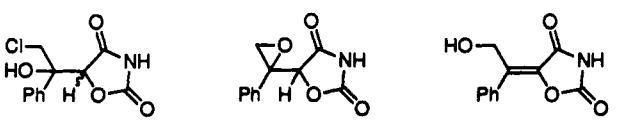
3			4a/4b		1	
R_1	R_2	X	% yield[a]	ratio[b]	% yield[a]	time (h)
t-Bu	H	Br	86	100:0	91	24
Ph	H	Cl	85	100:0	91	24
Ph	Me	Br	82	87:13	86	18
i-Pr	H	Br	73	80:20	87	17
Me	Me	Cl	95	43:57	63	3.5

[a] Yield of purified product. [b] Ratio determined by ^{1}H NMR (ref 9).

When R_1 = Ph or *t*-Bu, a single allylic alcohol was obtained (presumably **4a** due to steric interactions between the heterocyclic carbonyl and bulky R_1 groups). Smaller R_1 groups (Me and *i*-Pr) or an R_2 substituent gave mixtures of olefin isomers (**4a** and **4b**) as determined by ^{1}H NMR.[9]



The mechanism of the transformation was explored by treating dianion **2** with 2-chloroacetophenone and adding aqueous HCl shortly after the reaction mixture had warmed to 25 °C. Two reaction intermediates, halohydrin **5** and epoxide **6**, were isolated, along with a small amount



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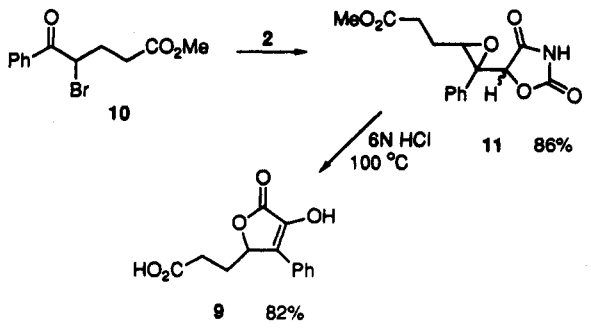
Scheme IV



of allylic alcohol **4a** (R_1 = Ph), suggesting a mechanism where dianion **2** adds to the α-chloro ketone carbonyl group to form chlorohydrin **5** which cyclizes to the corresponding epoxide **6**.[10] The basic reaction conditions effect an epoxide ring opening via abstraction of the C-5 oxazolidinedione proton to form the allylic alcohol.

Both allylic alcohol isomers were efficiently converted to the corresponding 3-hydroxy-2(5*H*)-furanones by hydrolysis of the 2,4-oxazolidinedione ring with 6 N aqueous HCl at 100 °C (Table I). Treatment of the allylic alcohols with 1 N aqueous NaOH at 80 °C also effected the hydrolysis, but in low yield.[11]

The method may also be used to synthesize 3,5-dihydroxy-2(5*H*)-furanones by oxidation of the allylic alcohol to the corresponding aldehyde with manganese dioxide followed by hydrolysis (Scheme III). Thus, oxidation of allylic alcohol **4a** (R_1 = Ph) gave aldehyde **7** and ultimately the 3,5-dihydroxyfuranone **8**. The intermediate aldehyde may be used to introduce substituents at C-5 of the furanone by addition of nucleophiles to the aldehyde carbonyl group. For example, addition of MeLi to **7** gave allylic alcohol **4a** (R_1 = Ph, R_2 = Me).

The methodology was applied in a short, efficient synthesis of the 4-phenyl-5-propionic acid derivative **9** (W-3681), a fungal metabolite with aldose reductase inhibitory activity of potential utility in the treatment of diabetic complications (Scheme IV).[12] Reaction of methyl 4-bromo-5-oxo-5-phenylpentanoate **10** with dianion **2** gave epoxide intermediate **11** as a 3:2 mixture of diastereomers in 86% yield.[13] Hydrolysis of the epoxides proceeded smoothly to give the natural product in 82% yield.

In summary, the dianion of 2,4-oxazolidinedione has been prepared for the first time and in its reaction with α-halo ketones, shown to be useful for the synthesis of substituted 3-hydroxy-2(5*H*)-furanones. The intermediate allylic alcohols produced may be oxidized to aldehydes and used for the introduction of C-5 furanone substituents or for the production of 3,5-dihydroxyfuranones. Finally, an application of the methodology towards an efficient synthesis of aldose reductase inhibitor **9** was accomplished.

Experimental Section

α-Halo ketones were commercially available. THF was distilled from sodium/benzophenone ketyl under nitrogen immediately before use. Column chromatography was done using flash chromatography conditions.[14] 2,4-Oxazolidinedione was prepared according to a literature procedure.[15] Lithium chloride was dried at 140 °C for 12 h and allowed to cool in vacuo immediately before use. ^{1}H NMR spectra were obtained at either 200 or 400 MHz, and coupling constants are expressed in Hz.

General Method for Allylic Alcohol Synthesis. 5-(1-(Hydroxymethyl)-2,2-dimethylpropylidene)-2,4-oxazolidinedione (4a; R_1 = *t*-Bu). To a rapidly stirred solution of lithium chloride (10.1 g, 238 mmol) and 2,4-oxazolidinedione[15] (4.0 g, 39.6 mmol) in THF (400 mL) under N_2 atmosphere at −78 °C was added *t*-BuLi (49 mL, 83 mmol, 1.7 M in pentane) dropwise over 5–10 min. The yellow reaction mixture was stirred at −78 °C for 15–30 min then warmed to 0 °C. Upon recooling to −78 °C a solution of 1-bromo-3,3-dimethyl-2-butanone (7.45 g, 41.6 mmol) in THF (50 mL) was added all at once. After 10 min at −78 °C, the mixture was allowed to warm to 25 °C. After 5 h the orange solution was treated with aqueous HCl (100 mL, 1.0 N) and the organic phase removed in vacuo. Extraction with EtOAc (3×), drying ($MgSO_4$), and concentration gave a solid which was triturated with hexane/ether (1:1) to give **4a** (R_1 = *t*-Bu) as a powder (5.46 g). The washings were chromatographed ($CHCl_3/CH_3CN$) to give 0.84 g of product (86% combined yield): recrystallization (EtOAc); mp 148–150 °C; ^{1}H NMR (DMSO-d_6) δ 1.24 (s, 9 H, $-C(CH_3)_3$, 4.58 (d, *J* = 5.2, 1 H, $-CH_2-$), 4.76 (t, *J* = 5.3, 2 H, −O*H*), 12.2 (s, 1 H, −N*H*−).

5-(2-Hydroxy-1-phenylethylidene)-2,4-oxazolidinedione (4a; R_1 = Ph): mp 178–180 °C; ^{1}H NMR (DMSO-d_6) δ 4.89 (bd d, *J* = 4.9, 2 H, $-CH_2-$), 5.04 (bd t, *J* = 5.3, 1 H, −O*H*), 7.35–7.46 (m, 3 H, Ar*H*), 7.57 (d, *J* = 7.0, 2 H, ArH), 10.7 (bd s, 1 H, −N*H*).

5-(2-Hydroxy-1-phenylpropylidene)-2,4-oxazolidinedione (4; R_1 = Ph, R_2 = Me). A 7:1 mixture of isomers was obtained. Major isomer **4a**: mp 168–170 °C; ^{1}H NMR (DMSO-d_6) δ 1.10 (d, *J* = 6.4, 3 H, $-CH_3$), 5.20 (bd s, 1 H, −O*H*), 5.80 (q, *J* = 6.4, 1 H, −C*H*−), 7.40 (bd s, 5 H, Ar*H*), 12.3 (bd s, 1 H, −N*H*). Minor isomer **4b**: ^{1}H NMR (acetone-d_6) δ 1.23 (d, *J* = 6, 3 H, $-CH_3$), 5.10 (q, *J* = 6, 1 H, −C*H*−), 7.25–7.55 (m, 5 H, Ar*H*).

5-(1-Hydroxymethyl)-2-methylpropylidene)-2,4-oxazolidinedione (4; R_1 = *i*-Pr). A 5:1 mixture of isomers was obtained. Major isomer **4a**: ^{1}H NMR (acetone-d_6) δ 1.19 (d, *J* = 6.4, 6 H, $-CH(CH_3)_2$), 2.99 (septet, *J* = 6.4, 1 H, −C*H*−), 4.64 (s, 2 H, $-CH_2-$). Minor isomer **4b**: ^{1}H NMR (acetone-d_6) δ 1.17 (d, *J* = 7.2, 6 H, $-CH(CH_3)_2$), 3.88 (septet, *J* = 7.2, 1 H, −C*H*−), 4.35 (s, 2 H, $-CH_2-$).

5-(2-Hydroxy-1-methylpropylidene)-2,4-oxazolidinedione (4; R_1, R_2 = Me). Chromatography gave an inseparable mixture of isomers (1.3:1) as a viscous oil: ^{1}H NMR (acetone-d_6) δ 1.27 (d, *J* = 6.4, 1.3 H, $-CHCH_3$), 1.28 (d, *J* = 7.2, 1.7 H, $-CHCH_3$), 1.95 (s, 1.3 H, $-CH_3$), 2.18 (s, 1.7 H, $-CH_3$), 4.88 (q, *J* = 7.2, 0.6 H, −C*H*−), 5.62 (q, *J* = 6.4, 0.4 H, −C*H*−).

General Method for 2(5*H*)-Furanone Synthesis. 4-*tert*-Butyl-3-hydroxy-2(5*H*)-furanone (1; R_1 = *t*-Bu). A mixture of **4a** (R_1 = *t*-Bu) (2.0 g, 10.8 mmol) and aqueous 6 N HCl (100 mL) was heated at 100 °C for 24 h. Upon cooling a white precipitate formed. Extraction of the aqueous phase with ether (4×), drying ($MgSO_4$), and concentration gave **1** (R_1 = *t*-Bu) as a white crystalline solid (1.53 g, 91%): recrystallization (Et_2O/hexane); mp 141–143 °C; ^{1}H NMR (DMSO-d_6) δ 1.16 (s, 9 H, $-C(CH_3)_3$), 4.74 (s, 2 H, $-CH_2-$), 9.35 (s, 1 H, −O*H*).

3-Hydroxy-4-phenyl-2(5*H*)-furanone (1; R_1 = Ph):[4a] mp 204–205 °C; ^{1}H NMR (DMSO-d_6) δ 5.17 (s, 2 H, $-CH_3$), 7.36 (t, *J* = 8.0, 1 H, Ar*H*), 7.44 (t, *J* = 8.0, 2 H, Ar*H*), 7.69 (d, *J* = 8.0, 2 H, Ar*H*), 10.70 (s, 1 H, −O*H*).

3-Hydroxy-5-methyl-4-phenyl-2(5*H*)-furanone (1; R_1 = Ph, R_2 = Me): mp 142–143 °C (lit.[16] mp 141–142 °C), ^{1}H NMR (DMSO-d_6) δ 1.39 (d, *J* = 6.4, 3 H, $-CH_3$), 5.61 (q, *J* = 6.4, 1 H, −OC*H*−), 7.35 (t, *J* = 7.3, 1 H, Ar*H*), 7.67 (d, *J* = 7.5, 2 H, Ar*H*), 8.62 (t, *J* = 7.5, 2 H, Ar*H*), 10.6 (s, 1 H, −O*H*).

3-Hydroxy-4-isopropyl-2(5*H*)-furanone (1; R_1 = *i*-Pr): ^{1}H NMR (acetone-d_6) δ 1.18 (d, *J* = 7.4, 6 H, $-CH(CH_3)_2$), 2.91 (septet, *J* = 7.4, 1 H, −C*H*−), 4.72 (s, 2 H, $-CH_2-$).

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3-Hydroxy-4,5-dimethyl-2(5*H*)-furanone (1; R_1, R_2 = Me):[17] short-path distillation (0.1 mm, 25–150 °C) gave a clear light amber liquid (0.985 g, 63% yield): ^{1}H NMR (acetone-d_6) δ 1.34 (d, J = 6.0, 3 H, $-CH_3$), 1.89 (s, 3 H, $-CH_3$), 4.83 (q, J = 6.0, 1 H, $-OCH-$), 8.13 (s, 1 H, $-OH$).

5-(2-Chloro-1-hydroxy-1-phenylethyl)-2,4-oxazolidinedione (5) and 5-(2-Phenyloxiranyl)-2,4-oxazolidinedione (6). Reaction of **2** (9.90 mmol) and 2-chloroacetophenone (1.61 g, 10.4 mmol) was carried out as described above except that 1 h after warming to 25 °C aqueous HCl (60 mL, 0.5 M) was added. Chromatography (silica gel washed with 2% H_3PO_4/MeOH, $CHCl_3/CH_3CN$) gave **5** as an inseparable 1.6:1 mixture of diastereomers (1.01 g, 40% yield): ^{1}H NMR (acetone-d_6) δ 4.21 (AB q, J = 12, $-CH_2-$), 4.28 (s, $-CH_2-$), 5.47 (s, 0.38 H, $-CH-$), 5.52 (s, 0.62 H, $-CH-$), 7.24–7.70 (m, 5 H, Ar*H*). The epoxide **6** was obtained as a single diastereomer (0.49 g, 23% yield). Recrystallization (hexane/ether): mp 98–99 °C. ^{1}H NMR (acetone-d_6) δ 2.90 (d, J = 5, 1 H, $-CH_2-$), 3.39 (d, J = 5, 1 H, $-CH_2-$), 5.33 (s, 1 H, $-CH-$), 7.25–7.53 (m, 5 H, Ar*H*). Allylic alcohol **4a** (R_1 = Ph) was also isolated (0.085 g, 4% yield).

(2,4-Dioxooxazolidin-5-ylidene)phenylacetaldehyde (7). A solution of **4a** (R_1 = Ph) (2.01 g, 11.4 mmol) in acetone (100 mL) was treated with MnO_2 (3 × 5 g, t = 0, 25 min, 4 h). After 6 h, filtration through Celite, concentration, and chromatography (CH_2Cl_2/CH_3CN/HOAc) gave **7** as a solid (1.56 g, 79%): recrystallization (Et_2O/hexane); mp 170–172 °C (effervescence); ^{1}H NMR (acetone-d_6) δ 7.42 (bd s, 5 H, Ar*H*), 10.9 (s, 1 H, $-CHO$).

3,5-Dihydroxy-4-phenyl-2(5*H*)-furanone (8). Aldehyde **7** (0.197 g, 0.907 mmol) and 1:1 HOAc–12 N HCl (1 mL) were heated at 100 °C for 20 min and then immediately cooled in an ice bath. Water was added, and the mixture was extracted repeatedly with Et_2O, dried ($MgSO_4$), and concentrated. Chromatography (CH_2Cl_2/MeOH/HOAc) gave **8** as a solid (0.089 g, 51% yield): mp 202–203 °C (effervescence); ^{1}H NMR (acetone-d_6) δ 6.52 (bd s, 1 H, $-OCH-$), 6.8 (bd s, 1 H, $-OH$), 7.3–7.5 (m, 3 H, Ar*H*), 7.90 (d, J = 7, 1 H, Ar*H*), 9.55 (bd s, 1 H, $-OH$).

Addition of Methyllithium to 7. MeLi (0.90 mL, 1.25 mmol, 1.4 M in Et_2O) was added dropwise to a solution of **7** (0.109 g, 0.502 mmol) in THF (10 mL) at −78 °C. After 30 min methanolic HCl was added and the solution allowed to warm to 25 °C, concentrated, and chromatographed ($CHCl_3/CH_3CN$/HOAc) to give **4a** (R_1 = Ph, R_2 = Me) as a solid (0.102 g, 87% yield).

Preparation of 9. A solution of **10** (1.5 g, 5.2 mmol) in THF (10 mL) at −78 °C was added all at once, via cannula, to **2** (4.95 mmol) in THF (50 mL) at −78 °C. After 1.5 h the mixture was allowed to warm to 25 °C. After 1.5 h, aqueous HCl (40 mL, 0.5 N) was added. Extraction (Et_2O), drying ($MgSO_4$), concentration, and chromatography ($CHCl_3$/HOAc) gave 3-[3-(2,4-dioxo-oxazolidin-5-yl)-3-phenyloxiranyl]propionic acid methyl ester (**11**) as a 3:2 mixture of diastereomers (oil, 1.30 g, 86% yield): ^{1}H NMR (acetone-d_6) δ 1.28–1.42 (m, 1 H, $-CH_2-$), 1.52–1.66 (m, 1 H, $-CH_2-$), 2.37–2.46 (m, 2 H, $-CH_2CO_2Me$), 3.58 (s, 3 H, $-OCH_3$), 3.62 (dd, J = 5.1, 7.1, 0.6 H, $-CH-$), 3.76 (dd, J = 5.0, 7.2, 0.4 H, $-CH-$), 5.29 (s, 0.6 H, $-CH-$), 5.49 (s, 0.4 H, $-CH-$), 7.34–7.51 (m, 5 H, Ar*H*). The epoxides (0.303 g, 0.992 mmol) were heated in aqueous HCl (6 N, 10 mL) at 100 °C for 61 h. Concentration gave a solid which was extracted repeatedly with acetone. Concentration gave a brown solid (0.289 g) which was filtered through silica gel (Et_2O) to give **9** as an off-white solid (0.202 g, 82% yield): recrystallization (EtOAc/hexane); mp 179–181 °C (lit.[12c] mp 177–179 °C); ^{1}H NMR, IR, and MS were identical to those reported in the literature.[12c]

Methyl 4-Bromo-5-oxo-5-phenylpentanoate (10). Methyl 5-oxo-5-phenylpentanoate was brominated according to the method of King and Ostrum.[18] Filtration through silica gel ($CHCl_3$–CH_3CN) gave **10** as a pale orange oil (98% yield): ^{1}H NMR (acetone-d_6) δ 2.2–2.7 (m, 2 H, $-(CH_2)_2-$), 3.66 (s, 3 H, $-OCH_3$), 5.65 (dd, J = 5.0, 7.5, 1 H, $-CHBr-$), 7.5–7.7 (m, 3 H, Ar*H*), 8.07 (d, J = 6, 2 H, Ar*H*).

5-Methyl-2,4-oxazolidinedione. Iodomethane (0.26 mL, 4.16 mmol) was added all at once to **2** (3.96 mmol) in THF (40 mL) at −78 °C. After 15 min the mixture was allowed to warm to 25 °C. After 1 h the pale yellow solution was treated with HCl in dioxane (2.1 mL, 4 N). The solution was concentrated, and the resulting solid was triturated with ether. The ether washings were filtered through silica gel. Concentration gave a clear colorless oil (0.57 g). Chromatography (silica gel, hexane/EtOAc) gave 5-methyl-2,4-oxazolidinedione (0.37 g, 82%): ^{1}H NMR (acetone-d_6) δ 1.5 (d, J = 6, 3 H, $-CH_3$), 5.0 (q, J = 6, 1 H, $-CHCH_3$).

Acknowledgment. The author would like to thank Philip F. Hughes for valuable discussions.

Supplementary Material Available: Spectral data and analytical results for **1**, **4a**, **6**, **7**, **8**, and **11** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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A δ-Keto Aldehyde Synthesis: Application to the Preparation of the Sex Pheromone of the Douglas-Fir Tussock Moth

John C. Stowell* and Michael A. Polito

Department of Chemistry, University of New Orleans, New Orleans, Louisiana 70148

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δ-Keto aldehydes are useful intermediates in many syntheses. They have been prepared by a variety of methods, most of which involve adding three carbons at the site α to the keto group. These methods include conjugate addition of an enamine to acrolein followed by hydrolysis,[1] alkylation of enolates with 1,3-dichloropropene or 2-(2-bromoethyl)-1,3-dioxolane followed by hydrolysis,[2] or alkylation with allyl bromide followed by hydroboration and oxidation.[3] Cycloaddition of a ketone enol ether with acrolein followed by hydrolysis does likewise.[4] Oxidative opening of 1-alkylcyclopentenones is another alternative.[5] Some methods afford δ-keto aldehydes under acidic or basic conditions where they become cyclohexenones in situ.[6]

We are interested in preparing δ-keto aldehydes from acid chlorides using Grignard reagents derived from the now readily available[7] 2-(3-halopropyl)-1,3-dioxolanes or dioxanes.[8] Simple Grignard reagents afford good yields of ketones upon reaction with acid chlorides at −78 °C in tetrahydrofuran,[9] and there was no evidence to suggest that our proposed Grignard reagents might not be successful also.

We prepared the Grignard reagents from 2-(3-bromopropyl)-4,4,6-trimethyl-1,3-dioxane and from 2-(3-bromopropyl)-4,4,5,5-tetramethyl-1,3-dioxolane with magnesium turnings[7] in THF at reflux or at 25–30 °C; however, adding

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