Agric. Biol. Chem., **48** (3), 783～787, 1984

Synthesis of ω-Chain Shortened Prostaglandins and Their Six-membered Ring Analogs†

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Received September 19, 1983

Prostaglandin E_1 analogs **5a** and **5b**, having methyl and ethyl groups as the ω-chain, were synthesized by a two-step alkylation system of diethyl 3-oxoglutarate (**1**) and their six-membered ring analogs **8a** and **8b** also derived from the first alkylation product **2** *via* a Michael reaction.

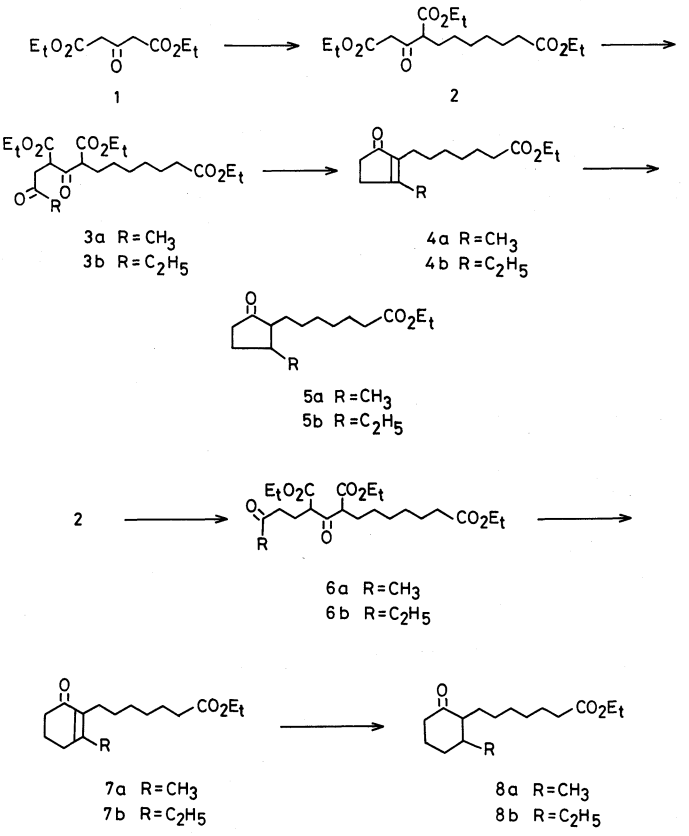
We have been active in utilizing diethyl 3-oxoglutarate (**1**), DEOG, as a convenient synthetic material for the synthesis of a wide variety of compounds including natural products, because DEOG would produce useful intermediates to synthesize these products through reaction with a number of organic reactants.[1] The present investigation has been undertaken in order to extend the regioselective two-step alkylation of DEOG to the synthesis of prostaglandin analogs.[2]

Much attention has been focused on the synthesis and medical application of diverse prostaglandin analogs possessing heteroatoms[3] and/or modified side chains[4] largely because of their potent and varied biological properties. Recently, Poletto *et al.* reported that prostaglandin E_1 analogs **5a**, **5b** and **8a**, which have a shorter alkyl group as the ω-side chain, exhibited inhibition to the secretion of gastric acid.[5] In this paper we describe the synthesis of the ω-chain shortened prostaglandins **5a** and **5b** and of their six-membered ring analogs **8a** and **8b** starting from DEOG.

DEOG was subjected to the first alkylation with ethyl 7-bromoheptanoate in the presence of magnesium ethoxide. The product **2**[1a] was then alkylated with chloroacetone in 1,2-dimethoxyethane to give the 2,4-dialkylated product **3a** in a 73% yield. Diketone triester **3a** was heated in an aqueous solution of sodium hydroxide to be decarboxylatively hydrolyzed and similtaneously cyclized to produce an acid which, on esterification, gave a five-membered ring keto ester (**4a**) in a 48% yield. The conjugated double bond in the α,β-unsaturated ketone **4a** was selectively hydrogenated over 5% Rh/C catalyst in ethanol and the desired keto ester **5a**, an 11-deoxyprostaglandin E_1 analog, was obtained in an 82% yield. GLC and ^{1}H NMR analyses of **5a** showed it to be a mixture of *trans* and *cis* isomers (α/ω-side chain configuration) in 70 : 30 proportions.[5,6] Similarly, another prostaglandin E_1 analog **5b** (*trans*/*cis* = 70/30) was synthesized according to the sequence described above from **3b**, which had been prepared in a 75% yield utilizing 1-bromo-2-butanone for the second alkylation.

For the synthesis of the six-membered ring analog **8a**, compound **2** was converted to a Michael adduct (**6a**) in an 80% yield by reaction with methyl vinyl ketone in the presence of catalytic amounts of sodium hydride. The adduct **6a** was treated with an aqueous solution of sodium hydroxide as mentioned above to yield a six-membered ring carboxylic

† Selective Alkylation of Diethyl 3-Oxoglutarate. Part X. This work was presented in part at the Annual Meeting of the Agricultural Chemical Society of Japan, Tokyo, Japan, April 1, 1982. For Part IX, see ref. 1c.



acid which, on esterification, gave the corresponding unsaturated keto ester **7a** in a 60% yield. The conjugated double bond was submitted to hydrogenation employing the same catalyst as used for **4a**. The keto ester, **8a**, a six-membered ring prostaglandin analog, was obtained as a mixture of *trans* and *cis* isomers (75:25) in a 74% yield. The 3-ethyl congener **8b** was also prepared as a mixture of *trans* and *cis* isomers (70/30) in a similar manner from **6b**, which had been derived from **2** in a 66% yield by a Michael reaction with ethyl vinyl ketone.

Next, we carried out the hydrogenation in various solvents. The table shows that the selective hydrogenation of **4a** predominantly gave the *cis* product in all of the solvents used except ethanol, whereas that of **4b** mainly afforded the *trans* product. Furthermore, we examined the equlibration under alkali conditions of all four hydrogenation products.

TABLE I. *trans*/*cis* ISOMER RATIOS OF THE HYDROGENATION PRODUCTS OF THE UNSATURATED KETONES **4a**, **4b**

Solvent	Product	*trans* (%)	*cis* (%)
Hexane	5a	7	93
	5b	65	35
THF	5a	15	85
	5b	77	23
t-BuOH	5a	20	80
	5b	70	30
Iso-PrOH	5a	32	68
	5b	60	40
EtOH	5a	70	30
	5b	70	30

The 2,3-dialkylcyclopentanone **5a**, a mixture of 70% *trans* and 30% *cis*, gave by treatment with sodium ethoxide the thermodynamic mixture of 85% *trans* and 15% *cis*, and the cyclopentanone **5b**, the mixture of 90% *trans* and 10% *cis*.[5,6] On the other hand, the 2,3-dialkyl-

cyclohexanones **8a** and **8b** yielded after the same treatment, respectively, an equilibrium mixture of *trans/cis* (65/35) and *trans/cis* (65/35). Although our attention was not directed at the mechanistic aspects for the stereochemistry of selective hydrogenation of **4a** and **4b** or **7a** and **7b**, these results may be partially rationalized from the fact that the product stereochemistry of hydrogenation of α,β-unsaturated ketone is largely affected by the nature of the reaction solvent (for **4a**) or by the substrate structure itself (for **4b**).[7]

EXPERIMENTAL

The homogeneity of each compound was always checked by TLC on silica gel (Merck Kieselgel 60H) with various solvent systems. Merck Kieselgel 60 (70~230 mesh) was used for column chromatography. IR spectra were obtained using neat liquids on a Hitachi 260-10 spectrometer. ^{1}H NMR spectra were taken with a Hitachi R-24B instrument in $CDCl_3$ solutions using Me_4Si as an internal standard. ^{13}C NMR spectra were obtained in $CDCl_3$ solutions. GC-MS was performed on a JEOL JMS-D300 spectrometer with a glass column (2 m × 2 mm i.d.) packed with 5% PEG-HT on chromosorb W (80~100 mesh) at an ionization potential of 70 eV. EI and CI mass spectra were recorded at 70 eV and 200 eV (isobutane), respectively, using a direct insertion probe. GLC analyses were carried out isothermally at 210°C using a Shimadzu GC-6A instrument with a glass column (2 m × 3 mm i.d.) packed with 10% PEG-20M on chromosorb W (80~100 mesh).

Triethyl 8,11-dioxo-1,7,9-dodecanetricarboxylate (**3a**). Compound **2** (30 g, 84 mmol) was dissolved in dry 1,2-dimethoxyethane (DME, 30 ml) and slowly added to a suspension of sodium hydride (50% mineral oil dispersion, 4.03 g, 84 mmol) in dry DME (100 ml) with constant stirring, this stirring being continued for an additional hour at room temperature. To the solution, chloroacetone (7.77 g, 84 mmol) and finely powdered sodium iodide (13 g) were then added and the mixture was refluxed with stirring for 15 hr. The usual work-up of the reaction mixture gave **3a** as a dark brown substance, which was purified by column chromatography (SiO_2, 150 g) with a hexane–ether mixed solvent (3:1) as a yellow viscous liquid (25.4 g, 73%). IR ν_{max} cm^{-1}: 1740, 1720. ^{1}H NMR δ: 1.10~1.90 (19H, m), 2.02~2.40 (5H, s at 2.15), 3.03 (2H, d, J=6.5 Hz), 3.70~4.42 (8H, m). ^{13}C NMR δ: 14.11 (q), 168.37 (s), 169.01 (s), 173.59 (s), 199.12 (s), 204.87 (s). EIMS m/z: 369 (M^+−EtO, 7), 125 (100), 43 (92). CIMS m/z: 415 [$(M+H)^+$, 44], 397 [$(M+H-H_2O)^+$, 100].

Triethyl 8,11-dioxo-1,7,9-tridecanetricarboxylate (**3b**). According to the procedure described above, compound **2** (25 g, 70 mmol) was treated with sodium hydride (50% mineral oil dispersion, 3.36 g, 70 mmol) and 1-bromo-2-butanone (10.57 g, 70 mmol). Column chromatography (SiO_2, 120 g) with hexane–ether (6:1) of the product gave **3b** as a yellow viscous liquid (22.5 g, 75%). IR ν_{max} cm^{-1}: 1740, 1720. ^{1}H NMR δ: 0.92~1.85 (22H, m), 2.20~2.55 (4H, m), 3.03 (2H, d, J=6.5 Hz), 3.70~4.40 (8H, m). ^{13}C NMR δ: 7.70 (q), 14.02 (q), 168.27 (s), 169.04 (s), 173.74 (s), 199.32 (s), 207.72 (s). EIMS m/z: 383 (M^+−EtO, 10), 139 (100), 57 (83). CIMS m/z: 429 [$(M+H)^+$, 45], 411 [$(M+H-H_2O)^+$, 100].

Ethyl 7-(2-methyl-5-oxo-1-cyclopentenyl)heptanoate (**4a**). A solution of **3a** (20.7 g, 50 mmol) in ethanol (80 ml) was refluxed under N_2 with a 3% aqueous solution of NaOH (600 ml) for 4 hr. The crude keto acid obtained by the usual work-up of the reaction mixture was subjected to esterification with a mixture of ethanol and catalytic amounts of conc. H_2SO_4. The product was usually worked up to give a dark brown oil, column chromatography (SiO_2, 130 g) of which, with petroleum ether–ether (10:1), gave the ethyl ester **4a** as a yellow liquid (6.05 g, 48%), 2,4-DNP mp 79~80°C. IR ν_{max} cm^{-1}: 1730, 1690, 1640. ^{1}H-NMR δ: 1.10~1.90 (11H, m), 2.05 (3H, s), 2.16~2.51 (8H, m), 4.05 (2H, q, J=7.0 Hz). GC-MS m/z: 252 (M^+, 4), 207 (M^+−EtOH, 11), 110 (100). *Anal.* Found: C, 71.31; H, 9.55. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59%.

Ethyl 7-(2-ethyl-5-oxo-1-cyclopentenyl)heptanoate (**4b**). As described for **3a**, treatment of **3b** (15 g, 35 mmol) with a 3% aqueous solution of NaOH (500 ml) and subsequent esterification gave a dark brown oil, which was chromatographed over silica gel (100 g) to be eluted with petroleum ether–ether (10:1) to give **4b** as a pale yellow liquid (1.87 g, 20%), 2,4-DNP mp 103~104°C. IR ν_{max} cm^{-1}: 1735, 1700, 1640. ^{1}H NMR δ: 0.95~1.70 (16H, m), 2.00~2.55 (8H, m), 4.07 (2H, q, J=7.0 Hz). GC-MS m/z: 266 (M^+, 24), 237 (12), 221 (M^+−EtO, 41), 220 (M^+−EtOH, 37), 124 (100). *Anal.* Found: C, 72.02; H, 9.78. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%. Further elution with petroleum ether–ether (5:1) afforded ethyl 8-(2-methyl-3-oxo-1-cyclopentenyl)octanoate (0.4 g), 2,4-DNP mp 102~103°C, an isomer arising from an alternative mode of aldolization-dehydration of the diketone **3b**.[8] IR ν_{max} cm^{-1}: 1735, 1700, 1645. ^{1}H NMR δ: 1.10~1.53 (13H, m), 1.76 (3H, s), 2.10~2.65 (8H, m), 4.06 (2H, q, J=7.0 Hz). GC-MS m/z: 266 (M^+, 25), 221 (M^+−EtO, 19), 123 (100), 110 (96).

Ethyl 7-(2-methyl-5-oxocyclopentyl)heptanoate (**5a**). To a solution of **4a** (2.52 g, 10 mmol) in absolute ethanol (80 ml) was added 5% Rh/C catalyst (0.25 g), and the mixture was hydrogenated at 25°C. After hydrogenation had been completed, the catalyst was filtered off and washed with ethanol. The filtrate and washings were

combined, distilled off *in vacuo*, and the residue was purified by column chromatography (SiO_2, 30 g) with a hexane-ether mixed solvent (10 : 1) to give a colorless liquid of **5a** (2.09 g, 82%) as a mixture of *trans*/*cis* (70/30) isomers in an analytically homogeneous state. GLC (carrier gas, N_2, 40 ml/min): *trans* isomer-t_R = 27.1 min, *cis* isomer-t_R = 33.9 min. IR ν_{max} cm^{-1}: 1735. ^1H NMR δ: 0.90 (*cis*) and 1.17 (*trans*) (3H, both d, J = 6.8 and 5.0 Hz, $CHC\underline{H}_3$), 1.14 ~ 1.97 (15H, m), 2.05 ~ 2.55 (6H, m), 4.10 (2H, q, J = 7.2 Hz). GC-MS *m*/*z*: *trans* isomer-254 (M^+, 4), 209 ($M^+ - EtO$, 12), 98 (69), 83 (100), *cis* isomer-254 (M^+, 3), 209 ($M^+ - EtO$, 11), 98 (63), 83 (100).

Ethyl 7-(2-ethyl-5-oxocyclopentyl)heptanoate (**5b**). As described above, hydrogenation of **4b** (0.4 g, 1.5 mmol) in absolute ethanol (25 ml) was carried out in the presence of 5% Rh/C catalyst (0.04 g). Column chromatography (SiO_2, 4 g) with hexane–ether (10 : 1) gave a colorless liquid of **5b** (0.274 g, 68%) as a mixture of *trans*/*cis* (70/30) isomers. GLC (carrier gas, N_2, 40 ml/min): *trans* isomer-t_R = 36.6 min, *cis* isomer-t_R = 43.4 min. IR ν_{max} cm^{-1}: 1735. ^1H NMR δ: 0.87 ~ 1.82 (22H, m), 2.12 ~ 2.35 (4H, m), 4.04 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: *trans* isomer-268 (M^+, 2), 239 (3), 223 ($M^+ - EtO$, 8), 112 (32), 83 (100), *cis* isomer-268 (M^+, 2), 239 (3), 223 ($M^+ - EtO$, 9), 112 (36), 83 (100).

Triethyl 8,12-dioxo-1,7,9-tridecanetricarboxylate (**6a**). Compound **2** (3.6 g, 10 mmol) was slowly added to a suspension of sodium hydride (50% mineral oil dispersion, 0.048 g, 1 mmol) in dry benzene (10 ml) with constant stirring, and stirring was continued for 0.5 hr. To the solution, methyl vinyl ketone (0.7 g, 10 mmol) was then added and the mixture was stirred for 5 hr at room temperature. The usual work-up of the product gave **6a** as a yellow substance, which was purified by column chromatography (SiO_2, 45 g) with a hexane–ether mixed solvent (3 : 2) to give a pale yellow liquid (3.4 g, 80%). IR ν_{max} cm^{-1}: 1730, 1715. ^1H NMR δ: 1.05 ~ 1.90 (21H, m), 2.10 ~ 2.60 (7H, s at 2.01), 3.35 ~ 3.80 (2H, m), 4.08 (2H, q, J = 7.0 Hz), 4.13 (4H, q, J = 7.0 Hz). ^{13}C NMR δ: 14.11 (q), 168.91 (s), 169.36 (s), 173.68 (s), 199.57 (s), 207.39 (s). EIMS *m*/*z* 383 ($M^+ - EtO$, 4), 139 (85), 55 (56), 43 (100). CIMS *m*/*z*: 429 [$(M+H)^+$, 57], 411 [$(M+H-H_2O)^+$, 76], 383 [$(M+H-EtOH)^+$, 100].

Triethyl 8,12-dioxo-1,7,9-tetradecanetricarboxylate (**6b**). As described above, **2** (3.6 g, 10 mmol) was treated with sodium hydride (50% mineral oil dispersion, 0.048 g, 1 mmol) and ethyl vinyl ketone (0.8 g, 10 mmol). Column chromatography (SiO_2, 45 g) with hexane–ether (5 : 2) of the product gave **6b** as a pale yellow liquid (2.9 g, 66%). IR ν_{max} cm^{-1}: 1740, 1720. ^1H NMR δ: 0.90 ~ 1.90 (24H, m), 2.16 ~ 2.60 (6H, m), 3.51 ~ 3.82 (2H, m), 4.10 (2H, q, J = 7.0 Hz), 4.14 (4H, q, J = 7.0 Hz). ^{13}C NMR δ: 7.81 (q), 14.20 (q), 169.01 (s), 169.45 (s), 173.68 (s), 199.75 (s), 210.18 (s). EIMS *m*/*z*: 397 ($M^+ - EtO$, 11), 153 (100), 57 (70), 55 (78). CIMS *m*/*z*: 443 [$(M+H)^+$, 12], 425 [$(M+H-H_2O)^+$, 39], 397 [$(M+H-EtOH)^+$, 100].

Ethyl 7-(2-methyl-6-oxo-1-cyclohexenyl)heptanoate (**7a**). A solution of **6a** (2 g, 4.7 mmol) in methanol (10 ml) was refluxed under N_2 with a 15% aqueous solution of NaOH (45 ml) for 4 hr. The crude keto acid obtained by the usual work-up of the reaction mixture was esterified with ethanol and catalytic amounts of conc. H_2SO_4. The product was usually worked up to give a dark brown oil, column chromatography (SiO_2, 20 g) of which with petroleum ether–benzene–ethyl acetate (10 : 1 : 1) gave the ethyl ester **7a** as a yellow liquid (0.74 g, 60%), 2,4-DNP mp 80 ~ 81°C. IR ν_{max} cm^{-1}: 1735, 1660, 1620. ^1H NMR δ: 1.10 ~ 1.80 (13H, m), 1.91 (3H, s), 2.11 ~ 2.45 (8H, m), 4.07 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: 266 (M^+, 65), 251 (31), 221 ($M^+ - EtO$, 68), 220 ($M^+ - EtOH$, 50), 124 (100), 96 (76). *Anal.* Found: C, 72.27; H, 9.86. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.

Ethyl 7-(2-ethyl-6-oxo-1-cyclohexenyl)heptanoate (**7b**). According to the procedure described above, **6b** (2.6 g, 6 mmol) was treated with a 15% aqueous solution of NaOH (60 ml) and the resulting keto acid was then esterified. Column chromatography (SiO_2, 20 g) with petroleum ether–benzene–ethyl acetate (20 : 5 : 1) of the product gave **7b** as a yellow liquid (0.13 g, 8%), 2,4-DNP mp 108 ~ 109°C. IR ν_{max} cm^{-1}: 1740, 1670, 1625. ^1H NMR δ: 0.91 ~ 1.90 (18H, m), 2.12 ~ 2.48 (8H, m), 4.07 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: 280 (M^+, 19), 251 (15), 235 ($M^+ - EtO$, 27), 234 ($M^+ - EtOH$, 32), 109 (44), 67 (99), 55 (100). *Anal.* Found: C, 72.59; H, 9.94. Calcd. for $C_{17}H_{28}O_3$: C, 72.82; H, 10.06%. Further elution with the same solvent gave ethyl 8-(2-methyl-3-oxo-1-cyclohexenyl)octanoate (0.62 g), 2,4-DNP mp 99 ~ 100°C, an isomer generating from an alternative mode of aldolization–dehydration of the diketone **6b**. IR ν_{max} cm^{-1}: 1740, 1670, 1630. ^1H NMR δ: 1.12 ~ 1.66 (15H, m), 1.77 (3H, s), 2.07 ~ 2.48 (8H, m), 4.08 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: 280 (M^+, 6), 235 ($M^+ - EtO$, 7), 137 (61), 124 (100).

Ethyl 7-(2-methyl-6-oxocyclohexyl)heptanoate (**8a**). Hydrogenation of **7a** (0.6 g, 2.26 mmol) in absolute ethanol (15 ml) was carried out in the presence of a 5% Rh/C catalyst (0.06 g). The product was purified by column chromatography (SiO_2, 8 g) with a hexane–ether mixed solvent (10 : 1) to give a colorless liquid of **8a** (0.46 g, 74%) in a mixture of *trans*/*cis* (75/25) isomers. GLC (carrier gas, N_2, 40 ml/min): *trans* isomer-t_R = 40.5 min, *cis* isomer-t_R = 46.8 min. IR ν_{max} cm^{-1}: 1730, 1705. ^1H NMR δ: 0.81 (*cis*) and 1.03 (*trans*) (3H, both d, J = 7.0 and 5.0 Hz, $CHC\underline{H}_3$), 1.10 ~ 1.83 (18H, m), 2.15 ~ 2.50 (5H, m), 4.09 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: *trans* isomer-268 (M^+, 1), 223 ($M^+ - EtO$, 3), 112 (57), 97 (100), *cis* isomer-268 (M^+, 1), 223 ($M^+ - EtO$, 3), 112 (64), 97 (100).

Ethyl 7-(2-ethyl-6-oxocyclohexyl)heptanoate (**8b**). As described above, **7b** (0.082 g, 0.29 mmol) was hydroge-

nated in the presence of a 5% Rh/C catalyst (0.008 g). Column chromatography (SiO_2, 15 g) with hexane–benzene–ethyl acetate (10 : 1 : 1) of the product gave a pale yellow liquid (0.05 g, 60%) of **8b** as a mixture of *trans*/*cis* (70/30) isomers. GLC (carrier gas, N_2, 40 ml/min): *trans* isomer-t_R = 52.3 min, *cis* isomer-t_R = 58.5 min. IR ν_{max} cm^{-1}: 1730, 1710. ^1H NMR δ: 0.80 ~ 1.85 (23H, m), 2.05 ~ 2.50 (5H, m), 4.07 (2H, q, J = 7.0 Hz). GC-MS *m*/*z*: *trans* isomer-282 (M^+, 1), 253 (1), 237 ($M^+ - EtO$, 5), 126 (29), 97 (100), *cis* isomer-282 (M^+, 1), 253 (1), 237 ($M^+ - EtO$, 5), 126 (31), 97 (100).

Isomerization of hydrogenation products. Isomerizations were carried out according to the method described previously.[9] The product was purified by column chromatography with a hexane–ether mixed solvent (5 : 1). The *trans*/*cis* ratios of the products were determined on the basis of GLC analyses.

Acknowledgments. This work was supported by the Agricultural Chemical Research Foundation. We wish to thank Dr. Mitsuru Nakayama and Dr. Yasuto Uchio, Department of Chemistry, Hiroshima University, for their measurement of the ^{13}C NMR spectra.

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