A Convenient Synthesis of 1-Oxaspiro[5.5]undecane Derivatives[1]

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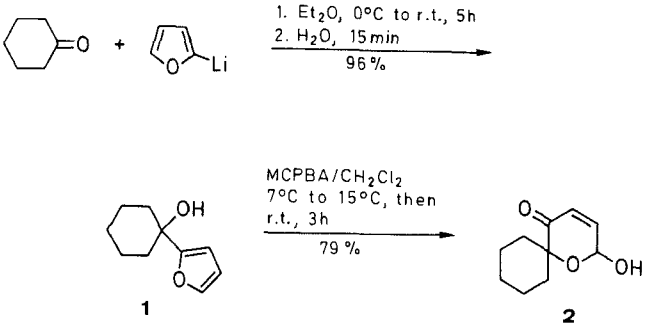
2-Hydroxy-1-oxaspiro[5.5]undec-3-en-5-one, which is derived from 1-(2-furyl)cyclohexan-1-ol, is used in a convenient synthesis of several 1-oxaspiro[5.5]undecane derivatives.

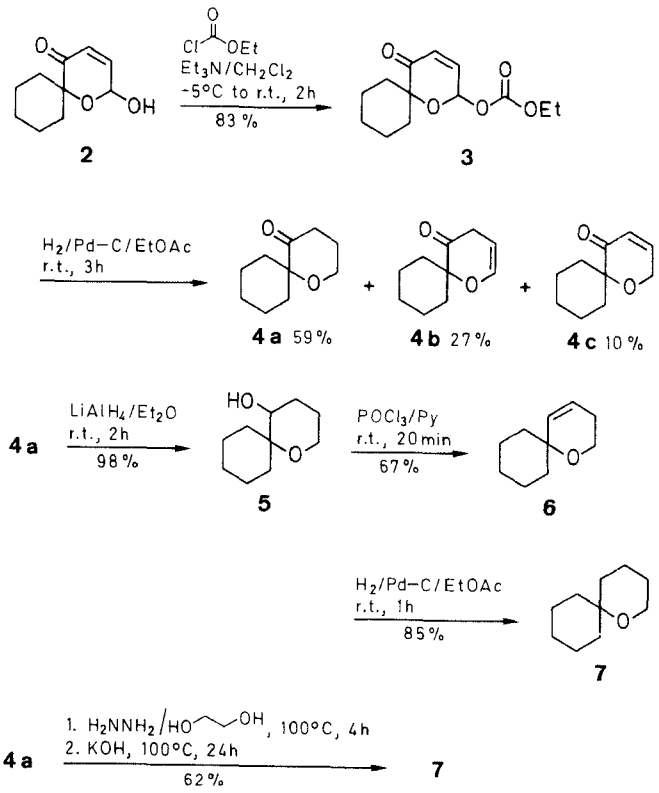
Spiroketals are important subunits of a growing variety of naturally occurring compounds with considerable current importance and interest.[2] They have been reported to be components of complex molecules such as calcimycin (A-23187),[3] okadaic acid,[4] monensin,[5] aplysiatoxin,[6] phyllanthocin,[7] milbemycins–avermectins[8] etc. Furthermore, 1,7-dioxaspiro[5.5]undecane was identified as the specific sex pheromone of female olive flies (*D. Oleae*),[9] while its mono oxacarbocyclic analogue 1-oxaspiro[5.5]undecane occurs as the key structural feature of numerous natural products.[10] Thus, they have attracted a great deal of synthetic work directed towards their facile and convenient snythesis.[11] The literature abounds with methods for the synthesis of spiroketals which may be classified in two groups: one that involves the assembly of a fully functionalized ketone precursor prior to spirocyclization,[12] while the other concerns the addition of a dianion to lactones followed by acid catalysed cyclization to spiroketals.[13] However, both pathways cannot be considered as general and efficient, since for each synthesis the target compound should carry suitable functional groups from the beginning. On the other hand they do not lead to several biologically important spiroketalic derivatives, such as the unsaturated spiroketals[14] or the spiroketals functionalized at C-2.[15]

In the course of our ongoing investigation concerning the synthesis of biologically active compounds from furan[16] we have studied the use of 2-hydroxypyran-5(2*H*)-one, 6-spiro derivatives which contain the structural framework of spiroketals, as key intermediates for the facile and efficient construction of several novel functionalized spiroketals. It is evident that the multitude of the reactions which can be carried out on the α,β-unsaturated ketone system as well as on the hydroxy and oxo groups, allow the incorporation of a wide variety of substituents and functionalities.

As substrate for our synthetic route we have used 2-furyllithium, which was reacted with cyclohexanone yielding the corresponding 1-(2-furyl)cyclohexan-1-ol (**1**). This compound upon treatment with 3-chloroperoxybenzoic acid (MCPBA, oxidizing agent) undergoes an oxidation–rearrangement sequence[17] on the furan nucleus producing pyranone derivative **2**, which is very stable and can be stored for a long period of time. The hydroxy group at C-2 was eliminated by conversion to the corresponding allylic ethyl carbonate **3** and subsequent treatment with hydrogen in the presence of palladium catalyst. Under these conditions the allylic carbonte was hydrogenolyzed and subsequently hydrogenated yielding the corresponding 1-oxaspiro[5.5]-undecan-5-one (**4a**). It is also noticeable that unsaturated hydrogenolysis products, **4b** and **4c**, were also obtained, indicating that the catalytic hydrogenation reaction was not completed presumably because of steric hindrance due to spiro configuration.[18] Thus, the rate of the reaction can be controlled and larger amount of catalyst, longer reaction time and more polar solvent led to better yields of the tetrahydro derivative over the unsaturated products. On the other hand compound **4a** was reduced with lithium aluminum hydride yielding the corresponding alcohol **5**, which was dehydrated on the



Scheme 1



Scheme 2

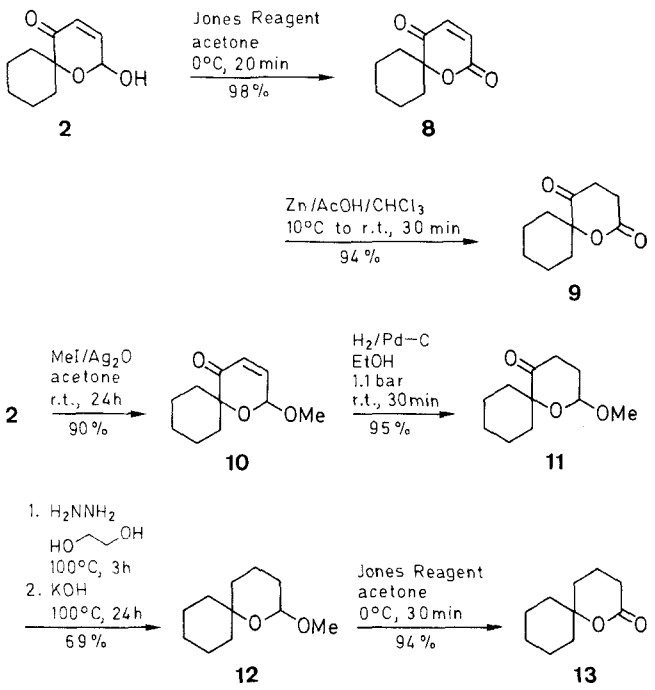
Table. Physical and Spectral data of Compounds **1–13** Prepared

Product	Yield[a] (%)	R_f[c]	mp (°C)[d] (solvent) or bp (°C)/mbar	Molecular Formula[e]	IR (neat)[f] ν (cm^{-1})	^{1}H-NMR (solvent/TMS)[h] δ, J (Hz)
1	96	0.62	106–107/13	$C_{10}H_{14}O_2$ (166.2)	3350s (OH), 2920s, 2850s, 1440m, 1255m, 1150s, 1050m, 955s, 850m (sharp, furan), 725s	CCl_4: 1.61 (m, 10H, CH_2), 2.18 (s, 1H, OH), 5.86 (d, 1H, J = 3.4, H-3), 5.98 (dd, 1H, J = 3.4, 1.7, H-4), 6.98 (d, 1H, J = 1.7, H-5)
2	79	0.32	115–117/0.1	$C_{10}H_{14}O_3$ (182.2)	3420m (OH), 2940s, 2870m, 1690s, (conjC=O), 1645m (C=C), 1455m, 1270m, 1035s	CCl_4: 1.55 (m, 10H, CH_2), 5.13 (br, 1H, OH), 5.35 (dd, 1H, J = 2.1, 0.9, H-2), 5.68 (dd, 1H, J = 10.3, 0.9), 6.52 (dd, 1H, J = 10.3, 2.1, H-3)
3	83	0.58	61–63 (Et_2O/hexane)	$C_{13}H_{18}O_5$ (254.3)	2940s, 2860m, 1755s (O–C=O), 1690s (conjC=O), 1640w (C=C), 1450w, 1265s, 1030s	$CDCl_3$: 1.31 (t, 3H, J = 7, CH_3), 1.58 (m, 10H, CH_2), 4.13 (q, 2H, J = 7, OCH_2), 6.03 (d, 1H, J = 9.8, H-4), 6.32 (d, 1H, J = 3, H-2), 6.67 (dd, 1H, J = 9.8, 3, H-3)
4a	59[b]	0.38	oil	$C_{10}H_{16}O_2$ (168.2)	2950s, 2865s, 1720s (C=O), 1450m, 1265m, 1150m, 1090s, 1010s	CCl_4: 1.53 (m, 10H, CH_2), 2.03 (m, 2H, H-3), 2.35 (m, 2H, H-4), 3.72 (t, 2H, J = 5.2, H-2)
4b	27[b]	0.76	oil	$C_{10}H_{14}O_2$ (168.2)	2920s, 2850s, 1715s (C=O), 1650m (C=C), 1440s, 1260s, 1050s, 950s, 730m	CCl_4: 1.60 (m, 10H, CH_2), 2.70 (dd, 2H, J = 3.4, 2.1, H-4), 4.61 (dt, 1H, 5.6, 3.4, H-3), 6.13 (dt, 1H, J = 5.6, 2.1, H-2)
4c	10[b]	0.54	oil	$C_{10}H_{14}O_2$ (168.2)	2935s, 2860m, 1685s (conjC=O), 1450w, 1270m, 1050w, 800w	CCl_4: 1.61 (m, 10H, CH_2), 4.31 (dd, 2H, J = 2.7, 1.8, H-2), 5.90 (dt, 1H, J = 10.3, 1.8, H4), 7.02 (dt, 1H, J = 10.3, 2.7, H-3)
5	98	0.20	oil	$C_{10}H_{18}O_2$ (170.2)	3410m (OH), 2940s, 2850m, 1450m, 1085s, 990m	CCl_4: 1.53 (m, 14H, CH_2, H-3, H-4), 3.02 (m, 2H, H-5), 3.11 (br, 1H, OH), 3.42 (m, 2H, H-2)
6	67	0.68	oil	$C_{10}H_{16}O$ (152.2)	2930s, 2860m, 1660w (C=C), 1450w, 1260m, 1075s, 780s, 760s	CCl_4: 1.49 (m, 10H, CH_2), 1.97 (m, 2H, H-3), 3.63 (t, 2H, J = 5.3, H-2), 5.52 (m, 2H, H-4, H-5)
7	62	0.54	72–72/8	$C_{10}H_{18}O$ (154.2)	2930s, 2855m, 1440w, 1260s, 1075s, 1020m, 910m, 800m	CCl_4: 1.52–2.03 (m, 16H, CH_2, H-3, H-4, H-5), 3.52 (t, 2H, J = 5.9, H-2)
8	98	0.39	76–78 (Et_2O)	$C_{10}H_{14}O_3$ (180.2)	2950m, 2860m, 1745s (O–C=O), 1690s (conjC=O), 1650m (C=C), 1440m, 1260s, 1110s, 990s, 845m[g]	$CDCl_3$: 1.77 (m, 10H, CH_2), 6.67 (d, 1H, J = 9.3, H-4), 6.90 (d, 1H, J = 9.3, H-3)
9	94	0.22	79–81 (Et_2O)	$C_{10}H_{14}O_3$ (182.2)	2940m, 2860w, 1730s (br) (C=O), 1430w, 1270m, 1130m, 1000m[g]	$CDCl_3$: 1.72 (m, 10H, CH_2), 2.77 (m, 4H, H-3, H-4)
10	90	0.51	oil	$C_{11}H_{16}O_3$ (196.2)	2970s, 2850m, 1695 (conjC=O), 1650m (C=C), 1440m, 1100m, 1030s, 960m	$CDCl_3$: 1.71 (m, 10H, CH_2), 3.52 (s, 3H, OCH_3), 5.20 (m, 1H, H-2), 6.03 (dd, 1H, J = 10, 1.5, H-4), 6.82 (dd, 1H, J = 10, 1.5, H-3)
11	95	0.55	oil	$C_{11}H_{18}O_3$ (198.3)	2930s, 2860s, 1710s (C=O), 1440m, 1110s, 1050s, 990s	$CDCl_3$: 1.66 (m, 10H, CH_2), 2.39 (m, 4H, H-3, H-4), 3.46 (s, 3H, OCH_3), 4.83 (m, 1H, H-2)
12	69	0.87	oil	$C_{11}H_{20}O_2$ (184.3)	2930s, 2870m, 1440w, 1120m, 1080m	$CDCl_3$: 1.51–1.98 (m, 16H, CH_2, H-3, H-4, H-5), 3.40 (s, 3H, OCH_3), 4.62 (m, 1H, H-2)
13	95	0.29	92–94/0.4	$C_{10}H_{16}O_2$ (168.2)	2925s, 2860m, 1725s (O–C=O), 1440w, 1240m, 1040m, 990m, 730m	$CDCl_3$: 1.41–2.03 (m, 14H, CH_2, H-4, H-5), 2.48 (m, 2H, H-2)

[a] Yield of isolated purified products.
[b] Overall hydrogenation yield 96% (59 + 27 + 10).
[c] TLC data: UV_{254}, 0.2 mm silica gel plastic coated sheets, Et_2O/hexane (1:1).
[d] Uncorrected, measured with a Büchi apparatus.
[e] Satisfactory microanalyses obtained (except compd. **1**), C ± 0.29, H ± 0.23.
[f] Recorded on a Perkin Elmer 283 B Infrared spectrophotometer.
[g] KBr.
[h] Obtained on a Varian EM 360 spectrometer. All OH proton signals are exchangeable with D_2O.

presence of phosphoryl chloride to compound **6**. Catalytic hydrogenation of the latter furnished the 1-oxaspiro [5.5]undecane (**7**). The same product was also obtained more efficiently by a Wolff–Kishner deoxygenation of compound **4a**. Furthermore the 2,5-dione derivatives of these compounds, **8** and **9**, are easily accessible by Jones oxidation and subsequent hydrogenation of pyranone **2**.

Derivatives of 1-oxaspiro[5.5]undecanes functionalized at C-2 (Scheme **3**) were obtained by converting the pyranone **2** to its methoxy derivative, catalytic hydrogenation and removal of the carbonyl group by a Wolff–Kishner reduction. Moreover, Jones oxidation of the compound **12** afforded a spiroketalic δ-lactone, **13**, which is a well-known structural feature of many natural products.



Scheme 3

In conclusion, the synthetic routes described here provide a convenient access to functionalized 1-oxaspiro[5.5]undecanes, which are valuable intermediates for the synthesis of natural compounds which otherwise are not readily available.

All reagents were of commercial quality from freshly opened containers and were obtained from Aldrich. Furan, cyclohexanone and pyridine were distilled immediately prior to use. BuLi was purchased from Merck and titrated prior to use. Reagent quality solvents, purchased from Merck, were used without further purification. THF was dried over CaH_2. TLC analyses were carried out on silica gel 60 F_{254} pre-coated plastic plates (Merck) and spots were visualized by spraying with a solution H_2SO_4/EtOH (8:2) Column chromatography was performed on silica gel 60 (230–400 mesh) purchased from Merck.

1-(2-Furyl)cyclohexan-1-ol (1):
To a solution of freshly distilled furan (50 mL) in anhydr. Et_2O (400 mL), BuLi (w/v 15% in hexane, 200 mL) is added dropwise under a N_2 atmosphere and the temperature maintained below −5°C. The reaction is allowed to reach r.t. and stirred for additional 1 h. Then is cooled to 0°C and cyclohexanone (26.5 g, 300 mmol) is added dropwise over 1 h and stirring is continued at r.t. for 4 h. The mixture is poured into ice water (100 mL) and stirred for 15 min. The organic layer is separated, washed with sat. aq NH_4Cl (75 mL) and dried ($MgSO_4$). The solvent is evaporated to dryness under reduced pressure yielding compound **1** as a colorless oil; yield: 43.1 g (96%) (Table).

2-Hydroxy-1-oxaspiro[5.5]undec-3-en-5-one (2):
To a stirred solution of compound **1** (8 g, 48 mmol) in CH_2Cl_2 (120 mL), maintained between 7°C and 15°C, MCPBA (80%, 12 g, 70 mmol) is added in small portions and stirring is continued at r.t for 3 h. Then the mixture is cooled and the precipitated solid (3-chlorobenzoic acid) is removed by filtration. The filtrate is washed successively with 20% aq KI (80 mL), 30% aq $Na_2S_2O_3$ (100 mL), sat. aq $NaHCo_3$ (130 mL) and dried ($MgSO_4$). The solvent is evaporated and the crude product is chromatographed on a silica gel column (hexane/Et_2O, 1:1, as eluent) giving pyranone **2** as a colorless oil; yield: 6.9 g (79%) (Table).

Ethyl 5-Oxo-1-oxaspiro[5.5]undec-3-en-2-yl Carbonate (3):
To a solution of compound **2** (10 g, 55 mmol) and Et_3N (10 g, 100 mmol) in CH_2Cl_2 (150 mL) cooled to −5°C ethyl chloroformate (13.7 g, 130 mmol) is added under stirring, in such rate that the reaction temperature is maintained below 0°C. The mixture is stirred at r.t. for 2 h, extracted with H_2O (2 × 50 mL), dried ($MgSO_4$) and the solvent is evaporated under reduced pressure yielding 11.6 g (83%) of compound **3**. For analytical purposes purification is achieved by chromatography on a silica gel column (hexane/Et_2O, 7:3, as eluent) (Table).

1-Oxaspiro[5.5]undecan-5-one (4a):
To a solution of compound **3** (5.1 g, 20 mmol) in EtOAc (180 mL) Pd–C (10%, 500 mg) is added and the mixture is treated with H_2 in a Parr apparatus at 1 bar pressure and r.t. for 3 h. After removal of the catalyst and evaporation of the solvent, the remaining slurry is chromatographed on a silica gel column (hexane/Et_2O, 6:4, as eluent). The fractions with the lower R_f value (0.38) gave 2 g (59%) of compound **4a** (Table).
Fractions with higher R_f value (0.76 and 0.54) yielded 0.9 g (27%) of 1-oxaspiro[5.5]undec-2-en-5-one **(4b)** and 0.33 g (10%) of 1-oxaspiro[5.5]undec-3-en-5-one **(4c)**, respectively (Table).

1-Oxaspiro[5.5]undecan-5-ol (5):
$LiAlH_4$ (0.4 g, 10 mmol) is added during 20 min to a solution of compound **4a** (2.5 g, 15 mmol) in anhydr. Et_2O (150 mL). The mixture is stirred at r.t. for another 100 min, then quenched with sat. aq NH_4Cl (2 mL), filtered on Celite and dried ($MgSO_4$). The solvent is evaporated in vacuo yielding 2.48 g (98%) of compound **5** (Table).

1-Oxaspiro[5.5]undec-4-ene (6):
To a solution of compound **5** (1.5 g, 8.8 mmol) in pyridine (40 mL), $POCl_3$ (2.7 mL) is added and the mixture is stirred for 20 min. Ice-water (50 mL) is then added and the mixture is extracted with Et_2O (3 × 50 mL). The combined organic layers are extracted successively with H_2SO_4 (10%, 40 mL), sat. aq $NaHCO_3$ (30 mL), brine and dried ($MgSO_4$). Evaporation of the solvent afforded 0.9 g (67%) of compound **6**. For analytical purposes purification is achieved by chromatography on a silica gel column (hexane/Et_2O, 8:2, as eluent) (Table).

1-Oxaspiro[5.5]undecane (7):
Method A: By Wolff–Kishner deoxygenation: A solution of compound **4a** (1 g, 6 mmol) and hydrazine (85% w/v in H_2O, 1.8 g) in ethylene glycol (10 mL) is stirred at 100°C (oil bath) for 4 h. Then KOH (1.8 g, 32 mmol) is added and the reaction is continued at 100°C for 24 h. The resulting mixture is partitioned in benzene (70 mL) and H_2O (30 mL) and the organic layer is separated, washed with 10% HCl (20 mL) and dried ($MgSO_4$). The solvent is evaporated in vacuo and compound **7** is obtained as pure colorless oil by bulb-to-bulb distillation; yield: 0.57 g (62%) (Table).

Method B: By Hydrogenation: A solution of compound **6**(0.76 g, 5 mmol) in EtOAc (30 mL) is hydrogenated over Pd–C (10%, 80 mg) at r.t. and atmospheric pressure for 2 h. Then the mixture is filtered, dried ($MgSO_4$) and evaporated in vacuo yielding 0.65 g (85%) of a material, identical with the obtained above.

1-Oxaspiro[5.5]undec-3-ene-2,5-dione (8):
To an ice cold stirred solution of compound **2** (4.9 g, 27 mmol) in acetone (130 mL), Jones reagent[19] (6 mL) is added dropwise. After stirring for additional 20 min the solid inorganic byproducts are eliminated by decantation, the liquid layer is evaporated under reduced pressure and the resulting residue is partitioned in Et_2O (200 mL) and H_2O (70 mL). The organic layer is separated, washed with H_2O (40 mL) and dried ($MgSO_4$). The solvent is evaporated in vacuo and the yellowish oily residue is dissolved in Et_2O (15 mL), chilled overnight and filtered to give **8** as pale yellow needles; yield: 4.75 g (98%) (Table).

1-Oxaspiro[5.5]undecane-2,5-dione (9):
To a stirred solution of compound **8** (2.5 g, 14 mmol) in $CHCl_3$ (200 mL) and AcOH (130 L), maintained below 15°C, well powdered Zn dust (9.4 g) is added in small portions. The mixture is stirred for 30 min at r.t. The inorganic salts are removed by

filtration and the filtrate is azeotroped in vacuo with benzene (3 × 70 mL). The oily residue is dissolved in Et_2O (100 mL), washed with sat. aq $NaHCO_3$ (50 mL) and dried ($MgSO_4$). Evaporation of the solvent in vacuo gave a colorless oily residue, which is crystallized from Et_2O (10 mL); yield: 2.38 g (94%) (Table).

2-Methoxy-1-oxaspiro[5.5]undec-3-en-5-one (10):
To a solution of compound **2** (11 g, 60 mmol) and MeI (17 g, 270 mmol) in anhydr. acetone (250 mL), powdered Ag_2O (20.9 g) is added portionwise and the mixture is stirred at r.t. for 24 h. Then the mixture is refluxed with Norite (4 g), filtered on Celite and the filtrate is evaporated in vacuo. The remaining residue is chromatographed on a silica gel column (hexane/Et_2O, 7:3, as eluent) yielding 10.66 g (90%) of compound **10** (Table).

2-Methoxy-1-oxaspiro[5.5]undecan-5-one (11):
A mixture of compound **10** (5 g, 25 mmol) and Pd–C (500 mg) in EtOH (100 mL) is hydrogenated in a Parr apparatus at 1.1 bar pressure and r.t. for 30 min. The catalyst is removed by filtration and the solvent is evaporated in vacuo yielding 4.8 g (95%) of compound **11** (Table).

2-Methoxy-1-oxaspiro[5.5]undecane (12):
A solution of compound **11** (3 g, 15 mmol) and hydrazine (85% w/v in H_2O, 8 mL) in ethylene glycol (17 mL) is stirred at 100°C (oil bath) for 3 h. Then KOH (6 g) is added and the reaction is continued at 100°C for 24 h. The mixture is worked up as described above to give compound **12**; yield: 1.92 g (69%) (Table).

1-Oxaspiro[5.5]undecan-2-one (13):
An ice cold solution of compound **12** (1.84 g, 10 mmol) in acetone (60 mL) is reacted with Jones reagent[19] (2 mL) for 30 min. Then the mixture is worked up as given for compound **8** to afford **13**; yield: 1.58 (94%) (Table).

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(1) This is No 20 in the series "Products from Furans" from this Lab; for No 19 see Georgiadis, M.P.; Couladouros. E.A.; Delitheos, A.K. *Eur. J. Med. Chem.*, in press; for previous parts see Ref. 16.
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