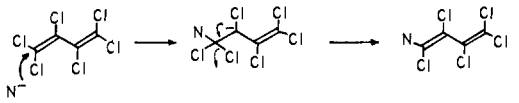
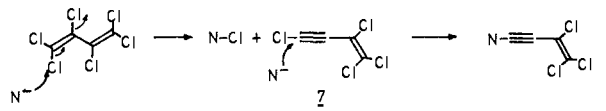
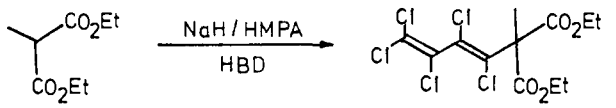
Scheme I



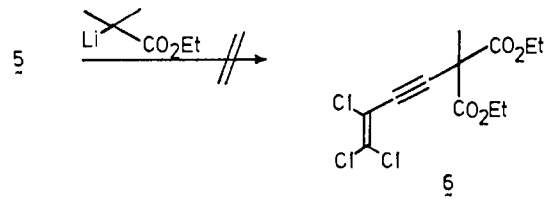
Scheme II



cleanly to yield 61% of a homogenous product having λ_{max} (MeOH) 220 nm (ϵ 12 000) and a molecular formula of $C_{12}H_{13}O_4Cl_5$. The structure of this adduct was shown from spectroscopic data and by catalytic reduction to diethyl methyl-*n*-butylmalonate to be the pentachlorodienylmalonate **5**.[5,6]



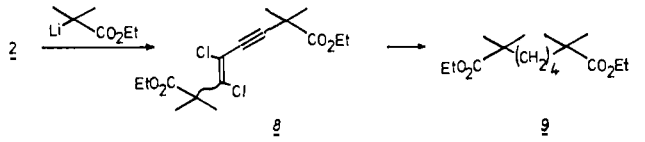
The formation of pentachlorodienylmalonate **5** is readily explained on the basis of an addition–elimination mechanism (Scheme I) whereby the enolate nucleophile (N^-) adds to the HBD acceptor to give an inductively and resonance stabilized perchloroallyl anion, which then ejects halide. The observed formation of the trichloro enyne **2** from ethyl isobutyrate is less straightforward. For example, the primary formation of a pentachlorodienylisobutyrate adduct (cf. **5**) followed by reductive dechlorination of the internal dichloro olefin is formally possible, but such high regioselectivity for the hindered internal dichloro olefin in a secondary reduction step is unreasonable. Indeed, treatment of the pentachlorodienylmalonate **5** with the lithium enolate of ethyl isobutyrate fails to yield any of the internal acetylene **6** corresponding to **2**.



We propose that perchlorobutenyne (**7**) *is an obligatory intermediate in the formation of* **2** (Scheme II). Thus the initial step in the condensation is attack by the isobutyrate enolate (N^-) on chlorine to give ethyl α-chloroisobutyrate and perchlorobutenyne (**7**). Reaction of a second molecule of the enolate at the terminal ethynyl carbon, possibly by addition–elimination, would yield the observed product **2**.

The suggested reductive dechlorination of HBD to form **7** is consistent with the isolation of 62% of ethyl α-chloroisobutyrate during generation of **2**. Subsequent addition–elimination to **7** is analogous to certain reactions of perchlorobutenyne observed by Roedig for nitrogen[7] and sulfur[8] nucleophiles. Indeed, reaction of the lithium enolate of ethyl isobutyrate (1 equiv each of the ester, LDA, and HMPA at −78 °C in THF) with preformed perchlorobutenyne **7** (from −78 °C to room temperature, 6 h) leads to our product 7 in 76% isolated yield.[9]

It is clear from these results that the formation of a new carbon to carbon bond from enolates with HBD can proceed by at least two mechanisms: direct addition–elimination or a secondary condensation with an intermediate 1-chloroalkyne. The latter mechanism may have general synthetic implications for 1-chloroalkynes as enolate acceptors and be involved in some of our previously reported dichlorovinylations.[4] It is clear, however, that the choice between these two mechanisms is delicately balanced! Thus, reaction of our initial product **2** with 1.1 equiv of the lithium enolate of ethyl isobutyrate leads in 64% yield to a new condensation product **8** (mixture of *E*/*Z* stereoisomers). Analytical and



spectroscopic data,[5] along with perhydrogenation to diester **9**, establish the structure of **8** as the dichloroenyne addition–elimination product shown.

We see from this that the addition–elimination pathway of Scheme I is not limited to the softer malonate anion but also depends in a subtle manner on the structure of the halo olefin acceptor. The possiblity of electron transfer from enolate to haloolefin (or haloalkyne) in some of the postulated addition–elimination steps cannot be excluded.[10] Futher studies on this point, the scope of these condensations, and the intricate chemistry of compounds **2**, **3**, and **8** will be described elsewhere.

Acknowledgment. Partial support of this work by Grant CA-18846 awarded by the National Cancer Institute, USPHS, is gratefully acknowledged. P. F. thanks the University of Rochester for a Sherman Clarke Fellowship.

Supplementary Material Available: UV, MS, ^{1}H NMR, and ^{13}C NMR spectra and elemental analyses for compounds **2**–**5** and **8** are available (3 pages). Ordering information is given on any current masthead page.

(6) The stereochemistry of compound **5** is assumed as *E* by analogy with the dichlorovinylation adducts described in ref 4.

(7) Roedig, A.; Faure, M. *Chem. Ber.* **1975**, *109*, 2159.

(8) Roedig, A.; Zaby, G. *Liebigs Ann. Chem.* **1979**, *1979*, 1606, and 1614.

(9) The yield of **2** from HBD drops precipitously when less than 2 equiv of the lithium enolate of ethyl isobutyrate is used. This is in accordance with our mechanism invoking perchlorobutenyne as an intermediate. For the preparation of perchlorobutenyne, see: Jenkins, D. K. *Chem. Ind.* (*London*) **1971**, 254.

(10) A referee's suggestion that perchlorobutenyne reacts with a nucleophile to yield a chlorinated nucleophile and the acetylide, followed by displacment to yield product **7** ("transfer alkylation") appears to be experimentally precluded by our observation that reaction of 1-lithio-1-hexyne with ethyl α-chloroisobutyrate yields no detectable (<10%) ethyl 2,2-dimethyl-3-octynoate.

Selective Functionalization of Doubly Coordinated Flexible Chains

Ronald Breslow,* Raghavan Rajagopalan, and Joshua Schwarz

Department of Chemistry, Columbia University
New York, New York 10027

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The process of remote oxidation has proven to be remarkably selective and useful with such rigid substrates as steroids.[1] Attack by bound benzophenone reagents[2] and template-directed chlorinations[3] give products determined by and predictable from the relative geometries of reagent and substrate segments. By contrast, remote functionalization of flexible substrates has not so far shown chemically useful selectivity. Mixtures are obtained from benzophenone attack or remote halogenations on long-chain alkyl groups[4] and template-directed epoxidations of flexible,[5] but not

(1) For a recent review, see: Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170.

(2) Breslow, R.; Flechtner, T.; Kalicky, P.; Liu, S.; Washburn, W. *J. Am. Chem. Soc.* **1973**, *95*, 3251.

(3) Breslow, R.; Corcoran, R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.

(4) Breslow, R.; Rothbard, J.; Herman, F.; Rodriguez, M. L. *J. Am. Chem. Soc.* **1978**, *100*, 1213. Mixtures are also obtained from the attack of unattached reagents on long-chain esters as in the work of: Eck, C. R.; Hunter, D. J.; Money, T. *J. Chem. Soc., Chem. Commun.* **1974**, 865.

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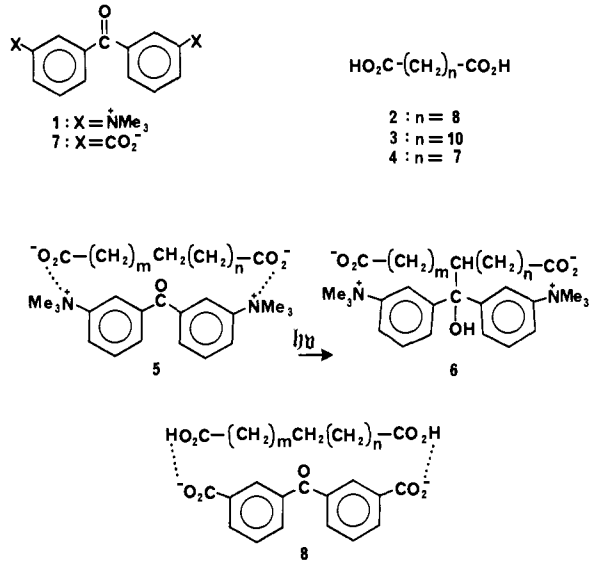
Scheme I



rigid,[6] polyenes. Even attempts to restrict the conformational freedom of flexible alkyl chains by their incorporation into micelles[7] or bilayers[8] did not result in selective attack on particular carbons, although very interesting conformational information was obtained from the distribution of attack sites actually observed. We now wish to report that flexible chains can indeed be selectively functionalized if *two* well-defined coordinations to an appropriate rigid reagent are used to lock in the correct conformation.

Two modes of interaction have been examined so far. In one, 3,3′-carbonylbis(phenyltrimethylammonium) dication (**1**) is allowed to ion pair in water with long-chain dicarboxylate ions derived from diacids **2**, **3**, or **4**, by neutralization of 3,3′-carbonylbis(phenyltrimethylammonium) dihydroxide with the diacids (Scheme I). Photolysis of the complex **5** (2–3 mM) until the benzophenone chromophore disappeared (8 h) produced products **6**. Analysis was by lyophilization, esterification with acetyl chloride and methanol,[9] dehydration to the olefin with $SOCl_2$, and oxidation to the keto diesters derived from **2**, **3**, or **4** with RuO_4. The aliphatic keto diesters were isolated by silica chromatography and converted to the ethylene dithioketals. These were also purified by silica chromatography and analyzed by mass spectroscopy; fragmentation at the thioketal established the ketone distribution pattern. The analytical method was checked with known mixtures of positional isomers, and the sequence is essentially that we have described previously.[4,7,8] It led to the functionalization distributions listed in Table I.

As the table shows, reaction with **2** was highly selective, 93% of the attack occurring on the two central carbons (which are equivalent by symmetry). This is as expected since double ion pairing of **1** with the **2** dianion should fully extend the chain of **2** and bring the benzophenone oxygen in **5** opposite the middle of the chain. By contrast, the dianion of **3** is too long to ion pair with **1** when fully extended. Thus there must be a kink in the chain of **3**, in complex **5**, which leads to a product distribution. Now there is significant attack at C-6, but maximum attack is still at C-5. In **4** there is a unique central carbon C-5, which must compete with both neighboring C-4 carbons. Even so attack at C-5 is reasonably selective, with 74% functionalization compared with 11% at each of the C-4′s.

The degradation scheme used to establish the data in Table I is long, and the overall yield is poor because of losses in the RuO_4 step. For this reason we have checked the principal conclusions by performing ^{13}C NMR spectroscopy[10] directly on the photolysis reaction products (**6**). In the reaction of **1** as the salt with **4** we obtained the photolysis insertion product in 75 ± 5% yield, the remainder being recovered **4**. The product showed two new methine carbons (doublets on off-resonance decoupling) at 46.5 and 49.3 ppm along with the expected signals for methylenes and aromatic carbons in **6**. Integration (gated decoupling) showed the expected total intensities for CH and CH_2 signals in the **6** positional mixture and that the mixture contained 74 ± 4% of the isomer with a signal at 46.5 ppm and 26 ± 4% of the isomer with a signal at 49.3 ppm. If these correspond[11] to the insertion products at C-5 and C-4, respectively, this is in perfect agreement with the data of Table I.

Table I. Percent Functionalization of Decandioic (**2**), Dodecandioic (**3**), and Nonandioic (**4**) Acids at Particular Carbons by Benzophenone Derivatives **1** and **7**[a]

reagent	substrate	carbon functionalized, % C-2	C-3	C-4	C-5	C-6
1	2	2.7	1.7	2.7	93	
1	3[b]	1	0.2	3.6	62 ± 4	34 ± 4
1	4	2.6	1.4	22[c]	74	
7	2[b]	4.3 ± 1.3	0.2 ± 0.2	13.7 ± 0.6	81 ± 1	
7	3	3.8	0.5	5.6	42	49
7	4			49[c]	51	

[a] All photolyses at ambient temperature. [b] Average of two independent experiments. All mass spectral analyses were repeatable with high precision. [c] Uncorrected for statistics, so each individual C-4 has half this value.

A similar study on the **6** mixture from the photolysis of complex **5** with 10 methylene groups (substrate **3**) showed signals at 46.7 and 51.9 ppm for the methines in **6**, with relative areas of 33 and 66%, respectively. Again assuming that the lower field signal is the one (C-5) nearer the end,[11] this agrees almost exactly with the C-5/C-6 ratio in Table I. Thus we conclude that the degradation scheme used to generate the data of Table I does not introduce a large bias.

The other mode of interaction examined was hydrogen bonding in nonpolar solvents. Benzophenone-3,3′-dicarboxylate dianion (**7**) was prepared as the bis(tetrabutylammonium) salt and dissolved in CH_2Cl_2 along with 1 equiv of dicarboxylic acids **2**, **3**, or **4**. Photolysis (ca. 2 mM) was followed by esterification with dimethyl sulfate/K_2CO_3 and then degradation essentially as described above. Again the functionalization reaction was quite selective for C-5 with decandedioic acid (**2**), but more random for C-5 and C-6 with dodecanedioic acid (**3**), which is too long to be fully extended in the doubly hydrogen-bonded complex (**8**). With nonanedioic acid (**4**) there is some preference (50%) for attack on the unique C-5 compared with either of the two C-4 positions (25% each).

The data show that for all the substrates there is greater selectivity with ion pairing (reagent **1**, complex **5**) than with hydrogen-bonding (reagent **7**, complex **8**) interactions. This may reflect greater "wobble" along the hydrogen bonds of **8** or greater ambiguity[12] in how they are formed (which atom and which orbital). Such wobble or ambiguity is partly a problem with the even-carbon substrate **2**, but displacement by more than a bond

(5) Breslow, R.; Maresca, L. M. *Tetrachedron Lett.* **1978**, 887.
(6) Breslow, R.; Maresca, L. M. *Tetrahedron Lett.* **1977**, 623.
(7) Breslow, R.; Kitabatake, S.; Rothbard, J. *J. Am. Chem. Soc.* **1978**, *100*, 8156.
(8) Czarniecki, M. F.; Breslow, R. *J. Am. Chem. Soc.* **1979**, *101*, 3675.
(9) R. B. Moffett and A. V. McIntosh, *Org. Synth., Coll. Vol. III* **1955**, 237.

(10) All ^{13}C NMR spectra were obtained in 70:30 (v/v) D_2O–$CH_3C{\equiv}N$ in 10-mm tubes on a Bruker WM 300-MHz spectrometer. Off-resonance decoupling experiments were performed in the standard fashion (decoupling frequency 3800 Hz, power 2 W). Inverse-gated decoupling experiments were done with 20-s pulse delays and a tip angle of 45°.
(11) Although the chemical shifts of methylenes in linear carboxylic acids or carboxylate anions are not a simple function of distance from the substituent (Hagen, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 4504), the deviations seem to reflect shielding effects from coiling of the chains. Such coiling should not be seen in **6**, in which ion pairing holds the carboxylate groups away from the chain.
(12) There is of course another ambiguity, since we have arbitrarily considered only substrate–reagent complexing and not substrate–substrate or reagent–reagent pairs. The system will be in rapid equilibrium, and only complex **8** leads to product.

length is needed to move the benzophenone oxygen from the center of the C-5/C-5′ bond so as to allow attack at C-4. Attack on substrate **4** is more demanding, since only a half-bond-length shift brings the attacking group in a position to abstract hydrogen from C-4 as well as C-5. Thus the poor selectivity in the reaction of **5** with **4** is not surprising, and the rather good selectivity of the **1**:**4** reaction is particularly striking.

As a control substrate **2** was photolyzed in CH_2Cl_2 with 3-carboxylbenzophenone, which is **7** with only one of the binding carboxylate groups. Here no attack on the chain was observed, the benzophenone reagent forming only products from attack on the solvent (identical with those formed if **2** was omitted). Furthermore, **2** was quantitatively (±2%) recovered unchanged. As a second control, the one-to-one salt of [3-(phenylcarbonyl)-phenyl]trimethylammonium cation (**1** with only one X group) and the monoanion of **4** was prepared and photolyzed in H_2O as above. Here too no functionalization of the chain could be detected, by ^{13}C NMR of the crude reaction mixture. While these experiments thus do not reveal how random the attack on **2** would be with only one coordination, they do show that both binding groups are needed for reaction and thus that two coordinations are undoubtedly present, as shown in **5** and **8**.

Electronic effects should make the central carbons of **2**–**4** the most reactive.[13] While such effects may be contributing to our results, we are clearly seeing geometric control as well. Some of the data in Table I, particularly the decreased reactivity at C-6 compared with C-5 in one case, can only be explained on a geometrical basis. The requirement for *two* binding groups for reaction makes it clear that geometrical control *should* be present. Further work will be needed to establish whether such double coordination of a flexible chain furnishes a general solution to the problem of producing complete selectivity in synthetically useful reactions.[14]

(13) Russell, G. A. *Free Radicals* **1973**, *1*, 273.

(14) Support of this work by the National Science Foundation is gratefully acknowledged.

A New Stereospecific Approach to Steroid Side Chains: Conversion of Dehydroepiandrosterone to Cholesterol, Isocholesterol, and Their 15β-Hydroxy Derivatives

J. P. Marino* and Hiroyuki Abe

Department of Chemistry, University of Michigan
Ann Arbor, Michigan 48109

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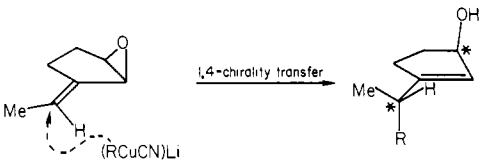
The stereocontrolled formation of carbon–carbon bonds in cyclic and acyclic systems presents a continuing challenge for synthetic chemists. Recently, we reported the regiospecific and stereospecific 1,4 addition of alkyl cyanocuprates to cyclic vinyloxiranes.[1,2] In this communication we wish to report that similar reactions may be applied to the stereospecific construction of side chains from substituted exo-methylene epoxycycloalkanes.[3,4] Our previous work revealed that mixed cyanocuprates can selectively generate *trans*-4-alkylcyclohex-2-enols. If this methodology is extended to a chiral alkylideneoxirane of known configuration there exists the possibility for a 1,4-chirality transfer[5] in which two asymmetric centers are generated in a 1,4 relationship. This overall transformation is depicted below for ethylidenecyclopentene oxide.



In order to demonstrate our approach, we tested its stereochemical efficacy in sterol side-chain synthesis. With the recent discoveries of many new sterols from marine and animal sources, as well as the active metabolites of vitamin D, there is a compelling need to develope general and stereospecific methods for the construction of the 20*R* configuration in naturally occurring sterols. Furthermore, the recent isolation by McMorris[6] of the naturally occurring 15β-hydroxysterol, oogoniol, and its partial synthesis by Djerassi[7] presented the additional incentive for introduction of 15β-hydroxy groups in sterols.

In this communication, we describe the stereospecific conversion of dehydroepiandrosterone (**1**) to cholesterol, isocholesterol, and their 15β-hydroxy derivatives, which possess the same configuration at C-15 as found in oogoniol.[7b] Our synthesis begins with 3β-hydroxyandrosta-5,15-dien-17-one (**2**) which is readily available from **1** in high yield.[8] Scheme I outlines the overall synthetic plan. Stereospecific epoxidation of the 15,16 double bond of **2** occurs regiospecifically,[9] and subsequent protection of the 3β-hydroxy group of **3a** with the *tert*-butyldimethylsilyl (TBDMS) group[10] leads to keto epoxide **3b** in an overall yield of 70%.[11]

The keto epoxide **3b** serves as a precursor to both cholesterol and isocholesterol. While a number of Wittig reactions have been carried out on 17-keto steroids,[12] no reports of such reactions on the 15,16-epoxy-17-keto sterols have come to our attention. The

(1) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.*, **1979**, 675.
(2) Marino, J. P.; Hatanaka, N. *J. Org.Chem.* **1979**, *44*, 4467.
(3) For reactions of *exo*-methylenecyclohexene oxides, see: Marino, J. P.; Abe, Hiroyuki *Synthesis* **1980**, *11*, 872.
(4) In a recent report, some reactions of dialkyl cuprates with alkylidene spiroepoxides are described: Ziegler, F. E.; Cady, M. A. *J. Org. Chem.* **1981**, *46*, 122.
(5) In recent years, there have been many elegant applications of 1,3-chirality transfer in steroid side-chain synthesis. Most notable are those that involve a Claisen rearrangement or π-allylpalladium intermediates. For some recent examples of the Claisen reaction, see: (a) Tanabe, M.; Hayashi, K. *J. Am. Chem. Soc.* **1980**, *102*, 862. (b) Koreeda, M.; Tanaka, Y.; Schwartz, A. *J. Org. Chem.* **1980**, *45*, 1172. (c) Piatak, D. M.; Wicha, J. *Chem. Rev.* **1978**, *78*, 199. For some leading references involving organopalladium intermediates, see: (d) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435. Trost, B. M.; Matsumura, Y. *J. Org. Chem.* **1977**, *42*, 2036. (f) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1976**, *98*, 630. (g) Dauben, W. G.; Brookhart, T. *Ibid.* **1981**, *103*, 237.
(6) McMorris, T. C.; Seshadri, R.; Weihe, G. R.; Arsenault, G. P.; Barksdale, A. W.; *J. Am. Chem. Soc.* **1975**, *97*, 2544.
(7) (a) Taylor, E. J.; Djerassi, C. *J. Org. Chem.* **1977**, *42*, 3571. (b) Wiersig, W. R.; Waespe-Sarcevic, N.; Djerassi, C. *Ibid.* **1979**, *44*, 3374.
(8) Kelly, R. W.; Sykes, P. J. *J. Chem. Soc. C* **1968**, 416.
(9) For the epoxidation of 5α-androst-15-en-17-one, see: Djerassi, C.; Von Mutzenbecher, G.; Fajkos, J.; Williams, D. H.; Budzikiewicz, H. *J. Am. Chem. Soc.* **1965**, *87*, 817. (b) Clark, I. M.; Denny, W. A.; Jones, E. H. R.; Meakins, G. D.; Pendlebury, A.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2765. All new compounds gave satisfactory elemental analyses and had spectral properties (IR, ^1H NMR, and ^{13}C NMR) consistent with the assigned structures.
(10) Hosoda, H.; Fukushima, D. K.; Fishman, J. *J. Org. Chem.* **1973**, *38*, 4209.
(11) **3a**: mp 165–166 °C (ether–petroleum ether); $[\alpha]^{27}_D$ −139° (*c* 0.54, $CHCl_3$); ^1H NMR (360 MHz) δ 1.05 (s, 3 H, H-18), 1.15 (s, 3 H, H-19), 3.28 (d, 1 H, *J* = 2.93 Hz, H-15), 3.80 (d, 1 H, *J* = 2.93 Hz, H-16), 3.45–3.48 (m, 1 H, H-3), 5.35–5.42 (br, 1 H, H-6); ^{13}C NMR (22.5 MHz) δ 213.0, 141.7, 120.2, 71.5, 55.6, 53.4, 53.2, 51.3, 42.3, 42.0, 37.1, 36.9, 32.9, 31.6, 30.3, 28.7, 20.0, 19.3, 19.0; IR ($CHCl_3$) 1745 cm^{-1}. **3b**: mp 138–140 °C (petroleum ether); $[\alpha]^{27}_D$ −99° (*c* 0.63, $CHCl_3$).
(12) Drefahl, G.; Ponsold, K.; Schick, H. *Chem. Ber.* **1965**, *98*, 604.

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