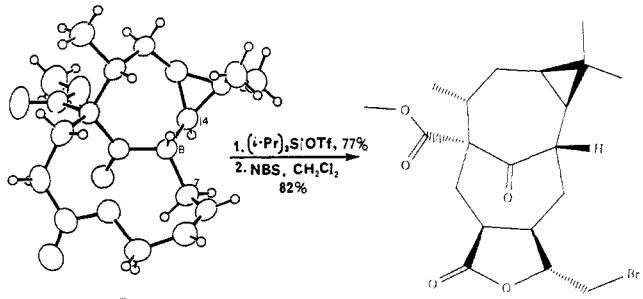
diastereomeric β-keto esters (9.5:6.6:4.5:1; 86%). The two major isomers (**11a,b**) were shown to be epimeric at C(10) (ingenane numbering) upon equilibration with NaOMe/MeOH and to possess the desired C(11) β-methyl substituent by decarbomethoxylation (NaCN, HMPA) to the known cycloheptenone **2**.[5a]

The β-keto esters **11a,b** are perfectly functionalized for the regio- and stereoselective attachment of the two side chains required to complete the *in,out*-bicyclo[4.4.1]undecan-7-one ring system. To that end, the β-keto esters **11a,b** were converted to the dianion[14] (2.25 equiv of LDA, 1 equiv of HMPA, THF, −78 °C → 0 °C, 3 h) and then alkylated with *cis*-1-(*tert*-butyldimethylsilyloxy)-4-chloro-2-butene (2 equiv, −78 °C → 30 °C, 4 h) to give one major product (>18:1) in 64% yield after column chromatography. Treatment of the alkylation product with methyl acrylate (10 equiv) in the presence of Triton-B (1 equiv, 0 °C dioxane, 30 min) gave a single Michael reaction adduct (85%). We tentatively assigned the stereochemistry shown in **12** based on the expected approach of the electrophiles from the enolate face opposite the substituents on the carbon β to the C(9) carbonyl (ingenane numbering). The stereochemical assignment was quickly confirmed by straightforward transformation of **12** to hydroxy acid **13** (Bu_4NF, THF, 0 °C; 90%; 2 equiv of K_2CO_3, MeOH, H_2O, 25 °C, 48 h; 94%) and subsequent lactonization (6 equiv of *N*-methyl-2-chloropyridinium iodide, 8 equiv of NEt_3, CH_3CN)[15] to provide the crystalline lactone **5** [62%; mp = 153–154.5 °C; $[a]_D^{25}$ = 256° (*c* 0.1; $CHCl_3$)] whose structure was solved by single-crystal X-ray analysis. As indicated in the ORTEP drawing below, the in,out-macrobicyclic [8.4.1] lactone possesses the desired relative stereochemistry, and the C(7)–C(8)–C(14) bond angle of 113.2° indicates minor bending deformation relative to that present in ingenol [C(7)–C(8)–C(14) bond angle = 126.5°].

Addition of triisopropylsilyl triflate (4 equiv) to a refluxing benzene solution of lactone **5** in the presence of triethylamine (8 equiv)[16] gave one major rearrangement product **7** (R = Si(*i*-Pr)$_3$; >15:1) after chromatography on Florisil. The stereochemical assignment for the two newly created stereogenic centers was based on the previously mentioned transition-state analysis and verified by single-crystal X-ray analysis of the bromolactone derivative **14** (mp 204–206.5 °C).



5 **14**

In conclusion, this concise, stereoselective synthesis of the BCD ring system of ingenol further illustrates the versatility of macrocyclic Claisen rearrangements for the rapid assemblage of strained ring systems.[8b,c] We are currently addressing the introduction of the A ring; our progress will be reported in due course.

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (Grant GM 28663), Eli Lilly and Company, and Alfred P. Sloan Foundation. High field (360 MHz) ^1H NMR and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (Grant CHE-80-24328). Mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (Grant CHE-82-11164).

Supplementary Material Available: X-ray crystallographic data for compounds **5** and **14** (16 pages). Ordering information is given on any current masthead page.

Cyclopentane Synthesis via Free-Radical-Mediated Addition of Functionalized Alkenes to Substituted Vinylcyclopropanes

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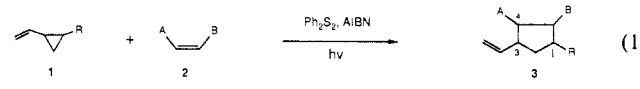
Herein we report a novel [3 atom + 2 atom][1] bond construction strategy for the synthesis of highly functionalized cyclopentane rings. Our approach relies on phenylthio radical catalyzed addition of substituted alkenes to vinylcyclopropane derivatives, eq 1. This



1 2 3 (1)

process transpires under mild experimental conditions, is tolerant of many organic functional groups, occurs with complete regiochemical control, and exhibits moderate stereoselectivity. These characteristics suggest that this chemistry may be broadly applicable to the efficient synthesis of cyclopentanoid natural products.

Treatment of a benzene solution of a vinylcyclopropane **1** and a 10–15-fold excess of an alkene **2** with a phenylthio radical precursor, either at reflux or at low temperature in the presence of Lewis acid, furnishes the vinylcyclopentane **3** in good yield. In addition to cyclopentane formation, varying amounts (5–50%) of the 1,5-phenyl disulfide adduct **17** are produced, presumably through addition of homoallylic radical **14** (vide infra) to phenyl disulfide.[2] Several selected examples are shown in Table I.[3-5]

(12) However, the intermolecular Knovenagel condensations of β-keto esters and malonates with aldehydes have been catalyzed by $TiCl_4$. (a) Lehnert, W. *Tetrahedron Lett.* **1970**, 4723. (b) Lehnert, W. *Tetrahedron* **1972**, *28*, 663. (c) Lehnert, W. *Tetrahedron* **1973**, *29*, 635.

(13) For a study of the stereochemistry of cuprate addition to 4-, 5-, and 6-alkylcycloheptenones, see: Heathcock, C. H.; Germroth, T. C.; Graham, S. L. *J. Org. Chem.* **1979**, *44*, 4481.

(14) Weiler, L.; Huckin, S. N. *J. Am. Chem. Soc.* **1974**, *96*, 1082.

(15) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49.

(16) The standard Ireland conditions for ester enolate rearrangement (LDA; $ClSiMe_2$-*t*-Bu) gave a retro-Michael addition product. Consequently, we employed the silyl triflate, triethylamine protocol for the preparation of ketene acetals which may proceed via a silylation and then deprotonation mechanism, see: (a) Simchen, G.; Kober, W. *Synthesis* **1976**, 259. (b) Simchen, G.; Emde, H. *Ibid.* **1977**, 867. (c) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455. (d) Mander, L. N.; Sethi, S. P. *Ibid.* **1984**, *25*, 5953.

(1) Other examples of [3 atom + 2 atom] strategies for cyclopentane synthesis can be found in the following: (a) Beal, R. B.; Dombroski, M. A.; Snider, B. B. *J. Org. Chem.* **1986**, *51*, 4391. (b) Demuth, M.; Wictfeld, B.; Pandey, B.; Schaffer, K. *Angew Chem.* **1985**, *97*, 777. (c) Tsuji, J.; Shimizu, I.; Ohashi, Y. *Tetrahedron Lett.* **1985**, *26*, 3825. (d) Molander, G. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1986**, *108*, 4683, and references cited therein. (e) Danheiser, R. L.; Carini, D. J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935. (f) Marino, J. P.; Laborde, E. *J. Am. Chem. Soc.* **1985**, *107*, 734. (g) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1, and references cited therein. (h) Beak, P.; Wilson, K. D. *J. Org. Chem.* **1987**, *52*, 218. (i) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1984**, *106*, 805. (j) Herndon, J. W. *J. Am. Chem. Soc.* **1987**, *109*, 3165. (k) Cekovic, Z.; Saicic, R. *Tetrahedron Lett.* **1986**, *27*, 5893. (l) Little, R. D.; Muller, G. W.; Venegas, M. G.; Carroll, G. L.; Bukhari, A.; Patton, L.; Stone, K. *Tetrahedron* **1981**, *37*, 4371. (m) Curran, D. P.; Chen, M.-H. *J. Am. Chem. Soc.* **1987**, *109*, 6558. (n) Clive, D. L. J.; Angoh, A. G. *J. Chem. Soc., Chem. Commun.* **1985**, 980.

(2) The rate constant for addition of 5-hexenyl radical to phenyl disulfide is 7.6×10^4 l·m^{-1} s^{-1} (80 °C): Russell, G. A.; Tashtoush, H. *J. Am. Chem. Soc.* **1983**, *105*, 1398. This competitive process sets a lower limit on useful rate constants for addition of substituted alkenes to homoallylic radical **14**.

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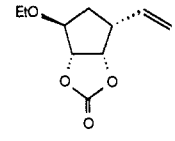
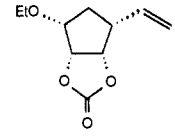
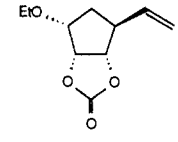
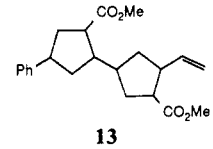
Table I

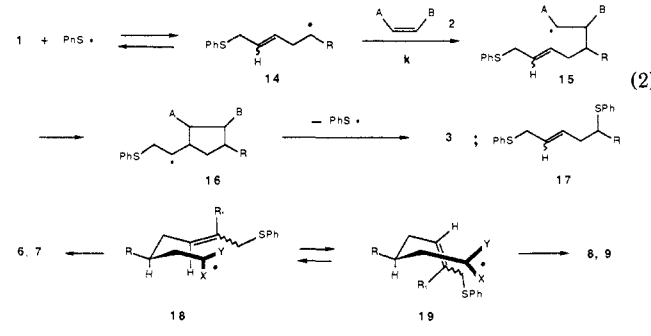
4[a] R	4[a] R_1	5 R_2	condn	6	7	8	9	yield[d] (%)
(a) CO_2-*t*-Bu	H	CO_2-*t*-Bu	A[b]	4.4	1.9	1.2	1.0	53
			B[c] (−50 °C)	10.6	4.1	1.4	1.0	52
(b) CO_2-*t*-Bu	CH_3	CO_2-*t*-Bu	A	3.7	3.0		1.0	44
(c) CO_2-*t*-Bu	H	OCO-*t*-Bu	B (−15 °C)	2.2	4.0	1.0		52
(d) OEt	H		A	 **10** (5.5)	 **11** (4.4)	 **12** (1.0)		42
(e)	H		A	 **13**				58

[a] The vinylcyclopropanes were mixtures of stereoisomers. [b] Condition A: refluxing benzene. [c] Condition B: 0.8 equiv of Me_3Al. Toluene solvent. [d] Isolated yields based on chromatographically pure material.

The combination of vinyl cyclopropyl ester **4a** with *tert*-butyl acrylate produces the four possible stereoisomeric cyclopentane products **6a–9a** in 53% yield in the ratios shown. The original cyclopropyl substituents, in this case vinyl and *tert*-butyl ester, preferentially emerge cis to one another (cf. **3**, C(1), C(3) cis) upon cyclization in refluxing benzene (condition A) (**6a** + **7a**/**8a** + **9a** = 3:1). In the cis (**6a** + **7a**) series, the C(4) *tert*-butyl ester originating from the alkene moiety exhibits a slight trans preference relative to the C(1) and C(3) substituents.[6] The combination of low-temperature conditions and Lewis acid catalysis (condition B) significantly improves the stereoselectivity of this transformation.[7] For example, reaction of cyclopropane **4a** with *tert*-butyl acrylate at −50 °C in the presence of trimethylaluminum increases the cis (**6a** + **7a**):trans (**8a** + **9a**) ratio to 6:1.

Use of oxygenated addends would allow facile preparation of highly oxidized five-membered rings that may find use in the synthesis of prostanoids, inter alia. Thus, addition of vinyl pivalate (entry c) across the cyclopropane ring of vinyl ester **4a** leads to only three of the four possible stereoisomeric cyclopentane products. The trend toward cis over trans products (**6c** + **7c**/**8c** = 6.2:1), noted in the previous example, is also observed here. Furthermore, combination of *O*-ethylcyclopropane **4a** with the disubstituted alkene vinylene carbonate (entry d) results in a moderate yield of the mixture of stereoisomeric trioxygenated vinylcyclopentanes **10–12**.

We believe that the mechanism of this novel cyclopentane synthesis is qualitatively similar to one which we proposed for the addition of molecular oxygen to vinylcyclopropanes.[8] Thus, this reaction proceeds by a radical chain mechanism featuring initiation, propagation, and termination stages en route to five-membered ring formation (eq 2). Initiation occurs by phenylthio



(2)

radical addition to the vinylcyclopropane **1**, followed by ring opening to the homoallylic radical **14**, bimolecular addition of the alkene **2** to produce the 5-hexenyl radical **15**, cyclization to cyclopentanyl carbinyl radical **16**, and termination via ejection of the phenylthio radical[9] to afford the vinylcyclopentane product **3**. In general, we have observed that a bimolecular rate constant k greater than 10^2 l·m^{-1} s^{-1} [2,10b] leads to good (>50%) yield of the five-membered ring. In contrast, combination of cyclopropyl ester **4a** with vinylene carbonate results in only a 13% yield of the product cyclopentane, in accord with a low (ca. 70 l·m^{-1} s^{-1})[11] rate

(3) In a typical experiment, a solution of phenyl disulfide (44 mg, 0.2 mmol) and AIBN (7 mg, 0.04 mmol) in 1.0 mL of deoxygenated toluene was added dropwise over 16 h to a cold (−15 °C) solution of 1-*tert*-butylcarboxy-2-vinylcyclopropane (**4a**) (51 mg, 0.3 mmol), trimethylaluminum (0.12 mL, 0.24 mmol), and vinyl pivalate (0.63 mL, 4.5 mmol) in 2 mL of deoxygenated toluene under an Ar atmosphere with concomitant sunlamp irradiation. After the starting material was consumed (TLC), the reaction mixture was concentrated in vacuo and purified by flash chromatography to yield 47 mg of cyclopentanes **6c–8c** (52%).

(4) All new compounds exhibited satisfactory ^{1}H NMR, ^{13}C NMR, IR, MS, and analytical data. Spectral data, including decoupling and DNOE characterization, can be found in the Supplementary Material.

(5) We have observed that alkynes and crotonates afford in good yield cyclopentene and tetrasubstituted cyclopentane derivatives, respectively, upon combination with vinylcyclopropanes. These studies will be reported in due course.

(6) For a related case, see: Julia, M.; Maumy, M. *Bull. Chim. Soc. Fr.* **1966**, 434.

(7) The utilization of Lewis acids to impart chemoselectivity and stereoselectivity to free-radical polymerizations and copolymerizations is well documented: (a) Afchar-Momtaz, J.; Polton, A.; Tardi, M.; Sigwalt, P. *Eur. Polym. J* **1985**, *21*, 1067. (b) Hirai, H. *J. Polymer Sci.: Macromol. Rev.* **1976**, *11*, 47, and references cited therein.

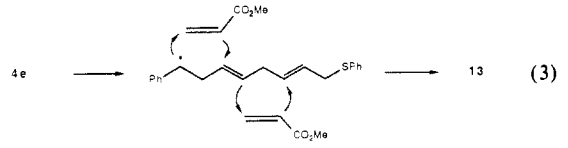
(8) Feldman, K. S.; Simpson, R. E.; Parvez, M. *J. Am. Chem. Soc.* **1986**, *108*, 1328.

(9) Related formal S_H2' processes on allyl sulfide substrates have been reported: (a) Ueno, Y. Aoki, S.; Okawara, M. *J. Am. Chem. Soc.* **1979**, *101*, 5414. (b) Ueno, Y.; Okawara, M. *Ibid.* **1979**, *101*, 1893. (c) Keck, G. E.; Byers, J. H. *J. Org. Chem.* **1985**, *50*, 5442.

(10) (a) Oxygenation of carbon radicals is fairly insensitive to substituent effects and occurs with a rate constant of $\sim 10^9$ l·m^{-1} s^{-1} (25 °C): Mallard, B.; Ingold, K. U.; Scaiano, J. *J. Am. Chem. Soc.* **1983**, *105*, 5095. (b) Additions of substituted carbon radicals to functionalized alkenes typically occur with rate constants of 10^1–10^5 l·m^{-1} s^{-1} (60 °C): *Polymer Handbook*, 2nd ed.; Brandrup, J., Immergût, E. H., Eds.; J. H. Wiley and Sons: New York, 1975.

constant for bimolecular addition. The stereochemical outcome of the [3 + 2] addition process, which is determined during closure of the substituted 5-hexenyl radical **15** (via conformers **18** or **19**), can be rationalized by modifying existing models for such cyclizations.[12]

The cyclopropylcyclopropane substrate **4e** was examined in an effort to exploit the chain reaction nature of this process. Thus, serial double alkene addition within the propagation portion of the reaction sequence affords bis cyclopentane **13**, isolated as a mixture of at least five (^{1}H NMR) isomers (eq 3). Despite the lack of stereocontrol, the regioselective formation of four carbon–carbon bonds in a single transformation demonstrates the potential of this strategy for the efficient construction of polycyclic systems.



(3)

The role that the Lewis acid plays in these free radical reactions is obscure at present. Generally, we have observed that trimethylaluminum increases the rate and improves the stereoselectivity of these free-radical-mediated [3 atom + 2 atom] additions. Application of this methodology to the stereoselective synthesis of substituted cyclopentane natural products is in progress.

Acknowledgment. We thank the National Institutes of Health (GM 37681) for financial support.

Supplementary Material Available: Spectral data for **6–13** (7 pages). Ordering information is given on any current masthead page.

(11) Estimated from the rate constant for addition of 2-propionitrile radical to vinylene carbonate.[10b]

(12) Experimental: (a) Beckwith, A. L. J.; Easton, C. J.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 482. (b) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1980**, 484, and references cited therein. Computational: (c) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959. (d) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373. (e) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925.

Electrophilic Catalysis by Vanadate of the Dehydration of Hydrated Glyoxylate

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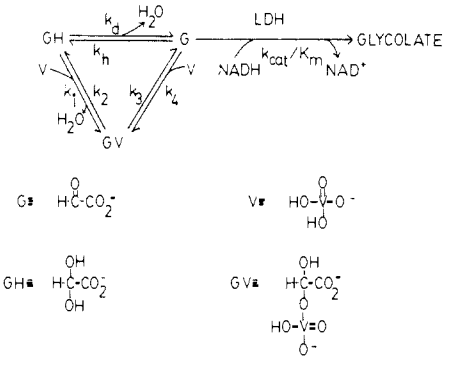
Vanadate was found to catalyze the dehydration of hydrated glyoxylate, and the results are interpreted in terms of Scheme I. In this model inorganic vanadate (V) condenses with one of the hydroxyl groups of the hydrated aldehyde (GH) to form a vanadate ester (GV), which eliminates vanadate to form the free aldehyde (G).

The dehydration rate was measured by utilizing the fact that only the free aldehyde is a substrate for lactate dehydrogenase (LDH)[1] and following the oxidation of NADH spectrophotometrically at 340 nm, by using an extinction coefficient of 6.22 × 10^3. As the concentration of LDH was increased, the reaction rate increased and approached a maximum as shown in Figure 1. This saturation behavior is attributed to the dehydration reaction becoming the rate-limiting step in the process. The rate increase in the presence of vanadate cannot reasonably be ascribed to general acid–base catalysis since similar concentrations of phosphate or arsenate did not observably affect the rate between pH 6 and 8.5, while vanadate increased the rate throughout this pH range.

Scheme I. The Uncatalyzed Reversible Hydration of Glyoxylate and an Alternate Pathway Which Proceeds via Formation of a Vanadate Ester[a]



[a] The free aldehyde is trapped by the lactate dehydrogenase-catalyzed reduction to glycolate.

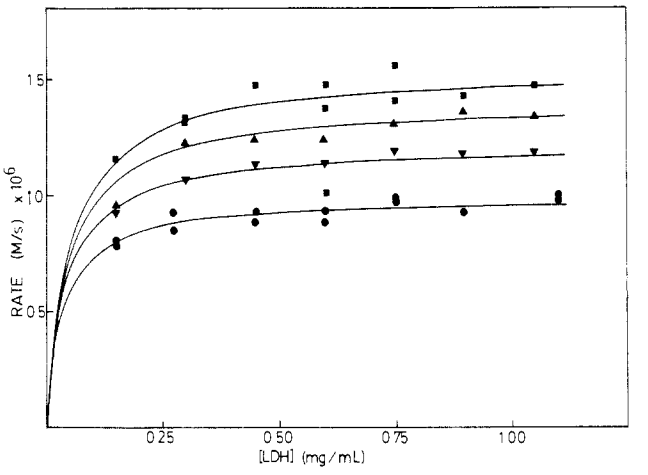


Figure 1. The effect of lactate dehydrogenase concentration on the rate of reduction of glyoxylate in the presence and absence of vanadate. Conditions were the following: 0.1 M HEPES, pH 7.2, 25 °C, 0.15 mM NADH, 0.1 mM glyoxylic acid, and the indicated concentrations of LDH (type XI from Sigma). Reactions were initiated by the addition of glyoxylic acid. Total vanadium atom concentrations (added as inorganic vanadate) were as follows: (●), 0 (▼) 0.2, (▲) 0.4, (■) 0.6 mM. The solid lines were calculated from eq 4 by using the constants k_d = 0.0098 s^{-1}, k_3K_{eq} = 12.66 $M^{-1}\cdot s^{-1}$, $k_h/(k_{cat}/K_m)$ = 0.0336 mg·mL^{-1}, and $k_4/(k_{cat}/K_m)$ = 36 mg·$mL^{-1}\cdot M^{-1}$. The values used in the calculations for vanadate concentrations were (▼) 0.179, (▲) 0.322, and (■) 0.437 mM.

The catalytic mechanism shown in Scheme I was suggested by the observations that vanadate esters form rapidly[2-4] and that elimination of phosphate from the phosphorylated hydrate of D-glyceraldehyde is several times faster than dehydration of the hydrate under similar conditions.[5]

The results shown in Figure 1 were analyzed as follows. Assuming that the vanadate ester formation is at equilibrium, which is reasonable in view of the rapid reversible formation of ethyl vanadate, results in eq 1; the fact that the concentration of free aldehyde is much below its K_m as a substrate for LDH[6] yields eq 2; and eq 3 results from applying the steady-state approximation to the free aldehyde. These equations yield eq 4.

(1) Everse, J.; Kaplan, N. O. *Adv. Enzymol.* **1973**, *37*, 61–133.

(2) Nour-Eldeen, A. F.; Craig, M. M.; Gresser, M. J. *J. Biol. Chem.* **1985**, *260*, 6836–6842.

(3) Gresser, M. J.; Tracey, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 2415–4220.

(4) Tracey, A. S.; Gresser, M. J.; Parkinson, K. M. *Inorg. Chem.* **1987**, *26*, 629–638.

(5) Rendina, A. R.; Cleland, W. W. *Biochemistry* **1984**, *23*, 5157–5168.

(6) Duncan, R. J. S.; Tipton, K. F. *Eur. J. Biochem.* **1969**, *11*, 58–61.

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