Practical Synthesis of (±)-Chlorovulone II

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We describe a total synthesis of (±)-chlorovulone II that is 10 steps shorter than the best alternative currently available (nine vs 19 steps). The key event of the synthesis is an aldol addition of the enolate of ethyl acetate into 4-cyclopentene-1,3-dione, a substance that has received little attention as an educt for prostanoid synthesis and for which little is known about carbonyl 1,2-addition with enolates. In addition, we provide chemical and stereochemical details of a route to a key intermediate toward the title compound that involves a carbonyl−ene reaction and a radical addition to an aldehyde carbonyl.

Introduction

Chlorovulone II, **1**, is a marine prostanoid isolated from the Okinawan soft coral, *Clavularia viridis*.[1] This organism has been a rich source of bioactive and structurally novel prostanoids, which have received much attention owing to their unusual architecture and physiological activity.[2] Prostanoids from *C. viridis* were first reported in 1982, when two groups simultaneously described clavulone I, **2**, and related substances (Figure 1).[3] Various related compounds were subsequently isolated from the same source.[4]

Clavulone I and congeners display antiinflammatory activity in a fertilized chicken egg assay (30 μg/mL).[3a] More significantly, these substances have shown remarkable cytotoxicity and antiproliferative activity against several transformed cell lines.[5] Antitumor activity is especially pronounced in halogenated congeners of clavulones, and chlorovulone II is one of the most active members of the group. The activity of **1** against HL-60

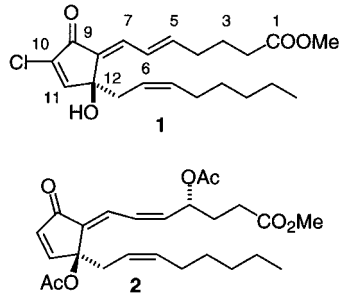

Figure 1.

cells corresponds to an IC_{50} of 30 nM (10 ng/mL), about 1 order of magnitude greater than that of clavulone I on a molar basis.[6] Preliminary studies have also defined some requirements for maximum activity. In particular, a C-10-11 olefin or epoxide is essential; a halogen atom at C-10 increases activity (Cl = F > Br = I > H), as does a C-5,7 diene; the hydroxyl group at C-12, the sole stereogenic carbon atom in the molecule, is required for highest activity, but remarkably, the antipodes of **1** possess identical potency.[6a]

The mode of cytotoxic action of chlorovulone and related substances remains poorly understood. Of course, chlorovulone could interfere with the biological functions of prostaglandins, due to its great similarity to the latter family of compounds. Alternatively, it may function as a relatively nonselective alkylating agent (it is a reactive Michael acceptor) that could damage proteins, glutathione, and other key factors involved in cellular function, including, perhaps, nucleic acids. The latter mode of action could explain why the stereochemistry of the C-12 OH is not important for activity. As shown below, conjugate addition of a bionucleophile (BioNu, Scheme 1) could promote expulsion of that OH group, preparing the molecule for subsequent Michael-type events and causing it to behave as a multiple alkylating agent; possibly a cross-linking one. It must be stressed, however, that at this time the mechanisms of Scheme 1 belong to the realm of conjecture.

Consensus exists that arachidonic acid is the progenitor of *Clavularia* prostanoids. On the other hand, several

(1) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *Tetrahedron Lett.* **1985**, *26*, 5787.

(2) Review: Gerwick, W. H. *Chem. Rev.* **1993**, *93*, 1807 and references cited therein. See also: Gribble, G. W. *Fort. Chem. Org. Naturst.* **1996**, *68*, 110.

(3) (a) Kikuchi, H.; Tsukitani, Y,; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171. (b) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1982**, *23*, 5331. The absolute stereochemistry of these compounds was established by degradative and chiroptical techniques [(c) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 1440. (d) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 1549] and confirmed by synthesis. (e) Hashimoto, S.; Arai, Y.; Hamanaka, N. *Tetrahedron Lett.* **1985**, *26*, 2679. (f) Corey, E. J.; Mehrotra, M. M. *J. Am. Chem. Soc.* **1984**, *106*, 3384. (g) Nagaoka, H.; Miyakoshi, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 3621. (h) Shibasaki, N.; Ogawa, Y. *Tetrahedron Lett.* **1985**, *26*, 3841. (i) Zhu, J.; Yang, J. Y.; Klunder, A. J. H.; Liu, Z. Y.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5847. (j) Takeda, K.; Nakajima, A.; Yoshii, E. *Synlett* **1997**, 255.

(4) (a) Iguchi, K.; Yamada, Y.; Kikuchi, H.; Tsukitani, Y. *Tetrahedron Lett.* **1983**, *24*, 4433. (b) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 981. (c) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y. *Chem. Pharm. Bull.* **1987**, *35*, 4375.

(5) (a) Honda, A.; Yamamoto, Y.; Mori, Y.; Yamada, Y.; Kikuchi, H. *Biochem. Biophys. Res. Commun.* **1985**, *130*, 515. (b) Fukushima, M.; Kato, T.; Yamada, Y.; Kitagawa, I.; Kurozumi, S.; Scheuer, P. J. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 980. *In vivo* testing of some *Clavularia* metabolites has furnished promising results. Thus, clavulone II gave a T/C = 151 at 10 mg kg^{-1} day^{-1} for 5 days and a T/C of 160 at 20 mg kg^{-1} day^{-1}. Additional biological effects are described in: Honda, A.; Hong, S.; Yamada, Y.; Mori, Y. *Res. Commun. Chem. Pathol. Pharmacol.* **1991**, *72*, 363.

(6) (a) Honda, A.; Mori, Y.; Iguchi, K.; Yamada, Y. *Mol. Pharmacol.* **1987**, *32*, 530. (b) Fukushima, M.; Kato, T. *Adv. Prostaglandin Thromboxane Leukotriene Res.* **1985**, *15*, 415. (c) Honda, A.; Mori, Y.; Iguchi, K.; Yamada, Y. *Prostaglandins* **1988**, *36*, 621.

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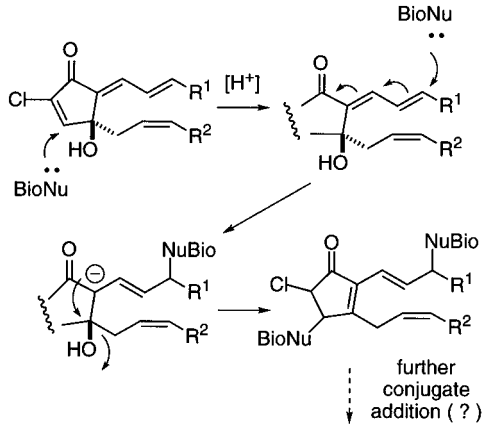
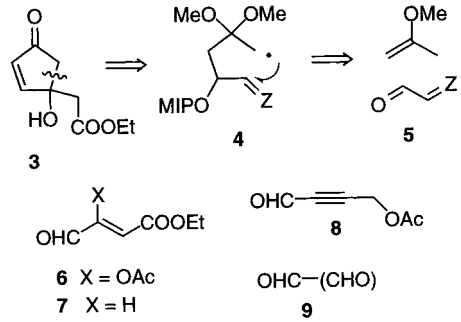
Scheme 1

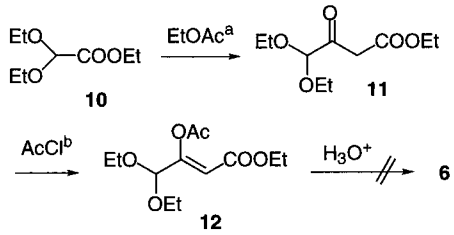


Scheme 2



questions regarding details of the biosynthesis of these compounds remain unanswered, despite much activity in this area.[7] Unresolved issues, both in biosynthesis and, more importantly, in pharmacology, could probably be explored if a stable supply of materials were to be secured. It appears that the sole practical solution for this problem resides in a total synthesis, because the natural compounds appear to be quite rare. This seems to be especially the case for the highly bioactive chlorovulone II, which constitutes only 0.002% of the freeze-dried weight of *C. viridis*.[1−4] Specifically labeled material may also be useful, or even necessary, to deal effectively with several of the above questions. Again, synthesis offers the sole practical avenue to such compounds: a biosynthetic route involving labeled precursors is unattractive, given the paucity of **1** in its natural source. Interestingly, only one total synthesis of **1**, by Yamada and collaborators,[8] has been recorded in the literature, while several syntheses of clavulones are known.[3e−g] The Yamada synthesis leads to (−)-chlorovulone II, the antipode of the natural product, in 19 linear steps and in ca. 6% yield from L-tartaric ester, by way of the *tert*-butyl ester analog of intermediate **3** (Scheme 2). However, there may not be a pressing need for an enantioselective synthesis of **1**, since the two antipodes of the molecules have identical potency. In this paper, we describe a practical, efficient total synthesis of (±)-**1** that requires nine linear steps from commercial materials and that proceeds in 21% overall yield. We also disclose a

Scheme 3[a]



[a] Key: (a) *t*-BuOK, 0 °C, 71%; (b) pyridine, cat. DMAP, rt, 91%.

route that should permit site-specific labeling of various ring atoms in the molecule. Chemical highlights of the work reported herein include the use of commercial 4-cyclopentene-1,3-dione as a building block for marine prostanoids; the use of our carbonyl−ene reaction as a key step toward intermediate **3**, and the investigation of chemical and stereochemical aspects of radical additions to aldehyde carbonyls.

Carbonyl−Ene Route to Intermediate 3

Enone **3** is the key intermediate for our synthesis (Scheme 2). The presence of an ethyl ester, instead of Yamada's *tert*-butyl ester,[8] should allow direct DIBAL reduction to an aldehyde, as a prelude to installation of the two side chains as described earlier.[8] Our strategy for **3** rests on our carbonyl ene-like reaction,[9] as apparent from Scheme 2. The key enone **3** could result through free-radical cyclization (cf. **4**) of a suitable derivative of the ene adduct of 2-methoxypropene ("2-MP") with an aldehyde of generic structure **5**. Plausible substrates for the planned transformations were aldehydes **6**−**8** or even a glyoxal analog, **9**. Whereas ene reaction of **6**−**8** would be followed by suitable activation of the vinyl ether and radical cyclization into an olefinic π system, use of glyoxal equivalent **8** would ultimately entail a radical−carbonyl cyclization.[10,11]

The preparation of aldehyde **6** was troublesome. Ethyl α,α-diethoxyacetate and ethyl acetate condensed easily in the presence of *t*-BuOK to give β-keto ester **11**, treatment of which with AcCl and pyridine in the presence of DMAP produced **12** (Scheme 3). However, it was not possible to promote selective hydrolysis of the ketal in **12**. Mild acidic conditions released the acetate to give back **11**, while stronger acid damaged the molecule. Ethyl 4-oxocrotonate (**7**)[12] was advanced easily to **15** by carbonyl ene reaction with 2-MP, methoxybromination of the resulting **13** (note: MIP = 2-methoxyisopropyl) with NBS/MeOH and radical cyclization (77% overall, Scheme 4). Unfortunately, introduction of the

(7) Cf. (a) Corey, E. J.; Matsuda, S. P. T. *Tetrahedron Lett.* **1987**, *28*, 4247. (b) Corey, E. J.; D'Alarcao, M.; Matsuda, S. P. T.; Lansbury, P. T., Jr.; Yamada, Y. *J. Am. Chem. Soc.* **1987**, *109*, 289. (c) Brash, A. R. *J. Am. Chem. Soc.* **1989**, *111*. 1891. (d) Brash, A. R.; Baertschi, S. W.; Ingram, C. D.; Harris, T. M. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 3382.

(8) Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 223.

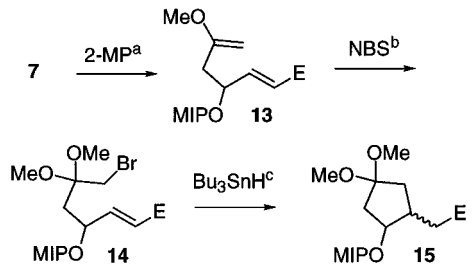
(9) Deaton, M. V.; Ciufolini, M. A. *Tetrahedron Lett.* **1993**, *34*, 2409.

(10) Flies, F.; Lalande, R.; Maillard, B. *Tetrahedron Lett.* **1976**, *17*, 439.

(11) (a) Tsang, R.; Dickson, J.K., Jr.; Pak, H.; Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1987**, *109*, 3484. (b) Walton, R.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1991**, *113*, 5791. Physical organic studies: (c) Beckwith, A. L. J.; Raner, K. D. *J. Org. Chem.* **1992**, *57*, 4954. Applications: (d) Grissom, J. W.; Klingberg, D. *J. Org. Chem.* **1993**, *58*, 6558. Related processes: (e) Naito, T.; Tajiri, K.; Harimoto, T.; Ninomiya, I.; Kiguchi, T. *Tetrahedron Lett.* **1994**, *35*, 2205. (f) Enholm, E. J.; Xie, Y.; Abboud, K. A. *J. Org. Chem.* **1995**, *60*, 1112. (g) Hays, D. S.; Fu, G. *J. Am. Chem. Soc.* **1995**, *117*, 7283. (h) Yuasa, Y.; Ando, J.; Shibuya, S. *J. Chem. Soc., Perkin Trans. 1* **1996**, 793.

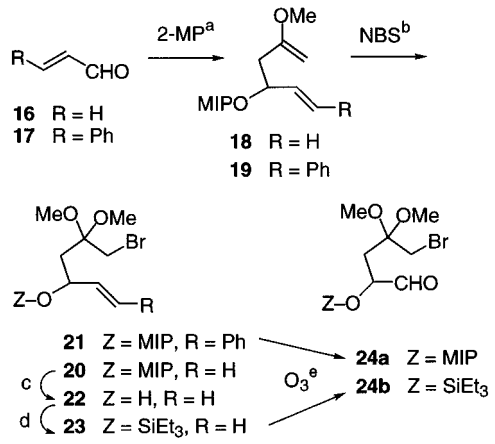
(12) Available in a low 20% yield by a laborious SeO_2 oxidation of ethyl crotonate: Rambaud, R.; Vessiere, M. *Bull. Soc. Chim. Fr.* **1961**, 1567. A similar oxidation of ethyl 3-acetoxycrotonate (from ethyl acetoacetate and Ac_2O/pyridine) as a route to **6** was unsuccessful.

Scheme 4[a]



[a] Key: (a) 10 equiv, 0.5 mol % of 1:1 Yb(fod)$_3$−AcOH complex, rt, 90%; (b) MeOH, CH_2Cl_2, K_2CO_3, −78 °C, 99%; (c) AIBN, PhH, reflux, 85%.

Scheme 5[a]



Key: (a) 10 equiv, 0.5 mol % of 1:1 Yb(fod)$_3$−AcOH complex, rt, 80% (R = H), 100% (R = Ph); (b) MeOH, CH_2Cl_2, K_2CO_3, −78 °C, 97% (R = H), 87% (R = Ph); (c) CSA, MeOH, 84%; (d) Et_3SiCl, Et_3N, CH_2Cl_2, 95%; (e) MeOH, CH_2Cl_2, $NaHCO_3$, −78 °C; then Me_2S, 78% (R = H), 80% (R = Ph).

requisite tertiary OH unit at this stage would have taken numerous steps. Finally, reactive ynal **8**, available by MnO_2 oxidation[13] of 1-acetoxy-2-butyn-4-ol,[14] was a poor substrate for our ene reaction.[15]

We thus turned our attention to a suitable glyoxal equivalent. Aldehydes containing ketal functionalities may react poorly in the ene process; furthermore, the multitude of ketals present in various late intermediates would have complicated the issue of selective hydrolysis. This ruled out the use of a true glyoxal monoketal in our synthesis. Ozonolytic cleavage of an olefin constituted an appealing way to reveal the requisite aldehyde function. Accordingly, we focused on the ene reaction of 2-MP with enals. The ene adduct of acrolein, **18**,[16] underwent smooth methoxybromination, but ozonolysis of the resulting **20** occurred with concomitant loss of the MIP group (Scheme 5). The resulting α-hydroxy aldehyde was isolable, but it was difficult to handle. Release of the MIP group is attributable to the generation of formic acid through over oxidation of formaldehyde, coproduced with **20** and arising from the terminal methylene portion of the olefin. The problem persisted when the ozonolysis reaction was run with suspended $NaHCO_3$. This forced upon us an awkward protection−deprotection sequence prior to ozonolysis (cf. **20** → **22**, Scheme 5). Triethylsilyl ether **24b** ultimately emerged as a substrate for carbonyl−radical cyclization. Parallel studies defined a more direct route to an alternative substrate starting with cinnamaldehyde, **17**. Thus, methoxybromination of ene adduct **19** followed by ozonolysis furnished aldehyde **24a**, which was readily purified by chromatography without loss of the MIP group.

Radical cyclization of **24a** and **24b** with *n*-Bu_3SnH and AIBN in refluxing benzene revealed new and interesting aspects of this poorly explored reaction. As shown in Scheme 6, compound **24a** produced a mixture of *cis* alcohol **26a** (56% chromatographed, major product), *trans* alcohol **27a** (6% chrom), and aldehyde **28a** (15% chrom). By contrast, compound **24b** furnished a mixture of *cis* alcohol **26b** (31% chrom) and aldehyde **28b** (27% chrom). *Trans* alcohol **27b** escaped detection, possibly due to the small quantities obtained.[17] The stereochemistry of **26** and **27** was assigned on the basis of cyclic acetonide formation (Scheme 7). Thus, *in all cases radical cyclization was appreciably diastereoselective for the cis isomer of the product*.

While a fair amount of stereochemical information is already available regarding radical additions to olefins,[18] the corresponding reactions of aldehydes have not been studied in detail.[11] It is significant that the observed selectivity is consistent with a Felkin−Ahn-like mode of addition[19] of the radical species to the carbonyl π system (Scheme 8). This may reflect the fact that the major frontier orbital interaction in the current process is probably one between the carbonyl π^* (LUMO) and the radical SOMO. Felkin−Ahn-type stereoelectronic effects that reduce the energy of the LUMO, thereby narrowing the SOMO−LUMO energy gap, should accelerate the rate of radical addition, much as they accelerate nucleophilic additions. It should be emphasized that the applicability of the Felkin−Ahn model to radical additions to carbonyls remains to be researched in greater detail.

Aldehyde **28** is believed to result from fragmentation of presumed oxy radical intermediates **32**/**33** (cf. Scheme 8).[11a,b] This fragmentation seems to occur at a rate comparable to that of bimolecular H-atom transfer from the tin hydride to the oxy radicals. Attempts to suppress fragmentation by varying the concentration of reactants, or by providing a large amount of *n*-Bu_3SnH in the hope of favoring bimolecular H-transfer, were unsuccessful. Whereas this may not be surprising, since intramolecular processes are often much faster than bimolecular ones, it is also noteworthy, in that it signifies that the ratio of cyclization product to aldehyde is an intrinsic function

(13) Review: Fatiadi, A. J. *Synthesis* **1976**, 65.

(14) Reaction of 2-butyne-1,4-diol with 1.0 equiv of Ac_2O in pyridine gave the monoacetate in 50% chromatographed yield, plus diacetate (25%) and unreacted starting diol (25%).

(15) A catalyst for enantioselective ene-like reactions similar to ours has been described by: Carreira, E.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. The Carreira catalyst is reported to produce excellent results with ynals, but not with enals. By contrast, our catalytic system works well with enals, but ynals are less successful.

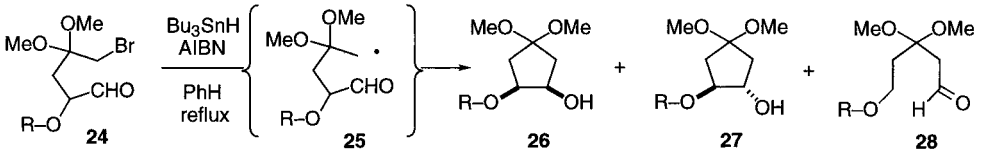
(16) This ene product was obtained in 80% yield, but it was contaminated with small amounts of byproducts of unknown structure. Purification to homogeneity was difficult.

(17) The stereochemistry of **26**−**27** was assigned on the basis of cyclic acetonide formation as described in: Ciufolini, M. A.; Zhu, S. *Tetrahedron Lett.* **1997**, *38*, in press.

(18) Cf., e.g.: (a) Morikawa, T.; Washio, Y.; Harada, S.; Hanai, R.; Kayashita, T.; Nemoto, H.; Shiro, M.; Taguchi, T. *J. Chem. Soc., Perkin Trans. 1* **1995**, 271. (b) Lesueur, C.; Nauguier, R.; Bertrand, M. P.; Hoffmann, P.; DeMesmaecker, A. D. *Tetrahedron* **1994**, *50*, 767. (c) Curran, D. P.; Sun, S. *Tetrahedron Lett.* **1993**, *34*, 6181 and references cited therein. See also ref 19, pp 935 ff.

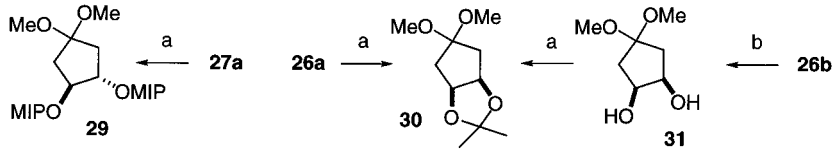
(19) For a detailed discussion of the Felkin−Anh model, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; pp 875−880.

Scheme 6



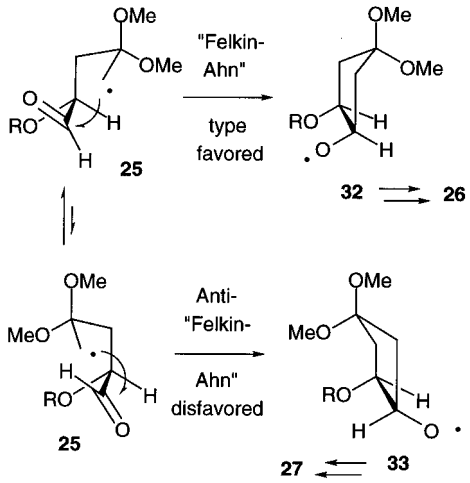
a series: R = MIP	56%	6%	15 %
b series: R = $SiEt_3$	31%	not detected	27%

Scheme 7[a]

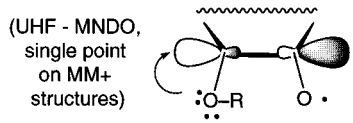


Key: (a) 2-methoxypropene, cat. PPTS, CH_2Cl_2, rt; (b) TBAF, THF, rt.

Scheme 8



Scheme 9



	Partial charge on R–O	Partial charge on O•
R = MIP	– 0.3 e	– 0.1 e
R = TES	– 0.6 e	– 0.1 e

of the nature of the O-protecting group present at the α-position of the aldehyde. The above observation may be rationalized as follows. Consider the electronic makeup of the C−C bond that undergoes fragmentation in presumed radical intermediates **32** and **33**. This bond is highlighted in Scheme 9. Hyperconjugative dispersal of nonbonding electrons from the protected O atom into the C−C antibonding σ orbital, σ^*_{C-C}, should facilitate C−C bond fragmentation, since it would lower the bond order between the two C atoms and thereby weaken the bond. Consequently, increasing negative charge concentration on the protected oxygen would be expected to accelerate the rate of bond breaking. A similar argument has been put forth to rationalize the greatly enhanced rate of oxy-Cope reactions, and anionic variants thereof, relative to plain Cope processes.[20] Considerations of relative electronegativity of C (more electronegative) vs Si (less electronegative) atoms already suggest that an O−Si bond will be more highly polarized than an O−C bond; therefore, a greater extent of partial negative charge will be present on the silyl ether oxygen relative to the MIP ether oxygen. Fragmentation should thus be favored in the silyl ether series. The above hypothesis was confirmed by the simple calculation summarized in Scheme 9.[21] Single point UHF-MNDO on MM+ structures of *cis* oxy radical intermediate **32** suggest that the electron density on the protected oxygen doubles in going from MIP acetals to silyl ethers. Thus, the C−C bond about to rupture is weaker in the silyl substrate, and a greater proportion of fragmentation product is observed. Notice also that the nature of the O-blocking group has no effect on the electronic properties of the oxy radical center. Identical electronic properties are are calculated for *trans* diastereomer **33**. The possibility that the rate of fragmentation of oxy radical intermediates may be sterically accelerated, in the sense that more sterically compressed molecules may fragment more readily, was briefly explored by estimating the steric energy content (MM+ force field) of structures **34** and **35**, computationally better tractable congeners of **32**−**33**. As seen in Figure 2, the MIP series of compounds is more sterically encumbered than the silyl series,[22] while *cis* diastereomers are slightly more energetic than the *trans* isomers. If steric acceleration of radical fragmentation were operative, one would expect a greater extent of fragmentation in the MIP series and among the *cis* disatereomers of the presumed radical intermediates. This is the exact opposite of what is observed experimentally. At this time, therefore, we do not believe that steric effects play a significant role here.

The conversion of the mixture of alcohols **26a**/**27a** to enone **3** was effected as shown in Scheme 10. Ley-type oxidation with *N*-methylmorpholine *N*-oxide (NMO) and

(20) Cf., e.g., (a) Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765. (b) Evans, D. A.; Baillargeon, D. J.; Nelson, J. V. *J. Am. Chem. Soc.* **1978**, *100*, 2242. (c) Koreeda, M; Luengo, J. I. *J. Am. Chem. Soc.* **1985**, *107*, 5572.

(21) Calculation were carried out with the Hyperchem 4.0 package, available from Hypercube, Inc., Ontario, Canada.

(22) Recall that an Si−O bond is rather long compared to a C−O bond: approximately 1.64 Å vs 1.43 Å. Because steric interactions are inversely dependent on the 6th power of the distance between groups, the steric interactions between the silyl subunit and the rest of the molecule are not as severe as those created by an MIP unit.

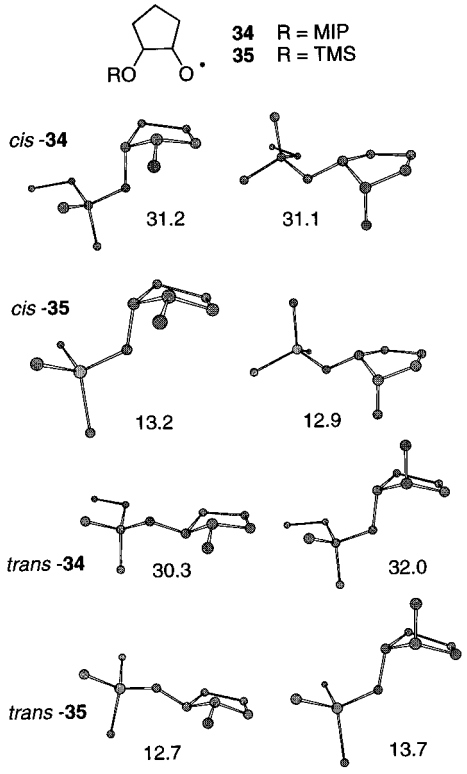
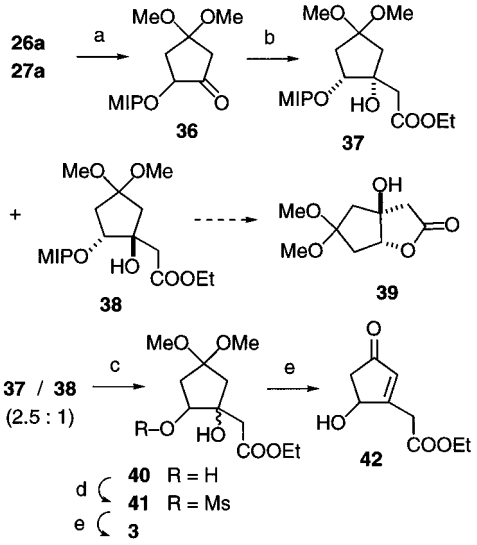


Figure 2. Steric energy content (MM+, kcal/mol) of the conformers of *cis* and *trans* diastereomers of radical intermediates **34** and **35**. For the sake of clarity, hydrogen atoms and lone pairs are not shown.

Scheme 10[a]

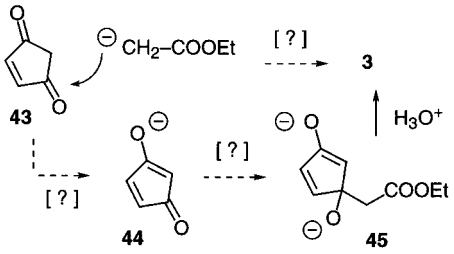


Key: (a) TPAP/NMO, CH_2Cl_2, 100%; (b) LDA, EtOAc, −78 °C, 81%; (c) 10% AcOH/H_2O 92%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C; (e) 80% AcOH/H_2O, 75% of **3d,e**.

catalytic tetrapropylammonium perruthenate (TPAP)[23] furnished ketone **36**, which combined with the enolate of EtOAc leading to a roughly 2.5:1 mixture of diastereomers **37** (major) and **38** (minor). The stereochemical assignment of these compounds rests on the facile lactonization of minor diastereomer **38** to give **39**, whereas the major product resisted lactonization. The observed

(23) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

Scheme 11



stereochemical course suggests a prevalent chelation-controlled addition of the enolate into the α-alkoxy ketone.[24] The poor diastereoselectivity observed in this reaction is probably a consequence of the generally weak ability of Li^+ organometallics to engage in chelation-controlled carbonyl additions.[25] On the other hand, acetals (cf. the MIP group in **36**) are well recognized for their strong coordinating/directing ability in metalation reactions by organolithium agents.[26] This directing ability may partially overcome inherent inadequacies of lithium enolates.

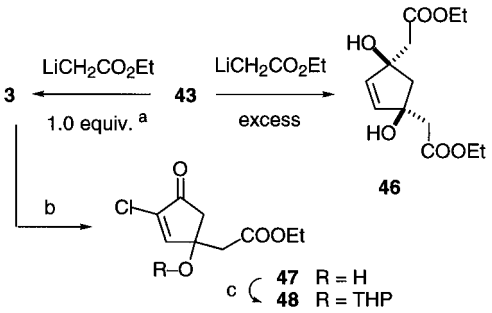
Removal of the MIP group in the mixture of **37**/**38** gave diol **40**, whose secondary hydroxyl unit was activated by conversion to mesylate **41** in preparation for acetal hydrolysis. This step was performed with 80% aqueous AcOH under conditions that induced simultaneous β-elimination of mesylate to afford enone **3**. It should be noted that direct acid hydrolysis of **37**/**38** or of **40** gave enone **42** via β- elimination of the sensitive tertiary OH. Creation of a mesylate was thus necessary to ensure the correct regioselectivity of enone formation.

A Practical Synthesis of (±)-Chlorovulone II

An even more efficient alternative for the assembly of **3** may be envisioned on the basis of a new strategic idea: a 1,2-addition of the enolate of ethyl acetate into 4-cyclopentene-1,3-dione, **43**. This commercially available, if moderately expensive ($14/g or $1.4/mmol), building block seems to have received very little attention as an educt for prostanoid synthesis.[27] Indeed, the compound has found primary use in Diels−Alder reactions,[28] conjugate addition,[29] and Knoevenagel chemistry,[30] but we were unable to find a recorded example of enolate addition to **43**. A potential difficulty with such an operation might be base-promoted enolization of the β-diketone (Scheme 11). However, the resultant anion **44** displays antiaromatic character by virtue of its cyclopentadienone nature. This should both disfavor enolization and promote 1,2-addition of excess enolate to the remaining, reactive carbonyl. Dianion **45** thus formed would still produce enone **3** upon acidic workup,

(24) Cf., e.g.: Still, W. C.; Schneider, J. A. *J. Org. Chem.* **1980**, *45*, 3375.
(25) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.
(26) Gschwend, H.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1.
(27) Cf., e.g.: Tolstikov, G. A; Miftakhov, M. S.; Danilova, N. A.; Vel'der, Y. L.; Shirikhin, L. V. *Zh. Org. Khim.* **1989**, *25*, 438.
(28) Cf. (a) Lu, H.-J.; Llinas-Brunet, M. *Can. J. Chem.* **1984**, *62*, 1747. (b) Cardinale, G.; Laan, J. A. M.; Ward, J. P. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 62. (c) Paquette, L. A.; Vannucci, C.; Rogers, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 5792. (d) Houwen-Claassen, A. A. M.; Klunder, A. J. H.; Kooy, M. G; Steffann, J.; Zwanenburg, B. *Tetrahedron* **1989**, *45*, 7109.
(29) Cf. Lepitskaya, M. A.; Manukina, T. A.; Pivnitskii, K. K. *Zh. Org. Khim.* **1986**, *22*, 872.
(30) Cf. Takahashi, K.; Namekata, N.; Takase, K.; Takeuchi, A. *Tetrahedron Lett.* **1987**, *28*, 5683.

Scheme 12[a]



Key: (a) from EtOAc + LDA, THF, −78 °C, 86%; (b) Cl_2 gas, CCl_4, then Et_3N, 77%; (c) DHP, CSA, CH_2Cl_2, rt, 100%.

rendering **43** still serviceable for the ultimate production of the desired subgoal.

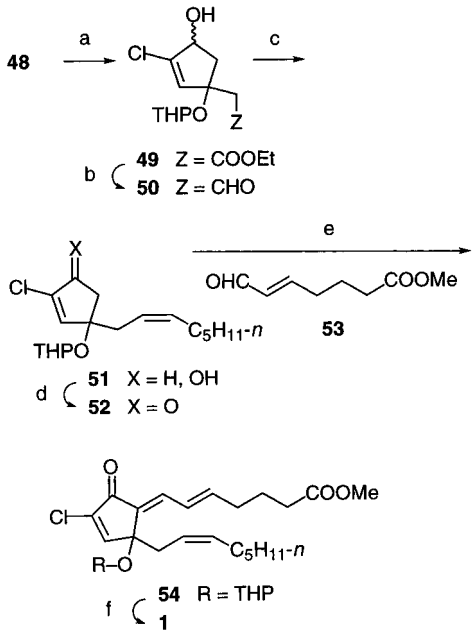
Treatment of **43** with 1.0 equiv of ethyl acetate enolate cleanly furnished enone **3** in 86% yield (Scheme 12). Excess enolate must be avoided in this reaction, in order to suppress formation of the double addition product, **46**. This material, which seemingly was obtained as a single diastereomer within the limits of ^{1}H NMR spectroscopy, represented as much as 30% of the product when **43** was treated with 2 equiv of the enolate. The stereochemistry of **46** is tentatively assigned as *cis*, by analogy with precedent.[8] The observed formation of **46** rules against the intervention of anion **44**, ergo enolization of **43**, since no further nucleophilic addition would be possible to dianion **45**.

Regioselective introduction of a chlorine atom into **3** was accomplished by standard treatment with excess Cl_2 gas in CCl_4, followed by Et_3N (Scheme 12). Subsequent experiments indicated that it is possible to advance chloroenone **47** into the synthesis without protection of the tertiary alcohol. However, several technical problems arose as a consequence, details of which will be discussed shortly. This necessitated protection of the tertiary OH group as a THP ether to give **48**. A minor problem with this protecting group was the introduction of a new stereogenic center (the "anomeric" site) without stereocontrol. Although diastereomers were formed as a consequence, no significant difficulties were encountered during scrutiny of the NMR spectra of this intermediate and subsequent derivatives thereof.

Reduction of **48** with DIBAL furnished aldehyde **50**, a good substrate for Wittig installation of the lower side chain. However, the cyclopentenone moiety underwent 1,4-reduction to a varying extent under such conditions, rendering the yield of this step unsatisfactory. This problem was corrected by Luche reduction[31] of **48** to allylic alcohol **49**, as a 1:1 mixture of diastereomers, followed by DIBAL reduction to aldehyde **50**. Fortunately, no protection of the secondary allylic alcohol in **50** was necessary during subsequent manipulations. By contrast, it was difficult to reduce compound **47** to an analog of aldehyde **50** lacking a THP protecting group at the tertiary alcohol. Severe difficulties were also observed upon reoxidation of the secondary alcohol in an unprotected variant of compound **51**. These hurdles vanished when the labile tertiary hydroxy unit was blocked as a THP ether.

Conversion of **50** to chlorovulone II proceeded uneventfully. Treatment of with *n*-hexylidenetriphenylphosphorane in THF/*N*,*N*′-dimethylperhydropyrimidin-2-one ("DMPU") gave the *Z*-olefin **51**,[32] which was oxidized to enone **52** by PDC in DMF.[33] The use of DMPU was essential for maximum efficiency and *Z* selectivity. Condensation of the lithium enolate of **52** with 1.0 equiv of known[8] aldehydo ester **53**[34] under conditions substantially similar to those described by Yamada[8] afforded chlorovulone II THP ether (**54**) as a single geometric isomer in 82% yield. Finally, removal of the THP group in **54** with TsOH in MeOH provided totally synthetic **1** (Scheme 13).

Scheme 13[a]



Key: (a) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, 88%; (b) DIBAL, THF, −78 °C, 79%; (c) $Ph_3P^+(CH_2)_5CH_3Br^-$, BuLi, THF, DMPU, −40 °C, 80%; (d) PDC, DMF, 83%; (e) LDA, **53**, THF, 82%; (f) TsOH, MeOH rt, 88%; 21% overall from **43** over nine steps.

In summary, quantities of chlorovulone II are now efficiently available in nine steps from commercial 4-cyclopentene-1,3-dione and in an overall yield of 21%. Other clavulones should be accessible by minor modifications of our strategy. Ring-labeled anologues of **1** that might be needed for biological studies are available through a combination of our carbonyl−ene-like reaction and aldehyde−radical cyclization. This latter step has been shown to proceed with significant stereoselectivity. Mechanistic and synthetic studies of these radical processes continue in our laboratory.

Experimental Section[35]

1-Phenyl-3-[(2-methoxy-2-propyl)oxy]-5-methoxyhexa-1,5-diene (19). Silica gel (1 g) was added to a solution of cinnamaldehyde (6.74 g, 51 mmol), 2-methoxypropene (30 mL, 6 equiv), CH_2Cl_2 (60 mL), AcOH (10 mL, 2 mol %), and Yb(fod)$_3$ (100 mg, 2 mol %). The mixture was stirred at rt for 18 h,

(31) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

(32) For a review of the Wittig reaction see: Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1.

(33) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

(34) Reference 8 describes a route to **53** that involves three steps from δ-valerolactone: (i) methanolysis, (ii) Swern oxidation of the hydroxy ester, and (iii) Wittig reaction. A more practical two-step alternative involving a Schreiber ozonolysis (Claus, R. E., Schreiber, S. L. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 168. Schreiber, S. L.; Claus, R. E.; Regan, J. *Tetrahedron Lett.* **1982**, *23*, 3867) is detailed in the Experimental Section.

and then it was diluted with ether (200 mL), washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated to give 14.1 g (100% yield) of **19** as a light yellow oil. ^1H (C_6D_6): 7.28−7.01 (5H), 6.53 (d, 1H, J = 16.0), 6.29 (dd, 1H, J = 16.0, 7.1), 4.82 (m, 1H), 3.97 (d, 1H, J = 1.7), 3.84 (d, 1H, J = 1.7), 3.18 (s, 3H), 3.15 (s, 3H), 2.70 (dd, 1H, J = 13.5, 6.2), 2.44 (dd, 1H, J = 13.5, 7.0), 1.39 (s, 3H), 1.36 (s, 3H). ^{13}C (C_6D_6): 161.3, 138.1, 133.3, 130.3, 129.1, 127.9, 127.1, 101.4, 83.7, 70.6, 54.7, 49.5, 44.2, 26.5, 25.8. IR: 1663, 1615, 1504, 1234, 1213, 1157, 1067, 1032. MS: 277 $(M + H)^+$, 245, 205, 187, 173, 73. HRMS: calcd for $C_{17}H_{25}O_3$ $(M + H)^+$ 277.1804, found 277.1800.

1-Phenyl-3-[(2-methoxy-2-propyl)oxy]-5,5-dimethoxy-6-bromohex-1-ene (21). A solution of **19** (10 g, 36.2 mmol) in CH_2Cl_2 (30 mL) was added into a mixture of NBS (6.5 g, 36.5 mmol), MeOH (20 mL), CH_2Cl_2 (120 mL), and powdered $NaHCO_3$ (0.5 g) at −78 °C. After 30 min, the mixture was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated to give 12.2 g (87%) of **21**, as a colorless oil. ^1H (C_6D_6): 7.41−7.21 (5H), 6.52 (d, 1H, J = 16.0), 6.30 (dd, 1H, J = 16.0, 8.1), 4.45 (m, 1H), 3.55 (s, 2H), 3.25 (s,2H), 3.23 (s, 3H), 3.21 (s, 3H), 2.25 (dd, 1H, J = 15.1, 5.9), 2.15 (dd, 1H, J = 15.1, 7.0), 1.44 (s, 3H), 1.37 (s, 3H). ^{13}C (C_6D_6): 137.1, 132.3, 130.3, 128.7, 127.7, 126.6, 101.3, 100.6, 69.1, 49.6, 48.6, 48.4, 38.6, 32.7, 26.0, 25.4. IR: 1254, 1212, 1150, 1067, 1019. MS: m/z 357 [$(M + H)^+$ − MeOH, ^{81}Br], 355 [$(M + H)^+$ − MeOH, ^{79}Br], 299, 297, 169, 167, 73. HRMS: calcd for $C_{17}H_{24}O_3{}^{79}Br$ [$(M + H)^+$ − MeOH] 355.0909, found 355.0906.

2-[(2-Methoxy-2-propyl)oxy]-4,4-dimethoxy-5-bromopentanal (24a). Ozonized oxygen was bubbled through a cold (−78 °C), well-stirred mixture of **21** (6.65 g, 17.2 mmol), powdered $NaHCO_3$ (0.75 g), MeOH (10 mL), and CH_2Cl_2 (100 mL) until the mixture turned blue. Me_2S (4.5 mL) was added, and then the reaction was warmed to rt, washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated. Chromatography (10% EtOAc/hexane) gave 4.3 g (80%) of **24a** as a colorless oil. R_f = 0.25. ^1H (C_6D_6): 9.50 (d, 1H, J = 3.0), 4.05 (dt, 1H, J = 5.6, 3.0), 3.60 (d, 1H, J = 11.0), 3.46 (d, 1H, J = 11.0), 3.20 (s, 3H), 3.15 (s, 3H), 3.11 (s, 3H), 2.19 (dd, 1H, J = 15.2, 5.6), 2.13 (dd, 1H, J = 15.2, 5.6), 1.36 (s, 3H), 1.29 (s, 3H). ^{13}C (C_6D_6): 202.9, 101.7, 100.4, 72.8, 49.6, 48.6, 48.5, 34.1, 33.4, 25.3, 24.5. IR: 1733, 1254, 1213, 1074, 1053. MS: m/z 283 [$(M + H)^+$ − MeOH, ^{81}Br], 281 [$(M + H)^+$ − MeOH, ^{79}Br], 251, 249, 223, 221, 73. HRMS: calcd for $C_{10}H_{18}O_4{}^{79}Br$ [$(M + H)^+$ − MeOH] 281.0388, found 281.0386.

***cis*- (26a) and *trans*-2-[(2-Methoxy-2-propyl)oxy]-4,4-dimethoxycyclopentan-1-ol (27a) and 3,3- Dimethoxy-5-[(2-methoxy-2-propyl)oxy]penntanal (28a).** A benzene (450 mL) solution of **24a** (3.6 g, 11.5 mmol), *n*-Bu_3SnH (4.0 g, 13.8 mmol), and AIBN (10 mg) was refluxed for 2 h. The solution was then cooled and concentrated. Chromatography (20% EtOAc/hexane) gave 1.67 g (62%) of a mixture of alcohol **26a** and **27a** (10:1 ratio, ^1H NMR), R_f = 0.15, and 0.41 g (15%) of aldehyde **28a**, R_f = 0.44, both as colorless oils. **26a** (major diastereomer). ^1H (C_6D_6): 4.20 (m, 2H), 3.08 (s, 3H), 3.00 (s, 3H), 2.99 (s, 3H), 2.35 (m, 2H), 1.93 (m, 2H), 1.26 (s, 6H). ^{13}C (C_6D_6): 107.2, 101.1, 77.6, 76.4, 49.1, 49.0, 48.7, 41.6, 41.4, 25.7, 25. IR: 3466, 1254, 1219, 1143, 1080, 1046. MS: 203 [$(M + H)^+$ − MeOH], 185, 113, 73. HRMS: calcd for $C_{10}H_{19}O_4$ [$(M + H)^+$ − MeOH] 203.1283, found 203.1281. **28a**: ^1H (C_6D_6): 9.65 (t, 1H, J = 2.9), 3.42 (t, 2H, J = 6.6), 3.01 (s, 3H), 2.93 (s, 3H), 2.57 (d, 2H, J = 2.9), 1.93 (t, 2H, J = 6.6), 1.18 (s, 6H). ^{13}C (C_6D_6): 199.8, 101.0, 100.4, 56.5, 48.6, 48.5, 48.1, 35.7, 24.7. IR: 1719, 1268, 1213, 1164, 1116, 1039. MS: 205 [$(M + H)^+$ − CHO], 161, 145, 113, 73. HRMS: calcd for $C_{10}H_{21}O_4$ [$(M + H)^+$ − CHO] 205.1440, found 205.1436.

(35) **Experimental protocols**. NMR spectra (ppm, δ, ^1H = 250; ^{13}C = 62.5 MHz, 25 °C, J in Hz) were recorded in $CDCl_3$, unless otherwise indicated. FTIR spectra (cm^{-1}) were obtained from thin films on NaCl plates. Low- and high-resolution mass spectra (*m/e*) were obtained in the CI (CH_4) mode. Microanalyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. All sensitive reactions were carried out under Ar. Reagent and solvent were used as received, except CH_2Cl_2, *i*-Pr_2NH, Et_3N: distilled from CaH_2; EtOAc and 2-methoxypropene: distilled; MeOH: dried over 4 Å molecular sieves; NBS: recrystallized from H_2O; THF: freshly distilled from Na/Ph_2CO.

Ethyl 2-(1-Hydroxy-3-oxocyclopent-4-enyl)acetate (3). (a) From Alcohols 26a/27a. A CH_2Cl_2 (10 mL) solution of the mixture of alcohols (1.23 g, 5.3 mmol) was added to a slurry of TPAP (50 mg, 0.03 equiv), NMO (770 mg, 1.25 equiv), and coarsely powdered molecular sieves (0.5 g) in CH_2Cl_2 (40 mL) at rt. After 1 h, the dark mixture was poured into hexanes (120 mL), causing precipitatation of Ru compounds. The solid was filtered off, and the filtrate was concentrated to give 1.22 g (100%) of ketone **36**, pale yellow oil. A a solution of this ketone in THF (3 mL) was added into a cold (−78 °C) solution of the enolate of ethyl acetate [preformed at −78°C in THF (10 mL), under Ar, from BuLi (2.5 M in hexane, 2.6 mL, 6.5 mmol), *i*-Pr_2NH (0.8 mL, 6.3 mmol), and EtOAc [0.5 mL, 5.3 mmol)]. After 20 min, the mixture was warmed to rt, quenched (saturated aqueous $NaHCO_3$), and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give 1.37 g (81%) of a mixture of esters **37** and **38** as a colorless oil, a solution of which in THF (10 mL) and 10% aqueous AcOH (5mL) was stirred at rt for 4 h, and then it was neutralized (saturated aqueous $NaHCO_3$) and extracted with CH_2Cl_2. The combined extracts were dried (Na_2SO_4) and concentrated to give 0.98 g (92%) of diols **40** as a colorless oil. These diols were treated with MsCl (0.3 mL, 4.3 mmol) and Et_3N (1.5 mL) in CH_2Cl_2 (15 mL) at 0 °C, and after 10 min the solution was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated. The resulting mesylates **41** were dissolved in 80% aqueous AcOH (4 mL) at rt, and after 2 h, the solution was neutralized (saturated aqueous $NaHCO_3$), and extracted (CH_2Cl_2). The combined extracts were dried (Na_2SO_4) and concentrated to give 0.55 g (75%, over two steps) of enone **3**, colorless oil.

(b) From 4-Cyclopentene-1,3-dione, 43. A THF (10 mL) solution of **43** (3.0 g, 31.0 mmol) was introduced into a cold (−78 °C) solution of ethyl acetate enolate prepared as described above from EtOAc (3.1 mL, 31.0 mmol). After 20 min, the mixture was warmed to rt, quenched (saturated aqueous $NaHCO_3$), and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give 4.8 g (86%) of **3** as a colorless oil. ^1H: 7.52 (d, 1H, J = 5.8), 6.17 (d 1H, J = 5.8), 4.22 (q, 2H, J = 7.1), 2.80 (d, 1H, J = 16.5), 2.70 (d, 1H, J = 16.5), 2.62 (d, 1H, J = 18.4), 2.49 (d, 1H, J = 18.4), 1.29 (t, 3H, J = 7.1). ^{13}C: 206.2, 171.5, 164.2, 133.8, 76.5, 61.3, 48.9, 43.8, 14.1. IR: 3452, 1719, 1213, 1026. MS: 185 $(M + H)^+$, 167, 139. HRMS: calcd for $C_9H_{13}O_4$ $(M + H)^+$ 185.0814, found 185.0812. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69;, H, 6.57. Found: C, 58.82; H, 6.54.

Ethyl 2-(4-Chloro-1-hydroxy-3-oxocyclopent-4-enyl)-acetate (47). Chlorine gas was bubbled through a CCl_4 (15 mL) solution of **3** (1.4 g, 7.6 mmol) at 0 °C, until the Cl_2 color persisted. After 20 min, Et_3N (5 mL) was added. The mixture was warmed to rt, diluted with ether (120 mL), washed (water, then brine), dried (Na_2SO_4), and concentrated to give 1.3 g (77%) of **47** as a colorless oil. ^1H: 7.47 (s, 1H), 4.23 (q, 1H, J = 7.2), 2.85 (d, 1H, J = 16.7), 2.77 (d, 1H, J = 18.4), 2.72 (d, 1H, J = 16.7), 2.64 (d, 1H, J = 18.4), 1.30 (t, 3H, J = 7.2). ^{13}C: 197.4, 171.5, 156.9, 137.1, 73.8, 61.6, 48.2, 43.8, 14.2. IR: 1726, 1594, 1296, 1206, 1019. MS: 221 and 219 $(M + H)^+$, 203 and 201. HRMS: calcd for $C_9H_{12}O_4{}^{35}Cl$ $(M + H)^+$ 219.0424, found 219.0421. Anal. Calcd for $C_9H_{12}O_4Cl$: C, 49.44; H, 5.07. Found: C, 49.35; H, 5.06.

Ethyl 2-(1-(2-Oxanyloxy)-4-chloro-3-hydroxycyclopent-4-enyl)acetate (49). Dihydropyran (0.5 g, 5.6 mmol) was added to a CH_2Cl_2 (15 mL) solution of **47** (1.1 g, 5.1 mmol) and camphorsulfonic acid ("CSA", 30 mg, 0.13 mmol) at 0 °C. The mixture was warmed to rt, and after 1 h Et_3N (0.1 mL) was added to neutralize CSA. The mixture was diluted (CH_2Cl_2, 20 mL), washed with water, dried (Na_2SO_4), and concentrated to give **48** (1.6 g, 100%, colorless oil). A cold (0 °C) MeOH (10 mL) solution of this compound and $CeCl_3{\cdot}7H_2O$ (1.9 g, 5.1 mmol) was treated with powdered $NaBH_4$ (0.3 g). After 15 min, the reaction was quenched (saturated aqueous NH_4Cl) (**CAUTION**: H_2 gas evolved) and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated. Chromatography (50% EtOAc/hexanes) gave 1.37 g (88%) of alcohols **49** as a colorless viscous oil. R_f = 0.62. ^1H NMR of

one of the four diastereomers: 6.03 (s, 1H), 4.85 (t, 1H, J = 3.7), 4.60 (m, 1H), 4.26 (d, 2H, J = 3.1), 4.03 (q, 2H, J = 7.1), 3.81 (m, 1H), 3.40 (m, 1H), 2.77 (dd, 1H, J = 15.0, 6.1), 2.66 (d, 1H, J = 12.3), 2.48 (d, 1H, J = 12.3), 2.15 (dd, 1H, J = 15.0, 3.5), 1.41−1.70 (m, 6H), 1.17 (t, 3H, J = 7.1). ^{13}C of one of the four diastereomers: 170.6, 143.0, 132.6, 94.6, 85.0, 76.1, 62.7, 60.6, 45.6, 45.2, 31.6, 25.3, 19.8, 14.2. IR: 3418, 1726, 1629, 1206, 1109, 1019. MS: 307 and 305 $(M + H)^+$, 289 and 287, 269, 205. HRMS: calcd for $C_9H_{22}O_5{}^{35}Cl$ $(M + H)^+$ 305.1156, found 305.1151. Anal. Calcd for $C_9H_{21}O_5Cl$: C, 55.17; H, 6.95. Found: C, 55.04; H, 6.95.

4-(2-Oxanyloxy)-2-chloro-4-oct-2-enylcyclopent-2-en-1-one (52). DIBAL-H (1.5 M in toluene, 6.3 mL) was added to a THF (20 mL) solution of alcohols **49** (1.3 g, 4.3 mmol) at −78 °C. After 2 h, MeOH was added dropwise to the cold solution until no more bubbling was apparent (**CAUTION**: flammable gases released). The mixture was partitioned between water (60 mL) and ether (200 mL). The combined extracts were dried (Na_2SO_4) and concentrated to give 0.9 g (79%) of aldehyde **50** as a colorless oil. Without further purification, this aldehyde in THF (5 mL) was added to a cold (−40 °C) slurry of hexylidenetriphenylphosphorane [preformed at 0 °C from $CH_3(CH_2)_5Ph_3P^+$ I^- (2.9 g, 6.6 mmol) and BuLi (2.5 M in hexane, 2.7 mL) in THF (20 mL), followed by addition of DMPU (10 mL) after 10 min]. After 15 min, the Wittig reaction was quenched (saturated aqueous $NaHCO_3$, 10 mL) and extracted with ether. The combined extracts were concentrated, and the residue was treated with petroleum ether (40 mL), causing formation of a precipitate (phosphine oxide), which was filtered off. The filtrate was concentrated to give 0.9 g (80%) of olefin **51** as a colorless oil. A DMF (3 mL) solution of this olefin was added to a DMF (5 mL) solution of PDC (2.0 g, 5.4 mmol) at rt. After 2 h, the mixture was diluted (ether, 150 mL), washed (H_2O), dried (Na_2SO_4), and concentrated. Chromatography (10% EtOAc/hexanes) gave 0.7 g (83%) of **52** as a colorless oil, R_f = 0.43. ^{1}H NMR of one of the two diastereomers: 7.47 (s, 1H), 5.57 (m, 1H), 5.33 (m,1H), 4.69 (t, 1H, J = 2.1), 3.89 (m, 1H), 3.42 (m, 1H), 3.00 (d, 1H, J = 18.5), 2.59 (m, 2H), 2.54 (d, 1H, J = 18.5), 2.01 (m, 2H), 1.52−1.81 (m, 6H), 1.28 (m, 6H), 0.87 (t, 3H, J = 6.7). ^{13}C of one of the two diastereomers: 197.5, 158.9, 136.9, 134.4, 122.0, 95.3, 80.6, 80.4, 63.1, 45.4, 37.2, 31.4, 29.0, 27.4, 25.1, 22.5, 19.9, 13.9. IR: 1729, 1603, 1297, 1198, 1105, 1018. MS: 329 and 327 $(M + H)^+$, 311 and 309. HRMS: calcd for $C_{18}H_{28}O_3{}^{35}Cl$ $(M + H)^+$ 327.1727, found 327.1724. Anal. Calcd for $C_{18}H_{27}O_3Cl$: C, 66.14; H, 8.33. Found: C, 66.02; H, 8.34.

Methyl 7-Oxohept-5-enoate (53). Ozonized oxygen was bubbled into a cold (−78 °C) mixture of cyclopentene (2 mL, 23 mmol), $NaHCO_3$ (300 mg), MeOH (6 mL), and CH_2Cl_2 (30 mL) until a blue color persisted, and then N_2 was bubbled through the solution until the blue color disappeared. The reaction mixture was diluted with benzene (150 mL) and concentrated to about 65 mL. This solution was treated with Et_3N (6.4 mL, 2 equiv) and Ac_2O (4.3 mL, 2 equiv) at 0 °C for 1 h, and then it was washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated (**CAUTION**: its is advisable to test the solution for residual peroxides) to give 2.8 g (92%) of methyl 5-oxopentanoate, colorless liquid. A solution of this material (0.7 g, 5.4 mmol) and (formylmethylene)triphenylphosphorane (3.5 g, 11.3 mmol) in toluene (30 mL) was heated at 60 °C for 3 h, and then it was cooled and poured into petroleum ether (200 mL). The precipitate was filtered off, the filtrate was concentrated, and the residue was chromatographed (30% EtOAc/hexane) to give 0.7 g (84%) of **53** as a colorless oil. R_f = 0.31. ^{1}H: 9.51 (d, 1H, J = 7.7), 6.82 (dt, 1H, J = 15.7, 6.7), 6.13 (ddt, 1H, J = 15.7, 7.7, 1.0), 3.68 (s, 3H), 2.35 (m, 4H), 1.86 (quintet, 2H, J = 7.4). ^{13}C (C_6D_6): 192.9, 173.0, 156.0, 133.9, 51.4, 33.3, 31.9, 23.4. IR: 1729, 1696, 1636, 1204, 1171, 1118. MS: 157 $(M + H)^+$, 125. HRMS: calcd for $C_8H_{13}O_3$ $(M + H)^+$ 157.0865, found 157.0864.

(±)-Methyl 7-(3-Chloro-5-hydroxy-5-oct-2-enyl-2-oxocyclopent-3-enylidene)hept-5-enoate (Chlorovulone II, 1). A THF (1 mL) solution of **52** (104 mg, 300 μmol) was added to a cold (−78 °C) solution of LDA [preformed in THF (0.5 mL) at −78 °C from i-Pr_2NH (45 μL, 340 μmol) and BuLi (2.5 M in hexane, 150 μL, 370 μmol), phenanthroline indicator]. After 30 min, a THF (1 mL) solution of compound **53** was introduced. The mixture was warmed to −30 °C, quenched with saturated aqueous $NaHCO_3$, and extracted with ether. The combined extracts were dried (Na_2SO_4) and concentrated to give **54** in 82% yield. A solution of **54** (84 mg) and TsOH (10 mg) in MeOH (1 mL) was stirred for 1 h at rt, and then it was diluted with ether (10 mL), washed (saturated aqueous $NaHCO_3$), dried (Na_2SO_4), and concentrated to give (±)-chlorovulone II, **1**, as a colorless oil, in 88% yield. ^{1}H: 7.21 (s, 1H), 7.07 (d, 1H, J = 11.8), 6.76 (ddt, 1H, J = 15.1, 11.8, 1.7), 6.28 (dt, 1H, J = 15.1, 7.1), 5.57 (m, 1H), 5.24 (m, 1H), 3.69 (s, 3H), 2.80 (dd, 1H, J = 14.5, 7.5), 2.68 (dd, 1H, J = 14.5, 8.1), 2.36 (t, 2H, J = 7.4), 2.31 (q, 2H, J = 6.9), 2.00 (br q, 2H J = 7.1), 1.82 (quintet, 2H J = 7.4), 1.31−1.23 (m, 6H), 0.88 (t, 3H, J = 6.4). ^{13}C: 187.9, 173.9, 153.9, 147.9, 138.2, 135.2, 135.0, 134.3, 126.2, 122.0, 77.8, 51.9, 36.9, 33.5, 33.0, 31.7, 29.3, 27.6, 24.0, 22.7, 14.2. IR: 1736, 1709, 1629, 1284, 1198, 1164, 1052, 1038. MS: 383 and 381 $(M + H)^+$, 365 and 363, 333 and 331. HRMS: calcd for $C_{21}H_{30}O_4{}^{35}Cl$ $(M + H)^+$ 381.1833, found 381.1831. Anal. Calcd for $C_{21}H_{29}O_4Cl$: C, 66.22; H, 7.67. Found: C, 66.08; H, 7.65.

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