60.00; H, 5.71. Found: C, 60.06; H, 5.81.

The mother liquor from isomer **6a** was evaporated, and the residue was purified by preparative TLC (ether/petroleum ether, 1:1). Isomer **6b** was obtained as an oil (30 mg, 10.7%); IR (film) 1740, 1720, 1690; NMR ($CDCl_3$) δ 3.25 (s, 3 H), 3.28 (s, 3 H), 3.76 (s, 3 H), 3.50–3.90 (m, 2 H), 4.15 (s, 1 H), 5.97 (s, 2 H), 6.63 (s, 2 H); MS, *m/e* 280 (M^+). (b) To a stirred solution of DMBU (342 mg, 3 mmol) and 2-carbomethoxy-1,4-hydroquinone (168 mg, 1 mmol) in benzene (10 mL) was added at once silver(I) oxide (694 mg, 3 mmol). The suspension was stirred overnight, diluted with ether, and filtered. The filtrate was evaporated, and the residue was purified by preparative TLC (ether/petroleum ether, 1:1). From the lower band isomer **6b** (50 mg, 18%) was obtained. From the upper zone a mixture of isomer **6a** and 1-carbomethoxy-10-methoxy-2,5-dioxobicyclo[4.4.0]deca-3,6,8-triene was obtained. The triene was purified by column chromatography on alumina and eluted with ether/petroleum ether (1:4). The yellow plates (50 mg, 20%), from ether–*n*-hexane, had the following: mp 100–101 °C; IR (KBr) 1740, 1680, 1665 cm^{-1}; NMR ($CDCl_3$) δ 3.38 (s, 3 H), 3.63 (s, 3 H), 4.75 (d, 1 H, J = 5 Hz), 6.17–6.76 (m, 2 H), 6,83–7.31 (m, 3 H); MS, *m/e* 248 (M^+). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 5.71. Found: C, 62.79; H, 5.08.

1,4-Diacetoxy-1,4-dimethoxy-2-butene. In attempting to carry out a cycloaddition between DMBU and 3,6-pyridazinedione, we obtained 1,4-oxidation of DMBU. DMBU (1.14 g, 10 mmol) and maleic hydrazide (1.12 g, 10 mmol) in acetonitrile (40 mL) were stirred at ca. 25 °C. Lead tetraacetate (4.43 g) was gradually (20 min) added and the solution was stirred for 2 h. The suspension was filtered and the filtrate was evaporated in vacuo. The residue was distilled to give an oil (1.18 g, 51%): bp 106 °C (0.8 mm); IR (film) 1735, 1225 cm^{-1}; NMR ($CDCl_3$) δ 2.13 (s, 6 H), 3.46 (s, 6 H), 5.90 (s, 2 H), 6.08 (s, 2 H); MS, *m/e* no parent 232, 189 $(M - 43)^+$, 173 $(M - 59)^+$, 142 $(M - 90)^+$. Anal. Calcd for $C_{10}H_{16}O_6$: C, 51.72; H, 6.89. Found: C, 52.01; H, 6.82.

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Registry No. **2a**, 762-42-5; **2b**, 623-47-2; **3a**, 83650-24-2; **4a**, 65489-47-6; **4b**, 32136-52-0; **4c**, 14963-97-4; **5a**, 83650-25-3; **5b**, 83650-26-4; **5c**, 83650-27-5; **5d**, 1159-86-0; **6**, 83650-28-6; **7**, 83650-29-7; (*Z,Z*)-DMBU, 83650-30-0; (*E,Z*)-DMBU, 83650-31-1; (*E,E*)-DMBU, 74503-35-8; 1,4-dihydroxy-2-butyne, 110-65-6; 1,4-dimethoxy-2-butyne, 16356-02-8; *m*-methoxybenzoic acid, 586-38-9; 1-methoxynaphthalene, 2216-69-5; anthranilic acid, 118-92-3; tetracyanoethylene, 670-54-2; fumaronitrile, 764-42-1; maleic anhydride, 108-31-6; *trans*-1,4-diphenyl-2-butene-1,4-dione, 959-28-4; 1,2-dicarboethoxy-3,6-dimethoxy-1,2,3,6-tetrahydropyridazine, 83650-32-2; diethyl azodicarboxylate, 1972-28-7; methyljuglone, 4923-61-9; benzoquinone, 106-51-4; anthraquinone, 84-65-1; 1,4-naphthoquinone, 130-15-4; 2-methylhydroquinone, 95-71-6; 2-methyl-5,8-dimethoxy-5,8-dihydro-1,4-naphthoquinone, 83650-33-3; 2-methyl-1,4-benzoquinone, 553-97-9; 2-methyl-1,4-naphthoquinone, 58-27-5; 2-methyl-8-methoxynaphthoquinone, 22273-29-6; 2-carbomethoxyhydroquinone, 2150-46-1; 1,4-diacetoxy-1,4-dimethoxy-2-butene, 83650-34-4; 1,2,3,6-tetrahydro-3,6-pyridazine, 123-33-1.

α-Keto Dianion Precursors via Conjugate Additions to Cyclic α-Bromo Enones

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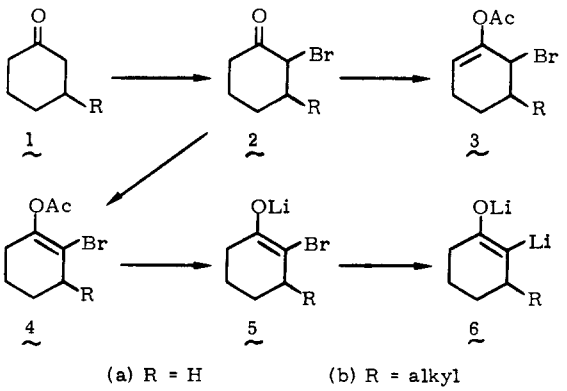
Successful conjugate additions to 2-bromocyclohexenone and 2-bromocyclopentenone have been achieved with a variety of lithium homocuprates, mixed cyanocuprates, and lithium tri-*sec*-butylborohydride as well. In all cases the resulting α-bromo enolate anions could be trapped on oxygen with acetic anhydride; 3-substituted 2-bromo enol acetates were thus obtained regiospecifically and in good yields (Table II, 65–95%). Attempts to extend this methodology to several acyclic bromo enones were largely unsuccessful, as was an attempt to utilize one of the cuprate-derived bromo enolate anions (**12**) directly for formation of an α-keto dianion (**13**). As expected, the α-keto dianion could be prepared in this system by using the corresponding bromo enol acetate (**14** → **13**). α-Bromo enones for all these studies were readily prepared by bromination/dehydrobromination of the corresponding enones in a one-pot procedure and in yields of 71–88% (Table I).

We have previously described[2] the preparation of α-keto dianions (e.g., **6a**, Scheme I) from the corresponding α-bromo enolate anions (**5a**) via metal halogen exchange using *tert*-butyllithium. For bromo ketones lacking enolizable hydrogens at the α′ position, bromo enolates are readily prepared by enolization using lithium hexamethyldisilazide.[2,3] For bromo ketones such as **2a**, however, enolization under these conditions occurs not only toward the bromine but also away, affording a mixture of enol acetates **4a** and **3a**, respectively, on quenching with acetic anhydride. The desired isomer for dianion preparation (**4a**) can be separated and obtained pure in 62% yield even in large-scale runs. While this is acceptable for cheap starting bromides such as **2a**, undesired formation

Scheme I



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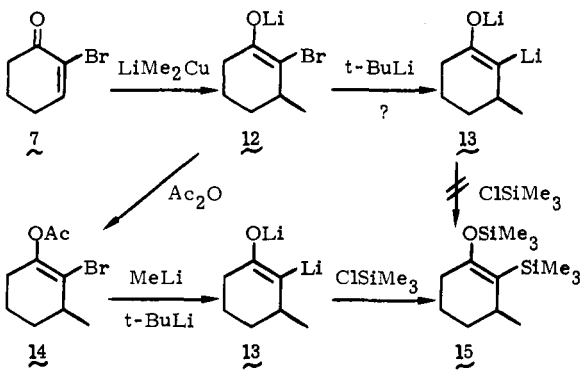
(2) Kowalski, C. J.; O'Dowd, M. L; Burke, M. C.; Fields, K. W. *J. Am. Chem. Soc.* **1980**, *102*, 5411.

(3) Kowalski, C.; Creary, X.; Rollin, A. J.; Burke, M. C. *J. Org. Chem.* **1978**, *43*, 2601.

0022-3263/82/1947-5088$01.25/0

Scheme II

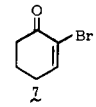
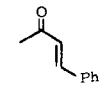
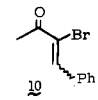
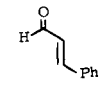


of the allylic isomer (e.g., **3a** in 21% yield) would be unacceptable for more costly starting materials. In addition, the problem of producing even slightly more substituted dianions such as **6b** (R = alkyl) becomes considerably more difficult via this approach. Apart from the problem of controlling the regiochemistry of enolization (i.e., **2b** → **3b** or **4b**), the additional question of how to control efficiently the regiochemistry of ketone bromination (i.e., **1b** → **2b**) must be answered for these systems. It is plain that for more highly substituted ketones, the bromination/enolization approach to α-keto dianions (**1** → **2** → **4** → **6**) has severe limitations.

As an alternative to the above methodology, specifically for preparing β-substituted dianions such as **6b**, the reaction of organocuprates with α-bromo-α,β-unsaturated ketones was examined as a route to bromo enolates (e.g., **7** → **12**, Scheme II). A variety of bromo enones such as **7** are easily prepared from the corresponding unsaturated ketones by using a variation of an earlier method.[4] Thus, treatment of a methylene chloride solution of cyclohexenone with 1.05 equiv of bromine at 0 °C, followed by addition of triethylamine and warming to room temperature, affords bromo enone **7** in a yield of 71% after recrystallization. Similarly, cyclopentenone affords chromatographed bromo enone **8** in 88% yield. Mesityl oxide, 4-phenylbuten-2-one, and cinnamaldehyde are also converted to the corresponding bromo enones in yields of 72%, 88%, and 79%, respectively (Table I). β-Substituted cyclic enones (e.g., cholest-4-en-3-one or 3-butylcyclohexenone) do not react well under these conditions, aforded mixtures of various bromination products. Except for these latter cases, however, the position of bromination in such enones is determined regiospecifically by the original olefin regiochemistry, and the bromo enone products are easily prepared.

Successful additions of organocuprates to α-bromo enones are not common in the literature. While cuprates add well to many chloro enones,[5] a number of unsuccessful additions to bromo enones have been reported.[6] Generally, these have involved β,β-disubstituted enones. At least one successful addition of lithium dimethylcuprate to a bromo enone had been reported at the outset of our work, that without any special comment by Kametani in his hibaol synthesis.[7] The generality of such additions was unclear, however, especially in view of the known substitution reaction of bromo enolates themselves with organocuprates.[8] Still, efforts were undertaken to utilize the addition of cuprates to afford bromo enolate anions (e.g., **7** → **12**, Scheme II), with the hope of direct conversion of these to α-keto dianions (**12** → **13**).

Table I. Preparation of Bromo Enones

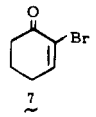
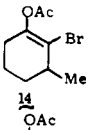
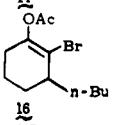
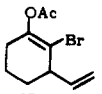
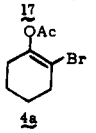
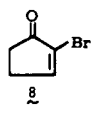
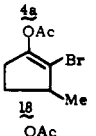
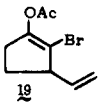
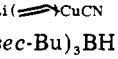
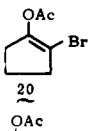
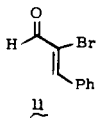
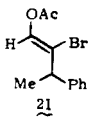
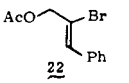
enone	bromo enone	yield, %
	 **7**	71
	 **8**	88
	 **9**	72
	 **10**	88
	 **11**	79

Addition of lithium dimethylcuprate to bromocyclohexenone (**7**) proceeded quite well, as evidenced by formation of enol acetate **14** in 87% yield upon acetic anhydride quenching. Comparable results were obtained by using either 1 or 10 equiv of the cuprate reagent, suggesting that the reaction of bromo enolate with dimethyl cuprate[8] was not a problem here. If the intermediate bromo enolate was treated directly with *tert*-butyllithium, a reaction ensued which consumed the bromo enolate. Formation of dianion **13** was uncertain, for on quenching with chlorotrimethylsilane the reaction afforded none of the bis(trimethylsilyl) enol ether **15**. The major component in the crude product mixture appeared to be the simple monosilyl enol ether, which one would obtain if dianion **13** were protonated once (on carbon) prior to silylation. Under the conditions of the reaction, such a simple protonation mechanism is unlikely, and almost certainly a more complex process involving copper ions was occurring. A copper-free reaction mixture was obtained by simply regenerating the bromo enolate from enol acetate **14** with methyllithium,[2] metal halogen exchange and disilylation to afford **15** then proceeded smoothyl in 71% yield, indicating normal formation of dianion **13**.

Since dianion formation directly from the cuprate-derived enolate failed, it was decided to pursue instead the preparation of other bromo enol acetates via conjugate additions. Bromo enol acetates formed the basis for one of our original procedures for preparing α-keto dianions,[2] and they provide the cleanest and most convenient entry into this species. It was unclear, however, whether the cuprate addition procedure would have any generality for preparing these acetates. Although enolates obtained from lithium–dimethylcopper addition to simple enones undergo O-acetylation,[9] enolates derived from other cuprates often produce substantial amounts of C-acylation.[10] The results of our study, shown in Table II, indicate that the bromine substituent directs the acetylation to provide reaction only

(4) Dunn, G. L.; DiPasquo, V. J.; Hoover, J. R. E. *J. Org. Chem.* **1968**, *33*, 1459.
(5) Chuit, C.; Sauvêtre, R.; Masure, D.; Normant, J. F. *Tetrahedron* **1979**, *35*, 2645 and ref 6 within.
(6) See notes 2–5 in ref 5 above.
(7) Kametani, T.; Suzuki, K.; Nemoto, H.; Fukumoto, K. *J. Org. Chem.* **1979**, *44*, 1036.
(8) Dubois, J-E.; Lion, C. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 217.
(9) House, H. O.; Wilkins, J. M. *J. Org. Chem.* **1976**, *41*, 4031.
(10) Tanaka, T.; Kurozumi, S.; Toru, T.; Kobayashi, M.; Miura, S.; Ishimoto, S. *Tetrahedron* **1977**, *33*, 1105.

Table II. Conjugate Addition Products

starting matl	reagent[a]	product	yield, %
 7	$LiMe_2Cu$	 14	87
	Li-*n*-Bu_2Cu	 16	92
	Li-*n*-BuCuCN	16	95
		17	89
	Li(*sec*-Bu)$_3$BH	 18	95
 8	$LiMe_2Cu$	 18	73
		 19	65
		19	79
	Li(*sec*-Bu)$_3$BH	 20	83
 11	$LiMe_2Cu$	 21	39[b]
	Li(*sec*-Bu)$_3$BH	 22	91

[a] Followed by acetic anhydride quench. [b] Single isomer of undetermined stereochemistry.

on oxygen,[11] regardless of the organocuprate employed. High yields of the bromo enol acetates are obtained, regiochemically pure in every case, with none of the isomeric products common to the direct enolization route.

In two instances, both homocuprates and mixed cyanocuprates[12] were employed. The latter reagents gave better yields and greater economy of reagents. To effect conjugate addition of "hydride", we employed the Ganem procedure[13] using lithium tri-*sec*-butylborohydride. Again it was found that the intermediate bromo enolates could be cleanly trapped by using acetic anhydride, leading to unsubstituted bromo enol acetates in both the six- and five-membered-ring cases (**4a** and **20**).

Attempts to extend these procedures to several acyclic compounds were not very successful. Both 3-bromomesityl oxide (**9**) and (*Z*)-3-bromo-4-phenylbutenone (**10**) afforded little, if any, of the desired bromo enol acetates; the resulting complex product mixtures were not characterized. On reaction with lithium dimethylcuprate, 2-bromocinnamaldehyde (**11**) produced after quenching only a meager 39% yield of the enol acetate **21**. Reaction of this same bromo aldehyde with lithium tri-*sec*-butylborohydride resulted in 1,2- rather than 1,4-addition, as might be expected for an unsaturated aldehyde.[13] While the acyclic examples above do not work well in these additions, the high yields of bromo enol acetates produced in the important five- and six-membered-ring cases make this an excellent route for regiospecific production of α-keto dianion precursors in such systems.

Experimental Section

NMR spectra were recorded on a Varian A-60 A or EM-390 spectrometer and are reported in δ values (parts per million) relative to tetramethysilane. Infrared spectra were recorded on a Perkin-Elmer 727B spectrophotometer as neat films for liquids or as ~10% solutions in chloroform for solids. Exact mass determinations were made on an AEI Scientific Apparatus MS 902 spectrometer. Dry ether was distilled from lithium aluminum hydride just before use, dry tetrahydrofuran (THF) from potassium–benzophenone ketyl under N_2, and chlorotrimethylsilane from calcium hydride. Methyl-, *n*-butyl-, and *tert*-butyllithium were obtained from Aldrich Chemicals as ether, hexane, or pentane solutions, respectively, and were periodically titrated to establish concentration. Lithium tri-*sec*-butylborohydride was also obtained from Aldrich as a 1 M solution in tetrahydrofuran. Cuprous iodide was obtained from Fisher Scientific Co. and cuprous cyanide from Mallinckrodt. Acetic anhydride was doubly fractionally distilled.

2-Bromocyclohex-1-enyl Acetate (4a) and 6-Bromocyclohex-1-enyl Acetate (3a) from 2-Bromocyclohexanone (2a). To a stirred, −78 °C solution of 22.7 mL (107.6 mmol) of hexamethyldisilazane in 250 mL of dry THF under an argon atmosphere was added 66.7 mL (101.4 mmol) of 1.52 M *n*-butyllithium in hexane. After 15 min, 17.1 g (96.6 mmol) of 2-bromocyclohexanone in 75 mL of dry THF was added over 1 h. The solution was stirred for 20 min, and then 22.8 mL (241.7 mmol) of Ac_2O was added. The mixture was stirred at room temperature for 1 h. It was diluted in 1.4 L of ether and washed with two 250-mL portions of 10% HCl, 300 mL of 2 M NaOH, and 200 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 25 g of a dark purple oil. Chromatography on silica gel with 2% EtOAc in hexanes afforded 13.2 g (62%) of bromo enol acetate **4a** as a pale yellow oil and 4.4 g (21%) of the isomeric compound **3a** as a pale yellow oil. Both of these compounds were spectrally identical with previously prepared samples.[3]

2-Bromocyclohex-2-en-1-one (7). To a stirred, 0 °C solution of 10 mL (98.7 mmol) of 2-cyclohexenone in 250 mL of CH_2Cl_2 was added dropwise 5.29 mL (103.2 mmol) of bromine in 100 mL of CH_2Cl_2 over 30 min. The solution was stirred at 0 °C for 1.5 h, and then 23 mL (165 mmol) of Et_3N was added dropwise. The solution was stirred at room temperature for 1.5 h. It was washed with two 50-mL portions of 3% HCl and 50 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained a crude solid. This was redissolved in CH_2Cl_2, treated with activated charcoal, and filtered, and the solvent was removed. Recrystallization from EtOAc and hexanes afforded 12.2 g (71%) of the previously reported[14] bromo enone **7** as white crystals: mp 75–76 °C; IR ($CHCl_3$) 1690 (C=O), 1600 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.50 (t, 1 H, J = 4 Hz, vinyl), 2.85–1.77 (m, 6 H, cyclohexyl).

2-Bromocyclopent-2-en-1-one (8). To a stirred, 0 °C solution of 1.5 mL (17.89 mmol) of 2-cyclopentenone in 40 mL of CH_2Cl_2 was added dropwise 0.92 mL (17.9 mmol) of bromine in 30 mL of CH_2Cl_2 over 10 min. The solution was stirred at 0 °C for 1 h, and then 3.75 mL (26.9 mmol) of Et_3N was added dropwise. The solution was stirred at room temperature for 1.5 h. It was diluted with 50 mL of CH_2Cl_2 was washed with 10% HCl. The aqueous layer was washed once with 30 mL of CH_2Cl_2. The organic layers were combined and washed with 50 mL of 0.1 M $NaHSO_3$ and 50 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 3.38 g of a pale yellow oil. Chromatography on silica gel with 10%

(11) For an instance in which an α-chloro enolate undergoes unexpected reaction at oxygen see: Kuwajima, I.; Nakamura, E. *J. Org. Chem.* **1977**, *42*, 346.

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ethyl acetate in hexanes afforded 2.53 g (88%) of the previously reported[4,14] bromo enone **8** which solidified on standing: IR (film) 1730 (C=O), 1590 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 7.87 (t, 1 H, J = 2 Hz, vinyl), 2.4–2.9 (m, 4 H, cyclopentyl).

3-Bromo-4-methyl-3-penten-2-one (9). To a stirred, 0 °C solution of 10 mL (88.0 mmol) of mesityl oxide in 125 mL of CH_2Cl_2 was added dropwise 4.5 mL (87.8 mmol) of bromide in 15 mL of CH_2Cl_2 over 15 min. To this solution was added 18.39 mL (132 mmol) of Et_3N. After being stirred for 2 h, the mixture was washed with 50 mL of 10% HCl and 50 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained a crude oil. Short-path distillation at 67–70 °C (17 mmHg) afforded 11.2 g (72%) of the previously reported[15] bromo enone **9** as a pale yellow oil: IR (film) 1685 (C=O), 1595 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.47 (s, 3 H, $COCH_3$), 2.07 (s, 3 H, CH_3), 2.03 (s, 3 H, CH_3).

(*E*)-3-Bromo-4-phenyl-3-buten-2-one [(*E*)-10)] and (*Z*)-3-Bromo-4-phenyl-3-buten-2-one [(*Z*)-10)]. To a stirred, 0 °C solution of 2.0 g (13.7 mmol) of *trans*-4-phenyl-3-buten-2-one in 100 mL of CH_2Cl_2 was added dropwise 0.70 mL (13.7 mmol) of bromine in 10 mL of CH_2Cl_2. The solution was stirred for 5 min, and then 2.86 mL (20.5 mmol) of Et_3N was added. The solution was stirred at room temperature for 1.5 h. It was washed with 50 mL of 10% HCl and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 3 g of an oil. Chromatography on silica gel with ether in hexanes afforded 550 mg (18%) of the previously reported[16] bromo enone (*E*)-**10** as an oil and 2.14 g (70%) of the *Z* isomer[16] (*Z*)-**10** as an oil. (*E*)-**10**: NMR ($CDCl_3$) δ 7.37 (br s, 6 H, aromatic and vinyl), 2.27 (s, 3 H, $COCH_3$). (*Z*)-**10**: IR (film) 1685 (C=O), 1610 (C=C), 1537 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 8.02 (s, 1 H, BRC=CH), 8.0–7.63 (m, 2 H, aromatic), 7.57–7.23 (m, 3 H, aromatic), 2.5 (s, 3 H, $COCH_3$).

(*Z*)-2-Bromo-3-phenylpropenal [(*Z*)-11]. To a stirred, 0 °C solution of 2.0 mL (15.88 mmol) of *trans*-cinnamaldehyde in 6 mL of CH_2Cl_2 was added dropwise 0.81 mL (15.8 mmol) of bromine in 10 mL of CH_2Cl_2 over 10 min. The solution was stirred at 0 °C for 5 min, and then 4.42 mL (31.7 mmol) of Et_3N was added. The solution was stirred at room temperature for 1 h. It was diluted in 100 mL of CH_2Cl_2 and washed with 40 mL of 10% HCl and 40 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 3 g of a yellow oil. Chromatography on 210 g of silica gel with 2.5% ether in hexanes afforded 2.65 g (79%) of the bromo enal (*Z*)-**11**[17] as yellow crystals: mp 70–71 °C; IR ($CHCl_3$) 1690 (C=O), 1600 (C=C), 1570 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 9.4 (s, 1 H, CHO), 8.3–7.8 (m, 3 H, olefinic and aromatic), 7.8–7.3 (m, 3 H, aromatic).

2-Bromo-3-methylcyclohex-1-enyl Acetate (14). (A) Using 1 Equiv of Lithium Dimethylcuprate. The dimethyl cuprate was prepared by using a modification of the procedure of House.[18] To a stirred room-temperature suspension of 284 mg (1.38 mmol) of CuBr·Me_2S in 15 mL of dry ether under an argon atmosphere was added 1.27 mL (17.3 mmol) of Me_2S. The solution was cooled to −78 °C, and 2.11 mL (2.5 mmol) of 1.2 M methyllithium in ether was added. This solution was stirred at −30 °C for 30 min and then cooled to −78 °C; 201 mg (1.15 mmol) of bromo enone **7** in 8 mL of dry ether was then added over 2 min. After being stirred at −40 °C for 20 min, the solution was cooled to −78 °C, and 0.33 mL (3.5 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature over 40 min. It was diluted with 85 mL of ether and washed with two 35-mL portions of 10% HCl, 35 mL of 0.2 N NaOH, and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 281 mg of a dark yellow oil. Chromatography on 20 g of silica gel with 1.5% ether in hexanes afforded 232 mg (87%) of bromo enol acetate **14** as a clear oil: IR (film) 1770 (C=O), 1670 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.80–2.00 (m, ~3H, allylic), 2.2 (s, ~3H, $COCH_3$), 2.00–1.3 (m, ~4H, cyclohexyl), 1.17 (d, 3 H, J = 6 Hz, CH_3); mass spectrum, m/e 232.003 (M^+; calcd for $C_9H_{13}BrO_2$, m/e 232.009).

(B) Using 10 Equiv of Lithium Dimethylcuprate. The cuprate addition was performed by following the procedure of Kametani.[7] To a stirred 0 °C suspension of 1.8 g (9.45 mmol) of CuI in 40 mL of dry ether under an argon atmosphere was added 15.5 mL (20.0 mmol) of 1.21 M methyllithium in ether. After 5 min, 164 mg (0.94 mmol) of bromo enone **7** in 5 mL of dry ether was added over 2 min. After being stirred for 1 h at 0 °C, the solution was cooled to −78 °C, and 2.22 mL (23.5 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature. It was diluted with 125 mL of ether and washed with two 40-mL portions of 3% NH_4OH and 40 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 240 mg of a yellow oil. Chromatography on 24 g of silica gel with 1.5% ether in hexanes afforded 188 mg (86%) of bromo enol acetate **14**.

Attempted Preparation and Silylation of Dianion 13 Directly from the Cuprate-Derived Enolate 12. To a stirred room-temperature suspension of 311 mg (1.5 mmol) of CuBr·Me_2S in 15 mL of dry ether under an argon atmosphere was added 1.39 mL (18.9 mmol) of Me_2S. The solution was cooled to −78 °C, and 2.31 mL (2.77 mmol) of 1.2 M methyllithium in ether was added. This solution was stirred at −30 °C for 30 min and then cooled to −78 °C; 220 mg (1.26 mmol) of bromo enone **7** in 8 mL of dry ether was then added over 2 min. After being stirred at −40 °C for 20 min, the solution was cooled to −78 °C, and 2.04 mL (4.28 mmol) of 2.1 M *tert*-butyllithium in pentane was added rapidly. The solution was allowed to warm to room temperature over 20 min. This solution was cooled to −78 °C and 1.20 mL (9.46 mmol) of chlorotrimethylsilane was added. The solution was allowed to warm to room temperature over 1 h, and 1.32 mL (9.48 mmol) of Et_3N was added. It was diluted with 85 mL of hexanes and washed *rapidly* with two 35-mL portions of saturated $NaHCO_3$ in brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained a green oil. NMR analysis of the crude product showed the complete absence of a signal at 0.07 ppm corresponding to the trimethylsilyl group attached to the olefinic carbon of disilylated material **15**. The major product appeared to be 3-methyl-1-(trimethylsiloxy)-1-cyclohexene, both from the NMR spectrum (δ 4.78, olefinic H) and from GC/MS (principal GC peak with m/e 184).

3-Methyl-2-(trimethylsilyl)-1-(trimethylsiloxy)-1-cyclohexene (15). To a stirred 0 °C solution of 371 mg (1.59 mmol) of bromo enol acetate **14** in 4 mL of dry ether under an argon atmosphere was added 2.92 mL (3.5 mmol) of 1.2 M methyllithium in ether. The solution was stirred for 10 min at 0 °C and then cooled to −78 °C; 1.67 mL (3.51 mmol) of 2.1 M *tert*-butyllithium in pentane was added rapidly. This solution was allowed to warm to room temperature over 20 min and then cooled to −78 °C, and 0.99 mL (7.8 mmol) of chlorotrimethylsilane was added. The solution was allowed to warm to room temperature over 1 h, and 1.11 mL (7.97 mmol) of Et_3N was added. It was diluted with 85 mL of hexanes and washed *rapidly* with two 35-mL portions of saturated $NaHCO_3$ in brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 395 mg of a yellow oil. Kuhgelrohr distillation at 85 °C (0.5 mm) afforded 290 mg (71%) of disilylated material **15** as a clear oil: IR (film) 1620 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.60–1.10 (m, 7 H, cyclohexyl), 0.95 (d, 3 H, J = 7 Hz, CH_3), 0.19 (s, 9 H, $OSi(CH_3)_3$), 0.07 (s, 9 H, $CSi(CH_3)_3$); mass spectrum, m/e 256.169 (M^+; calcd for $C_{13}H_{28}OSi_2$, m/e 256.168).

2-Bromo-3-butylcyclohex-1-enyl Acetate (16). (A) Using Lithium Di-*n*-butylcuprate. To a stirred −25 °C suspension of 598 mg (3.15 mmol) of CuI in 18 mL of dry ether under an argon atmosphere was added 3.90 mL (6.24 mmol) of 1.6 M *n*-butyllithium in hexane. The solution was stirred for 5 min, and 136 mg (0.78 mmol) of bromo enone **7** in 5 mL of dry ether was added over 2 min. This solution was stirred at −25 °C for 1 h and then cooled to −78 °C; 0.69 mL (7.31 mmol) of Ac_2O was added, and the mixture was allowed to warm to room temperature. It was diluted with 85 mL of ether and washed with two 35-mL portions

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of 3% NH_4OH and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 400 mg of a yellow oil. Chromatography on 24 g of silica gel with 1.75% ether in hexanes afforded 197 mg (92%) of bromo enol acetate **16**: IR (film) 1770 (C=O), 1675 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.77–2.17 (m, ~3 H, allylic), 2.17 (s, ~3 H, $COCH_3$), 2.13–1.60 (m, ~4 H, cyclohexyl), 1.60–1.13 (m, 6 H, CH_2), 1.13–0.67 (m, 3 H, CH_3); mass spectrum, *m/e* 274.054 (M^+; calcd for $C_{12}H_{19}BrO_2$, *m/e* 274.057).

(B) Using Lithium *n*-Butylcyanocuprate. The cyanocuprate was prepared by using a modification of the procedure of Marino.[12b] To a stirred −78 °C solution of 320 mg (3.54 mmol) of CuCN in 15 mL of dry ether under an argon atmosphere was added 2.48 mL (3.50 mmol) of 1.41 M *n*-butyllithium in hexane. This solution was stirred at −78 °C for 15 min, and 153 mg (0.87 mmol) of bromo enone **7** in 5 mL of dry ether was added over 2 min. The solution was stirred at −78 °C for 1 h, and 0.45 mL (4.7 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature. It was diluted with 85 mL of ether and washed with two 35-mL portions of 3% NH_4OH and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 320 mg of a yellow oil. Chromatography on 28 g of silica gel with 1.25% ether in hexanes afforded 227 mg (95%) of the bromo enol acetate **16**.

2-Bromo-3-ethenylcyclohex-1-enyl Acetate (17). To a stirred −78 °C solution of 0.74 mL (10.5 mmol) of vinyl bromide in 10 mL of dry ether under an argon atmosphere was added 10.79 mL (21 mmol) of 1.95 M *tert*-butyllithium in pentane.[19] This solution was stirred for 20 min at −78 °C and then 30 min at 0 °C. The 0 °C solution was added to a −78 °C solution of 1 g (5.26 mmol) of CuI and 5.77 mL (78.5 mmol) of Me_2S in 25 mL of dry ether. The solution was stirred at −23 °C for 20 min; 229 mg (1.31 mmol) of bromo enone **7** in 5 mL of dry ether was added over 2 min. This solution was stirred at −23 °C for 1 h and then cooled to −78 °C; 1.17 mL (12.5 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature. It was diluted with 125 mL of ether and washed with two 50-mL portions of 3% NH_4OH and 50 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 460 mg of a yellow oil. Chromatography on 40 g of silica gel with 1.5% ether in hexanes afforded 286 mg (89%) of the bromo enol acetate **17**: IR (film) 1765 (C=O), 1680 (C=CBr), 1640 ($C=CH_2$) cm^{-1}; NMR ($CDCl_3$) δ 6.20–5.53 (m, ~1 H, vinyl), 5.47–5.00 (m, ~2 H, vinyl), 3.40–3.00 (m, 1 H, doubly allylic), 2.57–1.40 (m, ~6 H, cyclohexyl), 2.52 (s, ~3 H, $COCH_3$); mass spectrum, *m/e* 244.006 (M^+; calcd for $C_{10}H_{13}BrO_2$; *m/e* 244.009).

2-Bromo-3-methylcyclopent-1-enyl Acetate (18). To a stirred −32 °C suspension of 309 mg (1.63 mmol) of CuI in 10 mL of dry ether under an argon atmosphere was added 2.52 mL (3.2 mmol) of 1.27 M methyllithium in ether. This solution was stirred for 2 min and then cooled to −78 °C; 150 mg (0.93 mmol) of bromo enone **8** in 5 mL of dry ether was added over 2 min. The solution was stirred at −40 °C for 20 min and then cooled to −78 °C; 0.35 mL (3.7 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature. It was diluted with 85 mL of ether and washed with two 35-mL portions of 3% NH_4OH and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 181 mg of a yellow oil. Chromatography on 20 g of silica gel with 1.5% ether in hexanes afforded 148 mg (73%) of bromo enol acetate **18**: IR (film) 1770 (C=O), 1670 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 3.00–2.20 (m, 3 H, allylic), 2.17 (s, 3 H, $COCH_3$), 1.90–1.33 (m, 2 H, cyclopentyl), 1.10 (d, 3 H, J = 7 Hz, CH_3); mass spectrum, *m/e* 217.994 (M^+; calcd for $C_8H_{11}BrO_2$, *m/e* 217.994).

2-Bromo-3-ethenylcyclopent-1-enyl Acetate (19). (A) Using Lithium Divinylcuprate. To a stirred −78 °C solution of 0.58 mL (8.22 mmol) of vinyl bromide in 10 mL of dry ether under an argon atmosphere was added 8.50 mL (16.6 mmol) of 1.95 M *tert*-butyllithium in pentane. The solution was stirred for 20 min at −78 °C and then 30 min at 0 °C. This 0 °C solution was added to a −78 °C solution of 794 mg (4.18 mmol) of cuprous iodide and 4.54 mL (61.7 mmol) of Me_2S in 20 mL of dry ether. The solution was stirred at −23 °C for 20 min; 166 mg (1.03 mmol) of bromo enone **8** in 5 mL of dry ether was added over 2 min. The solution was stirred at −23 °C for 1 h and cooled to −78 °C; 0.92 mL (9.75 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature over 1 h. It was diluted with 125 mL of ether and washed with two 50-mL portions of 3% NH_4OH and 50 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 395 mg of a yellow oil. Chromatography on 36 g of silica gel with 1.75% ether in hexanes afforded 151 mg (65%) of bromo enol acetate **19**: IR (film) 1770 (C=O), 1675 (C=CBr), 1640 ($C=CH_2$) cm^{-1}; NMR ($CDCl_3$) δ 6.20–5.50 (m, ~1 H, vinyl), 5.43–5.00 (m, ~2 H, vinyl), 3.70–3.00 (m, 1 H, doubly allylic), 2.80–1.70 (m, ~4 H, cyclopentyl), 2.21 (s, ~3 H, $COCH_3$); mass spectrum, *m/e* 229.996 (M^+; calcd for $C_9H_{11}BrO_2$, *m/e* 229.994).

(B) Using Lithium Vinylcyanocuprate. To a stirred −78 °C solution of 0.23 mL (3.26 mmol) of vinyl bromide in 10 mL of dry ether under an argon atmosphere was added 3.55 mL (6.39 mmol) of 1.80 M *tert*-butyllithium in pentane. The solution was stirred for 20 min at −78 °C and then for 30 min at 0 °C. This 0 °C solution was added to a −78 °C solution of 293 mg (3.24 mmol) of CuCN in 15 mL of dry ether. The solution was stirred at −78 °C for 15 min; 129 mg (0.80 mmol) of bromo enone **8** in 5 mL of dry ether was added over 2 min. The solution was stirred at −78 °C for 40 min; 0.41 (4.35 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature. It was diluted with 85 mL of ether and washed with two 35-mL portions of 3% NH_4OH and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 214 mg of a yellow oil. Chromatography on 21 g of silica gel with 1.5% ether in hexanes afforded 146 mg (79%) of bromo enol acetate **19**.

2-Bromo-3-phenylbut-1-enyl Acetate (21). To a stirred, 0 °C suspension of 657 mg (3.56 mmol) of CuI in 18 mL of dry ether under an argon atmosphere was added 5.7 mL (6.9 mmol) of 1.21 M methyllithium in ether. After 5 min, 180 mg (0.85 mmol) of bromo aldehyde **11** in 5 mL of dry ether was added over 2 min. The solution was cooled to −78 °C, and 0.76 mL (8.06 mmol) of Ac_2O was added. The mixture was allowed to warm to room temperature over 1 h. It was diluted with 85 mL of ether and washed with two 35-mL portions of 3% NH_4OH and 35 mL of saturated brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, there remained 178 mg of a yellow oil. Chromatography on 20 g of silica gel with 2% ether in hexanes afforded 90.3 mg (39%) of bromo enol acetate **21** as a pale yellow oil: IR (film) 1760 (C=O), 1665 (C=C), 1600 (aromatic) cm^{-1}; NMR ($CDCl_3$) δ 7.63 (br s, 1 H, C=CH), 7.45–7.00 (m, 5 H, aromatic), 3.8 (q, 1 H, J = 7 Hz, $CHCH_3$), 2.17 (s, 3 H, $COCH_3$), 1.52 (d, 3 H, J = 7 Hz, $CHCH_3$). This compound appeared to be a single isomer (stereochemistry undetermined).

General Procedure for Addition Using Lithium Tri-*sec*-butylborohydride. Compounds **4a**, **20**, and **22** were prepared on a 0.94–1.91-mmol scale by following the conjugate addition procedure of Ganem.[13] To a stirred, −78 °C, 0.2 M solution of the appropriate unsaturated carbonyl compound in dry THF under an argon atmosphere was added 1.1 equiv of 1.0 M lithium tri-*sec*-butylborohydride in THF over 5 min. After 1 h, 5 equiv of Ac_2O was added, and the −78 °C cooling bath was removed. After 1 h, the reaction mixture was diluted with 85 mL of ether. The organic layer was washed with two 35-mL portions of 0.25 N NaOH and 35 mL of saturated brine and dried ($MgSO_4$). Evaporation of solvent afforded crude product.

2-Bromocyclohex-1-enyl Acetate (4a) from Bromocyclohexenone (7). As indicated, 333 mg (1.91 mmol) of bromo enone **7** afforded 790 mg of a crude clear oil. Chromatography on 45 g of silica gel with 5.0% ether in hexanes afforded 396 mg (95%) of the bromo enol acetate **4a** as a clear oil.

2-Bromocyclopent-1-enyl Acetate (20). An indicated, 155 mg (0.96 mmol) of bromo enone **8** afforded 384 mg of a crude yellow oil. Chromatography on 38 g of silica gel with 2% ether in hexanes afforded 163 mg (83%) of the bromo enol acetate **20** as a clear oil: IR (film) 1770 (C=O), 1680 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 2.80–2.33 (m, 4 H, allylic), 2.33–1.83 (m, ~2 H, cyclopentyl), 2.19 (s, ~3 H, $COCH_3$); mass spectrum, *m/e* 203.977 (M^+; calcd for $C_7H_9BrO_2$, *m/e* 203.979).

2-Bromo-3-phenylprop-2-enyl Acetate (22). As indicated, 198 mg (0.94 mmol) of *trans*-3-bromocinnamaldehyde (**11**) af-

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forded 428 mg of a pale yellow oil. Chromatography on 40 g of silica gel with 5% ether in hexanes afforded 218 mg (91%) of the previously reported[20] acetate **22** as a clear oil: IR (film) 1750 (C=O); NMR ($CDCl_3$) δ 7.8–7.55 (m, 2 H, aromatic), 7.55–7.2 (m, 3 H, aromatic), 7.1 (br s, 1 H, vinyl), 4.9 (s, 2 H, CH_2), 2.13 (s, 3 H, $COCH_3$).

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Registry No. **2a**, 822-85-5; **3a**, 23029-03-0; **4a**, 56974-20-0; **7**, 50870-61-6; **8**, 10481-34-2; **9**, 5682-80-4; (*E*)-**10**, 32147-21-0; (*Z*)-**10**, 22965-96-4; (*Z*)-**11**, 33603-90-6; **12**, 83633-76-5; **13**, 83633-77-6; **14**, 83633-78-7; **15**, 83633-79-8; **16**, 83633-80-1; **17**, 83633-81-2; **18**, 83633-82-3; **19**, 83633-83-4; **20**, 83633-84-5; (*Z*)-**21**, 83633-85-6; (*Z*)-**22**, 14310-14-6; 2-cyclohexenone, 930-68-7; 2-cyclopentenone, 930-30-3; mesityl oxide, 141-79-7; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; *trans*-cinnamaldehyde, 14371-10-9; $Lime_2Cu$, 15681-48-8; Li-*n*-Bu_2Cu, 24406-16-4; Li-*n*-BuCuCN, 41742-63-6; Li(CH_2=$CH)_2Cu$, 22903-99-7; Li(*sec*-Bu)$_3$BH, 38721-52-7; Li(CH_2=CH)CuCN, 77043-46-0.

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Improved Preparation of Methyl 3-Oxo-1-cyclohexene-1-carboxylate and Its Use in the Synthesis of Substituted 1,5-Cyclodecadienes

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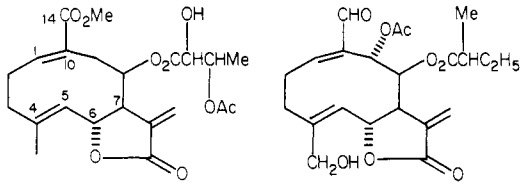
An improved preparation of methyl 3-oxo-1-cyclohexene-1-carboxylate (**6**) is reported in which cyclohexanecarboxylic acid is converted to methyl 1-bromocyclohexanecarboxylate by a variation of the Hell–Volhard–Zelinsky reaction and then the bromo ester is dehydrohalogenated with quinoline and the resultant unsaturated ester is oxidized at an allylic position with chromium trioxide in acetic acid and acetic anhydride to give **6**. The overall conversion proceeds in 49% yield, which is a substantial improvement over previous attempts reported for this sequence. Photoaddition of **6** and cyclobutene-1-carboxylic acid yields adduct **8**, which after esterification and thermolysis gives the 1,5-cyclodecadiene **12**. In addition, reduction of adduct **8** with $NaCNBH_3$ followed by spontaneous lactonization yields **10**, which upon thermolysis gives the lactone diene **11**. This approach should have applications in the synthesis of germacranolides that have an ester or related carbonyl function on C(14).

Numerous germacranolides possess oxygen functionality in the form of an ester (or lactone), an aldehyde, or a primary alcohol at C(14)[1] [e.g., melampolidin (**1**)[2] and acanthospermal B (**2**)[3]]. Many of these compounds exhibit



1 **2**

significant cytotoxic or other biological activity.[1] We wished to develop an approach to the synthesis of related 1,5-cyclodecadienes in which C(14) was present as an ester function. The approach is an extension of our previous work[4,5] employing photoaddition of a substituted cyclobutene and a 2-cyclohexenone followed by thermolysis of the photoadduct or a compound derived from it.

In our initial model studies, the ester **6** was chosen as the cyclohexenone component for the photoaddition. **6** may be prepared from cyclohexanecarboxylic acid (**3**) by bromination/esterification to give **4**[6] followed by dehydrohalogenation with collidine to yield **5**[6] and finally allylic oxidation with CrO_3 in acetic acid and water,[7] but the reported yields in the three steps are not encouraging (43%, 43%,[8] 49%, respectively).[9] We herein report a substantial improvement in the yield for the conversion of **3** to **5** and a modest improvement for the oxidation of **5** to **6**. The procedures are experimentally simple and are suitable for large-scale preparations because of the inexpensive reagents involved.

Conversion of **3** to **4** was effected in 92% yield with use of the Hell–Volhard–Zelinsky reaction followed by esterification of the resultant acid chloride in a procedure similar to that described for the preparation of a bromocyclobutanecarboxylate.[10] Dehydrohalogenation to give **5** was accomplished in 96% yield by warming **4** with 1.6 equiv of quinoline. This base has previously been used for

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(7) W. C. Agosta and W. W. Lowrance, Jr. (*J. Org. Chem.* **1970**, *35*, 3851) employed the ethyl ester.

(8) R. Damico (*J. Org. Chem.* **1968**, *33*, 1550) reported a yield of 57% for the conversion of **3** to **5** following Bailey's procedure.[6]

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