Intramolecular Conjugate Addition Reactions via Organozinc Compounds

Brian S. Bronk, Stephen J. Lippard,* and Rick L. Danheiser*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

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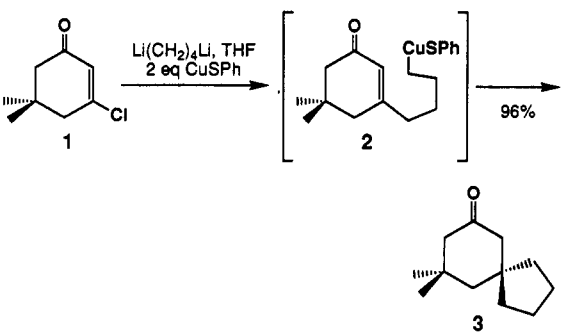
This paper describes the application of organozinc compounds in a general strategy for achieving intramolecular conjugate addition with nonstabilized carbanion derivatives. Organozinc iodides, prepared by the reaction of the corresponding organoiodides with activated zinc metal, undergo an intramolecular 1,4-addition reaction with α,β-unsaturated ketones and esters to form five- and six-membered-ring products. A mechanistic study suggests that, at most, only a small part of the cyclization product can result from a radical-mediated pathway. Both olefinic and acetylenic unsaturated carbonyl compounds participate in the intramolecular conjugate addition reaction. Addition of electrophilic reagents such as methyl iodide and acetaldehyde permits the in situ synthetic elaboration of the product enolates.

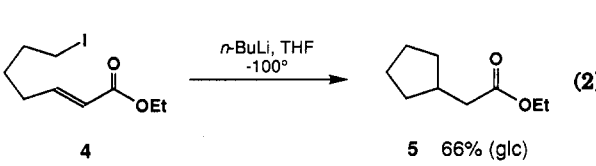
Introduction

Conjugate addition is defined as the addition of a nucleophile to a carbon–carbon π bond conjugated with an electron-withdrawing group. Historically, the conjugate addition reaction ranks as one of the most powerful methods for the construction of carbon–carbon bonds.[1] The Michael reaction, defined as the addition of a *stabilized* carbanionic synthon to an activated carbon–carbon π bond, is the oldest version of the conjugate addition reaction and continues to find wide use in synthesis. The advent of organocopper compounds has made the conjugate addition of *nonstabilized* carbanionic synthons a practical synthetic transformation, and in recent years the *intermolecular* conjugate addition of organocopper reagents to electron-deficient carbon–carbon π bonds has emerged as one of the most important strategies in organic synthesis.[2]

Considerable effort has been devoted to the development of the *intramolecular* variant of the conjugate addition reaction as a general method for ring construction. The utility of the intramolecular Michael reaction of stabilized carbanionic synthons is well documented, and recently this strategy has been of great service in the synthesis of complex natural products.[1a,b,3] On the other hand, the intramolecular conjugate addition of *nonstabilized* carbanionic synthons remains a strategy with very limited utility in organic synthesis. The fundamental problem complicating the design of this type of intramolecular conjugate addition reaction is the tactical difficulty of generating a reactive (nonstabilized) carbanionic species in the presence of an electrophilic π bond. To date, only a few scattered reports have appeared in the literature describing the successful implementation of this approach to ring formation. Prominent among the successful transformations in this area is the spiroannulation strategy of Wender, which employs the conjugate addition–elimination of an organobis(cuprate) reagent to generate a nonstabilized organocopper intermediate suitable for cyclization (eq 1).[4] More limited in scope are the intramolecular conjugate addition reactions reported by Cooke, in which halogen–metal exchange under carefully controlled conditions provides access to organolithium intermediates which undergo cyclization to form four- and five- (but not six-) membered rings (eq 2).[5] More recently,



1 2 3 (1)



4 5 66% (glc) (2)

Curran has described samarium iodide promoted intramolecular conjugate addition reactions leading to five-membered rings (eq 3) in which the samarium enolate

(1) For reviews, see: (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992. (b) Jung, M. E. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 1–67. (c) Lee, V. J. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 69–137. (d) Lee, V. J. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 139–168. (e) Schmalz, H.-G. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 199–268.

(2) For reviews, see: (a) Kozlowski, J. A. In *Comprehensive Organic Synthesis*; Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 169–198. (b) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (c) Posner, G. H. *Org. React.* **1972**, *19*, 1.

(3) For some recent examples of the application of the intramolecular Michael reaction in natural product synthesis, see: (a) Stork, G.; Winkler, J. D.; Shiner, C. S. *J. Am. Chem. Soc.* **1982**, *104*, 3767. (b) Baraldi, P. G.; Barco, A.; Benetti, S.; Pollini, G. P.; Polo, E.; Simonetta, D. *J. Org. Chem.* **1985**, *50*, 23. (c) Holton, R. A.; Kennedy, R. M.; Kim, H.-B.; Krafft, M. E. *J. Am. Chem. Soc.* **1987**, *109*, 1597. (d) Corey, E. J.; Su, W. *J. Am. Chem. Soc.* **1987**, *109*, 7534.

(4) (a) Wender, P. A.; White, A. W. *J. Am. Chem. Soc.* **1988**, *110*, 2218. (b) Wender, P. A.; White, A. W.; McDonald, F. E. *Org. Synth.* **1991**, *70*, 204.

(5) Cooke, M. P. *J. Org. Chem.* **1984**, *49*, 1144.

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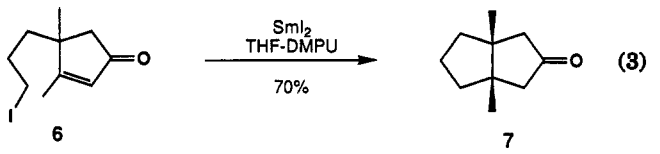
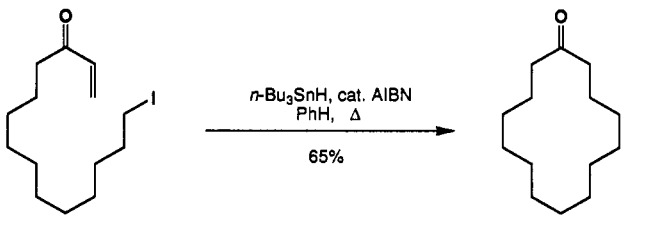


6 7 (3)

intermediates can be trapped in aldol condensations with aldehydes.[6] Kocovsky has recently reported an example of four-membered ring formation via the intramolecular conjugate addition of an organocopper compound generated by transmetalation from an organomercury precursor.[7] Finally, it should be noted that *effective* intramolecular conjugate addition can in some cases be achieved via free-radical intermediates.[8] Although subject to many limitations, this strategy has found considerable application in synthesis and serves as a valuable route to many carbocyclic and heterocyclic systems, including macrocycles (eq 4).[9]



8 9 (4)

In the present article we describe the application of organozinc compounds in a general strategy for achieving intramolecular conjugate addition with nonstabilized carbanion derivatives. The application of organozinc compounds as synthetic intermediates has been the focus of increased attention during the past decade. It is now well established that highly functionalized organozinc reagents can be generated by a variety of methods, including, most importantly, oxidative addition of activated zinc to carbon–iodine bonds. Organozinc compounds incorporating a wide variety of reactive functional groups have now been produced in this manner.[10] Although the low polarity of the carbon–zinc bond limits the synthetic utility of these reagents, transmetalation can provide access to organometallic derivatives such as organopalladium and organocopper compounds that more readily participate in carbon–carbon bond-forming reactions.

The original aim of the study reported here was to employ the tactic of tandem zinc oxidative addition/ transmetalation as the basis for a general strategy for effecting intramolecular conjugate addition reactions. In principle, this chemistry could provide an attractive solution to the longstanding and fundamental synthetic problem of achieving intramolecular conjugate addition with nonstabilized carbanionic synthons. Of additional interest was the possibility that enantioselective and catalytic versions of this process might ultimately be realized.

Results and Discussion

Discovery and Scope of the Intramolecular Conjugate Addition Reaction. The feasibility of the intramolecular conjugate addition strategy was initially examined by using the iodo enone **10** (eq 5). Oxidative

10 11 (5)

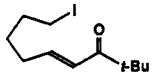
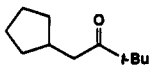
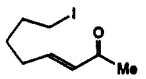
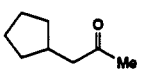
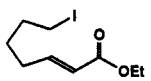
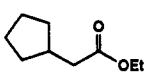
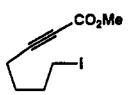
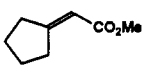
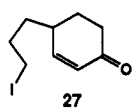
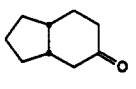
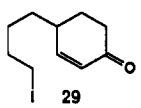
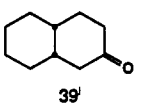
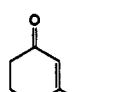
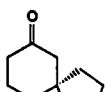
addition was carried out by employing several varieties of zinc metal, with the original intention of then adding an appropriate metal salt to effect transmetalation and thus form a more reactive organometallic intermediate for the 1,4-addition step. Our initial experiments quickly revealed, however, that such a transmetalation step was unnecessary because simple treatment of **10** with zinc dust promoted the desired cyclization.

The successful transformation of **10** to **11** in the presence of zinc alone suggested that the organozinc iodide species generated from **10** might itself participate in intramolecular conjugate addition reactions. In this regard, it is relevant to note that *intermolecular* conjugate addition reactions of several classes of organozinc compounds are in fact well documented. The first example of such a reaction was the 1,4-addition of diphenylzinc to chalcone, reported by Gilman and Kirby in 1941.[11] Since that time, a variety of organozinc halide and organozincate derivatives have been found to participate in intermolecular conjugate additions.[12]

Table I summarizes results that reveal the scope of the *intramolecular* conjugate addition reaction of nonstabilized organozinc compounds. The preparation of the substrates required for this study was straightforward, and is outlined in the schemes which follow. The α,β-unsaturated ketones **13** and **14** and the analogous ester **16** were obtained from 5-chloropentanal (**12**) via the aldol, Wittig, and Horner–Wadsworth–Emmons routes shown in Scheme I. Displacement of chloride with iodide then furnished the desired iodo carbonyl compounds in 50–65% overall yield from 5-chlorovaleronitrile (the precursor

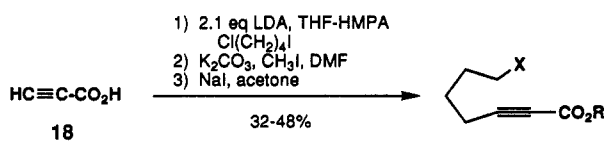
(6) Curran, D. P.; Wolin, R. L. *Synlett* **1991**, 317.
(7) Kocovsky, P.; Srogl, J. *J. Org. Chem.* **1992**, *57*, 4565.
(8) For reviews, see: (a) Curran, D. P. *Synthesis* **1988**, 417. (b) Curran, D. P. *Synthesis* **1988**, 489. (c) Curran, D. P. In *Comprehensive Organic Synthesis*: Semmelhack, M. F., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 4, pp 779–831.
(9) Porter, N. A.; Magnin, D. R.; Wright, B. T. *J. Am. Chem. Soc.* **1986**, *108*, 2787.
(10) For notable early examples, see: (a) Tamaru, Y.; Ochiai, H.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1983**, *24*, 3869. (b) Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 3368. (c) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1984**, *25*, 1475. (d) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Tsubaki, K.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 5559. (e) Tamaru, Y.; Ochiai, H., Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955. (f) Nakamura, T.; Kuwajima, I. *Tetrahedron Lett.* **1986**, *27*, 83. (g) Ochiai, H.; Tamaru, Y.; Tsubaki, K.; Yoshida, Z. *J. Org. Chem.* **1987**, *52*, 4418. (h) Tamaru, Y.; Ochiai, H.; Nakamura, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1157. (i) Comins, D. L.; O'Conner, S. *Tetranhedron Lett.* **1987**, *28*, 1843. (j) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390. (k) Yeh, M. C. P.; Chen, H. G.; Knochel, P. *Org. Synth.* **1991**, *70*, 195.
(11) Gilman, H.; Kirby, R. H. *J. Am. Chem. Soc.* **1941**, *63*, 2046.
(12) (a) Daviaud, G.; Miginiac, P. *Bull. Soc. Chim. Fr.* **1970**, 1617. (b) Moreay, J.-L.; Frangin, Y.; Gaudemar, M. *Bull. Soc. Chim. Fr.* **1970**, 4511. (c) Daviaud, G.; Massy-Barbot, M.; Miginiac, P. *C. R. Seances Acad. Sci., Ser. C* **1971**, *272*, 969. (d) Bertrand, M. T.; Coutrois, G.; Miginiac, L. *Tetrahedron Lett.* **1974**, 1945. (e) Isobe, M.; Kondo, S.; Nagasawa, N.; Goto, T. *Chem. Lett.* **1977**, 679. (f) Bellassoued, M.; Frangin, Y.; Gaudemar, M. *Synthesis* **1978**, *232*, 150. (g) Shono, T.; Nishiguchi, I.; Sasaki, M. *J. Am. Chem. Soc.* **1978**, *100*, 4314. (h) Seebach, D.; Langer, W. *Helv. Chim. Acta* **1979**, *62*, 1701. (i) Langer, W.; Seebach, D. *Helv. Chim. Acta* **1979**, *62*, 1710. (j) Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993. (k) Tückmantel, W.; Oshima, K.; Nozaki, H. *Chem. Ber.* **1986**, *119*, 1581. (l) Jansen, J. F. G. A.; Feringa, B. L. *Tetrahedron Lett.* **1988**, *29*, 3593. (m) Jansen, J. F. G. A.; Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1989**, 741.

Table I. Intramolecular Conjugate Addition Reactions

entry	substrate	time[a]	product	yield, %[b]
1	 10	1 h	 11[c]	60-63
2	 15	50 min	 35[d]	52-56
3	 17	24 h[e]	 36[f]	30-37
4	 21	5 d	 37[g]	66
5	 27	1 h	 38[h]	65-70
6	 29	48 h[e]	 39[i]	45-51
7	 34	24 h	 40[j]	67-74

[a] Cyclizations were carried out with 1.1–4.0 equiv of Zn at room temperature. [b] Isolated yields of product purified by column chromatography on silica gel. [c] Reference 29. [d] Reference 30. [e] This cyclization was carried out by adding 2.5 equiv of Me_3SiCl after 30 min. [f] Reference 31. [g] Reference 32. [h] Reference 23. [i] Reference 24. [j] Reference 4.

to **12**).[13] As outlined in eq 6, the related acetylenic ester **21** was prepared by utilizing the alkylation of the dianion of propiolic acid[14] as a key step.



19 X=Cl, R=H
20 X=Cl, R=Me
21 X=I, R=Me

(6)

Scheme II describes the synthesis of several 4-cyclohexenone substrates via routes based on the Stork–Danheiser alkylation strategy.[15] The iodo enones **27**, **29**, and **31** were obtained in 41–62% overall yield from 3-ethoxycyclohexenone in this fashion.

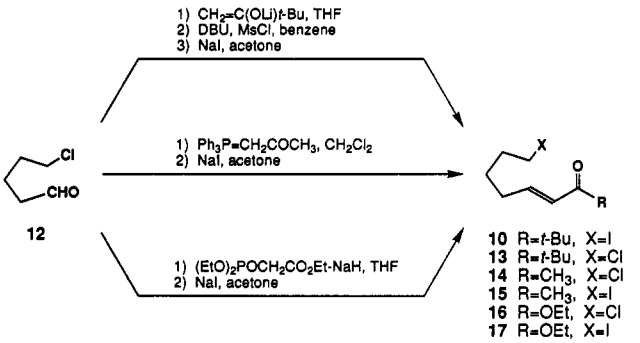
Finally, 3-(4-iodobutyl)-2-cyclohexenone (**34**) was obtained from the corresponding chloride **33**, which is itself

(13) For the DIBAL reduction of 5-chlorovaleronitrile to **12**, see: Kuehne, M. E.; Matsko, T. H.; Bohert, J. C.; Motyka, L.; Oliver-Smith, D. *J. Org. Chem.* **1981**, *46*, 2002.

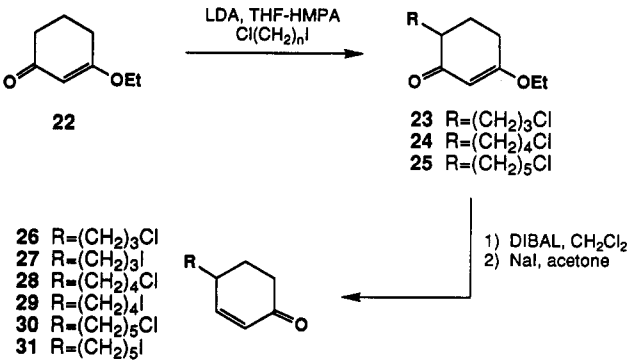
(14) Carlson, R. M.; Oyler, A. R.; Peterson, J. C. *J. Org. Chem.* **1975**, *40*, 1610.

(15) Stork, G.; Danheiser, R. L. *J. Org. Chem.* **1973**, *38*, 1775.

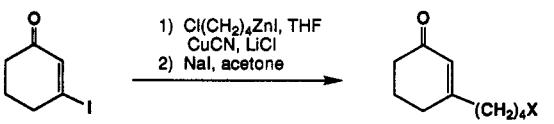
Scheme I



Scheme II



available, as described by Knochel,[16] from the reaction of the organocopper reagent derived from 4-chloro-1-iodobutane with 3-iodocyclohexenone[17] (eq 7).



33 X=Cl
34 X=I

(7)

Initial conjugate addition experiments carried out with iodo enone **10** revealed that the success of the cyclization was highly sensitive to the type of zinc metal used for the reaction.[18] Best results were obtained with active zinc generated in situ by the reduction of zinc chloride with lithium naphthalenide.[19] Reactions were conducted using 1.1–4.0 equiv of zinc, with no significant difference in results noted when the amount of metal was varied within this range. Under these conditions, the organoiodide starting material reacted almost instantly at room temperature, whereas elevated temperatures were required to complete the oxidative addition when other forms of activated zinc were employed.

The optimal cyclization procedure thus involved adding a solution of the iodide substrate in THF to a suspension of 1.1–4.0 equiv of freshly prepared zinc at a final concentration of 0.1–0.2 M in the same solvent. Complete cyclization required 50 min to 5 days, depending on substrate structure (*vide infra*). THF proved to be the

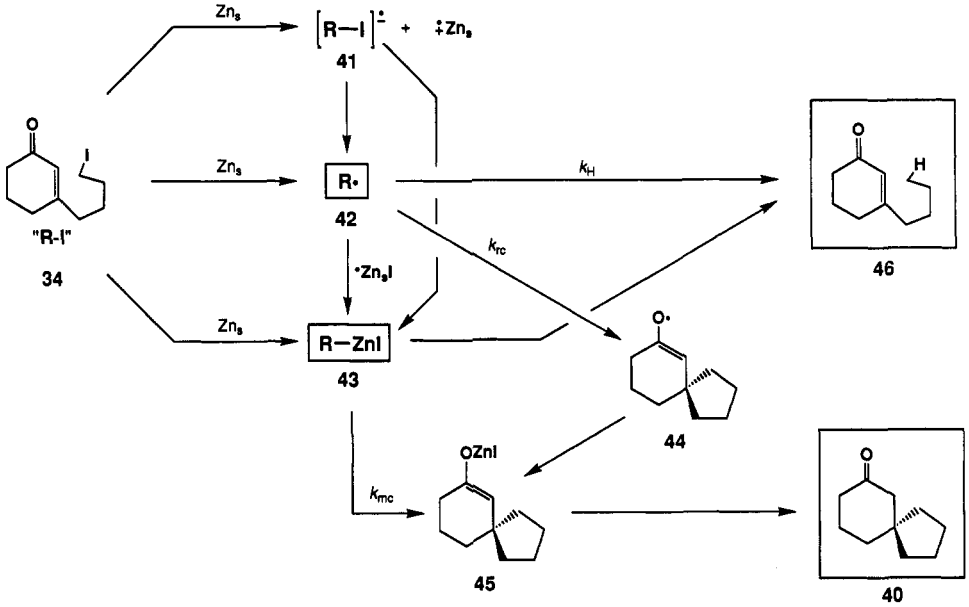
(16) Chang, M.; Yeh, M. C. P.; Knochel, P.; Butler, W. M.; Berk, S. C. *Tetrahedron Lett.* **1988**, *29*, 6693.

(17) Kowalski, C. J.; Fields, K. W. *J. Org. Chem.* **1981**, *46*, 197.

(18) For a discussion of procedures for the activation of zinc metal, see: (a) Erdik, E. *Tetrahedron* **1987**, *43*, 2203. (b) Gawronski, J. K. *Tetrahedron Lett.* **1984**, *25*, 2605. (c) Picotin, G.; Miginiac, P. *J. Org. Chem.* **1987**, *52*, 4796. (d) Picotin, G.; Miginiac, P. *Tetrahedron Lett.* **1987**, *28*, 4551.

(19) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

Scheme III



best solvent for the intramolecular conjugate addition reaction, and the addition of various cosolvents such as HMPA did not facilitate the cyclization. In a few cases (Table I, entries 3 and 6), addition of 2.5 equiv of trimethylsilyl chloride improved the reaction; in the absence of this additive the yield was lower by 10–15%. Finally, the intramolecular conjugate addition reaction was attempted with a variety of other reducing agents, including lithium naphthalenide, magnesium, magnesium amalgam, and zinc–copper couple,[20] but activated zinc gave the best results.[21] Under our optimal cyclization conditions the only significant byproduct isolated was the reduction product resulting from replacement of iodine with hydrogen. This byproduct was obtained in 1–5% yield in cases 3, 4, 6, and 7 but did not form in the other reactions.

As illustrated by the reactions summarized in Table I, the intramolecular conjugate addition strategy can be applied to the synthesis of both five- and six-membered rings. The cyclization was unsuccessful when applied to the iodo enone **31**: none of the desired seven-membered-ring product formed, and the only product obtained upon quenching the reaction mixture was the reduction product which presumably resulted from protonolysis of the organozinc intermediate. Both α,β-olefinic and acetylenic compounds can serve as the electrophilic partners in the intramolecular conjugate addition, and the method can be employed for the construction of *cis*-fused bicyclic ring systems as well.[22] Also notable is the formation in good yield of the spiro-fused product **40**, which involves intramolecular conjugate addition at a β,β-disubstituted center.

Mechanism of the Intramolecular Conjugate Addition Reaction. The pivotal question regarding the mechanism of the intramolecular conjugate addition reaction is the identity of the intermediate undergoing cyclization. Scheme III sets forth several alternative pathways for the formation of the conjugate addition product in the representative case of the cyclization of iodo enone **34**. Also shown here are pathways for the generation of a "reduction byproduct" (**46**) of the type isolated in the cyclization of iodides **17**, **21**, **29**, and **34**.

Whereas the mechanism of the oxidative addition of zinc to organohalogen compounds has received relatively little attention, the closely related reaction of magnesium metal (Grignard reagent formation) has been the subject of intensive investigation.[25] It is now evident that the generation of organomagnesium halides proceeds via radical intermediates, although some controversy remains regarding the nature of these radical species (e.g., "freely diffusing" vs "surface adsorbed"). By analogy, Scheme III outlines several pathways for the conversion of alkyl iodide **34** to the corresponding organozinc iodide (**43**). Single electron transfer from a zinc atom on the metal surface (Zn_S) to the alkyl iodide could generate the radical anion **41**. This species could then dissociate to form iodide ion and the radical **42**, which is expected to combine rapidly with ·Zn_SI on the metal surface to produce **43**. Alternatively, electron transfer to **34** might produce the radical **42** directly.

With these pathways in mind, two alternative mechanisms can then be envisioned for the formation of the cyclization product **40**. Cyclization of **43** to form the zinc enolate **45** is expected to be a facile process; as discussed earlier, ample precedent exists for the *intermolecular* 1,4-addition of organozinc compounds to α,β-unsaturated

(20) This reaction was carried out using the conditions of: Petrier, C.; Dupuy, C.; Luche, J.-L. *Tetrahedron Lett.* **1986**, *27*, 3149.

(21) Complex mixtures of products were formed when the reaction was attempted with lithium naphthalenide and magnesium metal, and the cyclization was extremely slow using magnesium amalgam and zinc–copper couple.

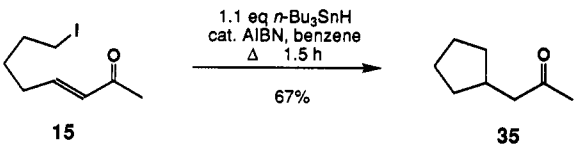
(22) The stereochemical identity of these products was determined by comparison of ^{1}H and ^{13}C NMR data (and 2,4-DNP derivative melting points) with data previously reported for **38**[23] and **39**.[24]

(23) (a) Krawczyk, A. R.; Jones, J. B. *J. Org. Chem.* **1989**, *54*, 1795. (b) Okuda, Y.; Morizawa, Y.; Oshima, K. *Tetrahedron Lett.* **1984**, *25*, 2483. (c) Metzger, P.; Casadevall, E. *Org. Magn. Reson.* **1982**, *19*, 229. (d) Granger, R.; Nau, P.; Nau, J. *Bull. Soc. Chim. Fr.* **1958**, 531.

(24) (a) Abraham, R. J.; Bergen, H. A.; Chadwick, D. J. *Tetrahedron* **1982**, *38*, 3271. (b) Browne, L. M.; Klinck, R. E.; Stothers, J. B. *Org. Magn. Reson.* **1979**, *12*, 561. (c) Pehk, T.; Laht, A.; Lippama, E. *Org. Magn. Reson.* **1982**, *19*, 21. (d) Reference 23c.

(25) (a) Walling, C. *Acc. Chem. Res.* **1991**, *24*, 255. (b) Garst, J. F. *Acc. Chem. Res.* **1991**, *24*, 95. (c) Walborsky, H. M. *Acc. Chem. Res.* **1990**, *23*, 286. (d) Root, K. S.; Hill, C. L.; Lawrence, L. M.; Whitesides, G. M. *J. Am. Chem. Soc.* **1989**, *111*, 5405. (e) Ashby, E. C.; Oswald, J. *J. Org. Chem.* **1988**, *53*, 6068. (f) de Boer, H. J. R.; Akkerman, O. S.; Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 687 and references cited therein.

carbonyl compounds.[11,12] An alternative plausible pathway to **45**, however, proceeds via the radical **42**; ring closure of this intermediate would furnish the enoloxy radical **44**, which upon further reduction would provide enolate **45**. The expectation that cyclization of radical intermediates such as **42** should be a facile process was confirmed by the experiment outlined in eq 8, in which the proposed radical



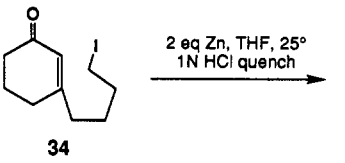
15 35 (8)

intermediate was generated under homogeneous conditions by the reaction of alkyl iodide **15** with tin hydride. 5-Exo radical cyclizations are known to be very rapid processes,[8] and it is not unreasonable that the cyclization of radical **42** to **44** might be competitive with its combination with $^{\bullet}ZnI$ to yield the organozinc iodide.

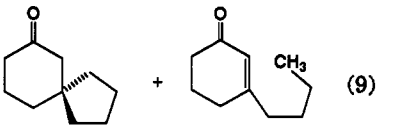
The results summarized in eq 9 and Figure 1 suggest that the formation of cyclization product **40** cannot be proceeding exclusively via a radical-mediated pathway. In this experiment, the intramolecular conjugate addition reaction was carried out with 2 equiv of zinc at room temperature, and aliquots were quenched at intervals with 1 N HCl and analyzed by gas chromatography. As shown in Figure 1, a mixture of the cyclization product **40** and the reduction product **46** was obtained in ca. 80% total yield. It is noteworthy that no alkyl iodide starting material could be detected after only a 15-min exposure of **34** to zinc. Quenching an aliquot at this stage of the reaction produced a mixture of **40** and **46** in 28% and 48% yield, respectively, as judged by gas chromatographic analysis (integration vs biphenyl as an internal standard). Upon further reaction, the amount of reduction product **46** decreased, while the amount of cyclization product **40** increased concomitantly, with the combined yield of the two products remaining constant at ca. 80% over the entire course of the reaction.

In principle, the reduction product **46** could arise from protonolysis of the organozinc compound **43** during workup or, alternatively, could be formed prior to quench via hydrogen atom abstraction from solvent by a radical intermediate such as **42**. However, the only reasonable interpretation of the experimental results summarized above is that both **40** and **46** are, at least for the most part, derived from a common, persistent intermediate. It is highly unlikely that this intermediate is radical in character, since both the cyclization of **42** to **44** and the collapse of **42** to form **43** are expected to be extremely rapid processes. On the other hand, these results are fully compatible with the identification of the key intermediate as the organozinc derivative **43**, which either cyclizes to **45** or, upon quenching with HCl undergoes protonolysis to afford **46**. Also consistent with our data is the possibility that the reaction proceeds through a combination of pathways, in which a small amount of the cyclization product **40** is formed during the initial stages of the reaction from a radical intermediate which cyclizes to **44** competitively with its conversion to **43**.

Synthetic Utility of the Intramolecular Conjugate Addition Reaction. We anticipate that the intramolecular organozinc conjugate addition reaction will prove to be a valuable method for the construction of cyclic molecules. Operationally, this chemistry enjoys several



34



40 + 46 (9)

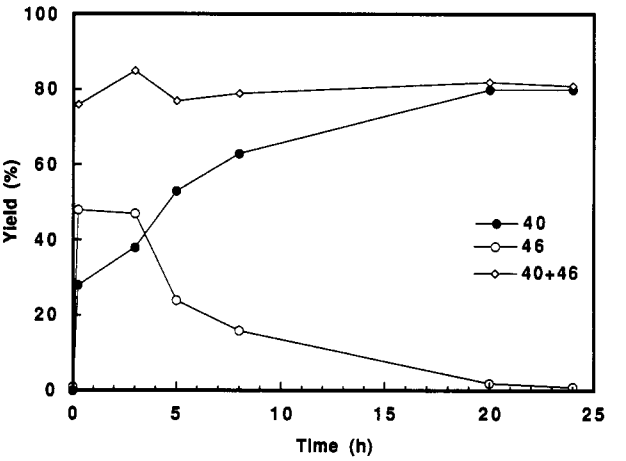


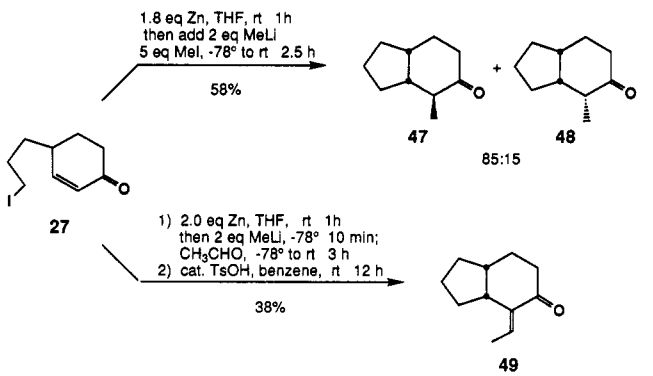
Figure 1. Yield of cyclization product **40** and reduction product **46** as determined by GLC analysis after HCl quench.

advantages over the alternative tin hydride promoted radical cyclization strategy, the attractiveness of which is limited by the practical difficulties and safety concerns associated with organotin compounds. Another advantage of the organozinc strategy is the facility with which the cyclization can be linked to the synthetic elaboration of the enolate product; the trapping strategies available for radical cyclizations are relatively limited in scope.[8] The reaction of zinc enolates with carbon electrophiles is of course well documented, the most familiar example being the addition to aldehydes and ketones which constitutes the classic Reformatsky reaction.[26] The elaboration of zinc enolates with a variety of other electrophiles[26a] is possible, and this process has been extended to include coupling with aryl and vinyl halides through the application of transition-metal catalysis.[27]

In a preliminary study, the transformations outlined in Scheme IV were examined to confirm the feasibility of the intramolecular conjugate addition–electrophilic trapping strategy. Alkylation of the cyclization product derived from **27** proved to be a sluggish process but was facilitated by the addition of methyllithium, which may serve to convert the initial enolate product to a more reactive lithium derivative. In this fashion methylation was achieved in good overall yield from **27**, with the major product (**47**) derived from reaction on the less hindered (exo) face of the enolate.[28] Interception of the same enolate intermediate with acetaldehyde produced the expected

(26) (a) Furstner, A. *Synthesis* **1989**, 571. (b) For an example of tandem *intermolecular* conjugate addition–Reformatsky reactions, see ref 12g.
(27) (a) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1977**, *132*, C17. (b) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1979**, *177*, 273. (c) Fauvarque, J. F.; Jutand, A. *J. Organomet. Chem.* **1981**, *209*, 109.
(28) The identity of **47** and **48** as epimers (rather than regioisomers) was confirmed by their interconversion upon treatment with base. The stereochemical assignments were made on the basis of ^{1}H NMR analysis.

Scheme IV



β-hydroxy ketone contaminated with its dehydration product; treatment of the mixture with a catalytic amount of *p*-TsOH furnished **49** in 37% overall yield from iodo enone **27**. The chemical shift of the vinyl proton in **49** identified this enone as the *E* isomer, suggesting that the intermediate aldol product is the *syn* ketol.

In summary, the studies reported in this paper establish the ability of nonstabilized organozinc compounds to undergo intramolecular conjugate additions with olefinic and acetylenic Michael acceptors. In conjunction with the further electrophilic trapping of the resultant enolates, this reaction provides a valuable strategy for the assembly of a variety of mono- and polycyclic systems.

Experimental Section

General Procedures. All reactions were performed in flame-dried glassware under a positive pressure of argon and stirred magnetically with a Teflon-covered stirbar, except for reactions involving lithium naphthalenide solutions, which were stirred with a glass-covered stirbar. Sensitive liquids were transferred via syringe or cannula and were introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by using a Büchi rotary evaporator at ca. 20 mmHg. Column chromatography was performed on Baker silica gel (230–400 mesh).

Materials. Commerical grade reagents and solvents were used without further purification except as indicated below. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), chlorotrimethylsilane, hexamethylphosphoric triamide (HMPA), diisopropylamine, and dichloromethane were distilled from calcium hydride. Benzene and tetrahydrofuran were distilled from sodium benzophenone ketyl or its dianion. Pinacolone, 3-ethoxy-2-cyclohexen-1-one, and methanesulfonyl chloride were distilled at reduced pressure before use. All commercial alkyl iodides were filtered through alumina immediately prior to use.

5-Chloropentanal (12). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, 25-mL pressure-equalizing addition funnel, and rubber septum was charged with 5-chlorovaleronitrile (4.2 mL, 4.4 g, 37.4 mmol) and 40 mL of dichloromethane and cooled to −78 °C while a solution of diisobutylaluminum hydride (DIBAL; 1.0 M in hexane, 50 mL, 50 mmol) was added via the addition funnel over 30 min. After 1.5 h, the reaction mixture was allowed to warm to 0 °C and quenched with 50 mL of 10% H_2SO_4 solution. The organic layer was separated and extracted with three 30-mL portions of diethyl ether. The combined organic phases were washed with 40 mL of water, two 30-mL portions of saturated sodium potassium tartrate solution, and 50 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 4.26 g of a pale yellow oil which exhibited spectral data consistent with those reported previously:[13] IR (film) 2953, 2829, 2725, 1721, 1450, 1397, 1362, 1309, 1281, 1130, 1077, 732, 649 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 1.5 Hz, 1 H), 3.47–3.52 (m, 2 H), 2.41–2.46 (m, 2 H), 1.72–1.79 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.7, 44.4, 42.9, 31.7, 19.3.

(*E*)-2,2-Dimethyl-9-chloro-4-nonen-3-one (13). A 250-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, 60-mL pressure equalizing addition funnel, and rubber septum was charged with diisopropylamine (5.4 mL, 3.9 g, 38.5 mmol) and 10 mL of THF and cooled to 0 °C while a solution of *n*-butyllithium (2.48 M in hexane, 15.0 mL, 37.2 mmol) was added via syringe over ca. 2 min. After 5 min, the flask was cooled to −78 °C while a solution of pinacolone (4.4 mL, 3.5 g, 35.0 mmol) in 40 mL of THF was added via the addition funnel over 20 min. After 30 min, a solution of 5-chloropentanal (**12**) (4.26 g) in 30 mL of THF was added rapidly via the addition funnel over ca. 2 min. After 2 h at −78 °C, the reaction was quenched at 0 °C by the addition of 40 mL of saturated sodium bicarbonate solution and then diluted with 10 mL of diethyl ether. The aqueous phase was separated and washed with two 15-mL portions of ether, and the combined organic layers were washed with 20 mL of 1 N HCl solution, 25 mL of saturated sodium bicarbonate solution, 20 mL of water, and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 7.06 g of the β-hydroxy ketone as a colorless oil used in the next step without further purification: IR (film) 3390, 2969, 2937, 2912, 2869, 1699, 1469, 1467, 1367, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.02–4.04 (m, 1 H), 3.57 (t, *J* = 6.6 Hz, 2 H), 3.33 (bs, 1 H), 2.73 (dd, *J* = 2.7, 17.9 Hz, 1 H), 2.57 (dd, *J* = 9.0, 17.9 Hz, 1 H), 1.79–1.86 (m, 2 H), 1.43–1.65 (m, 4 H), 1.1 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 217.7, 67.5, 44.9, 44.4, 43.0, 35.6, 32.5, 26.3, 22.9.

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, 25-mL pressure-equalizing addition funnel, and rubber septum was charged with the product of the aldol reaction described above (7.06 g), methanesulfonyl chloride (3.2 mL, 4.7 g, 41 mmol), and 40 mL of benzene and cooled to 0 °C while a solution of DBU (11.5 mL, 11.7 g, 77.0 mmol) in 20 mL of benzene was added via the addition funnel over 10 min. After 4 h at room temperature, the reaction mixture was poured into ca. 50 mL of 1 N HCl solution. After 15 min, the aqueous layer was separated and washed with two 15-mL portions of diethyl ether, and the combined organic layers were washed with 25 mL of 1 N HCl solution, 25 mL of saturated sodium bicarbonate solution, and 25 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 5.97 g of a pale yellow oil used in the next step without further purification: IR (film) 2960, 2870, 1689, 1625, 1468, 1362, 1299, 1074, 982 cm^{-1}; UV (hexane) λ_{max} 222 (ε = 11 700); ^1H NMR (300 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 6.9, 15.2 Hz, 1 H), 6.51 (dt, *J* = 1.5, 15.2 Hz, 1 H), 3.55 (t, *J* = 6.5 Hz, 2 H), 2.25 (apparent dq, *J* = 1.5, 7.2 Hz, 2 H), 1.76–1.83 (m, 2 H), 1.61–1.68 (m, 2 H), 1.1 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.2, 146.3, 124.6, 44.6, 42.9, 32.0, 31.6, 26.2, 25.4.

General Procedure A for the Conversion of Alkyl Chlorides to Alkyl Iodides. (*E*)-2,2-Dimethyl-9-iodo-4-nonen-3-one (10). A 250-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet was charged with sodium iodide (43.0 g, 290 mmol) and 80 mL of acetone. A solution of **13** (5.97 g) in 20 mL of acetone was added, and the reaction mixture was heated at reflux in the dark for 24 h. After it was cooled to room temperature, the reaction mixture was concentrated and the residue was dissolved in 40 mL of diethyl ether and 40 mL of water. The aqueous layer was separated and washed with two 20-mL portions of ether, and the combined organic layers were washed with two 30-mL portions of saturated sodium sulfite solution and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 8.06 g of a yellow oil. Column chromatography on silica gel (elution with 0–5% EtOAc–hexane) gave 5.871 g (53% yield overall from 5-chlorovaleronitrile) of **10** as a colorless oil: IR (film) 2966, 2937, 2867, 1689, 1624, 1470, 1364, 1338, 1212, 1089, 993, 975, 786 cm^{-1}; UV (hexane) λ_{max} 222 (ε = 12 500); ^1H NMR (300 MHz, $CDCl_3$) δ 6.91 (dt, *J* = 7.3, 15.3 Hz, 1 H), 6.51 (dt, *J* = 1.4, 15.3 Hz, 1 H), 3.20 (t, *J* = 6.9 Hz, 2 H), 2.25 (dq, *J* = 1.4, 7.3 Hz, 2 H), 1.81–1.89

(m, 2 H), 1.57–1.64 (m, 2 H), 1.1 (s, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 204.2, 146.3, 124.8, 42.9, 32.9, 31.3, 29.0, 26.2, 6.2; HRMS *m/e* calcd for $C_{11}H_{19}IO$ 294.0481, found 294.0478.

(*E*)-8-Chloro-3-octen-2-one (14). A 50-mL, one-necked, round-bottomed flask equipped with a reflux condenser fitted with an argon inlet was charged with 1-(triphenylphosphoranylidene)-2-propanone (1.46 g, 4.60 mmol) and 20 mL of dichloromethane. The aldehyde **12** (0.555 g, prepared by reduction[13] of 0.576 g (4.90 mmol) of 5-chlorovaleronitrile) was added in one portion via syringe, and the reaction mixture was then heated at reflux for 3 h. The resulting pale yellow mixture was stirred at room temperature for 12 h and then concentrated at reduced pressure. The resulting off-white slurry was suspended in pentane, stirred for 30 min, and then filtered with the aid of 60 mL of pentane. The filtrate was extracted with 30 mL of water and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 0.706 g of a pale yellow oil used in the next step without further purification: IR (film) 3006, 2938, 2864, 1678, 1630, 1433, 1362, 1256, 981 cm^{-1}; UV (hexane) λ_{max} 214 (ε = 13 900); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 6.9, 16.0 Hz, 1 H), 6.10 (dt, *J* = 1.5, 16.0 Hz, 1 H), 3.56 (t, *J* = 6.5 Hz, 2 H), 2.25 (s, 3 H), 2.25 (dq, *J* = 1.4, 7.3 Hz, 2 H), 1.77–1.87 (m, 2 H), 1.60–1.70 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.4, 147.2, 131.7, 44.5, 31.9, 31.6, 26.9, 25.3.

(*E*)-8-Iodo-3-octen-2-one (15). Reaction of chloro enone **14** (0.706 g) with sodium iodide (6.60 g, 44.0 mmol) in 60 mL of acetone was performed according to general procedure A. Purification by column chromatography on silica gel (elution with 0–15% EtOAc–hexane) provided 0.782 g (63% overall from 5-chlorovaleronitrile) of **15** as a colorless oil: IR (film) 3006, 2930, 2859, 1671, 1629, 1428, 1361, 1254, 1209, 1177, 978 cm^{-1}; UV (hexane) 215 (ε = 14 400); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.79 (dt, *J* = 6.9, 15.7 Hz, 1 H), 6.10 (dt, *J* = 1.8, 15.7 Hz, 1 H), 3.20 (t, *J* = 6.8 Hz, 2 H), 2.26 (s, 3 H), 2.26 (dq, *J* = 1.4, 7.4 Hz, 2 H), 1.81–1.89 (m, 2 H), 1.58–1.66 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.4, 147.1, 131.7, 32.7, 31.2, 28.9, 27.0, 6.1; HRMS *m/e* calcd for $C_8H_{13}IO$ 252.0011, found 252.0009.

(*E*)-Ethyl 7-Chloro-2-heptenoate (16). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, 25-mL pressure-equalizing addition funnel, and rubber septum was charged with sodium hydride (60% dispersion in oil, 2.04 g, 51.0 mmol), which was then washed sequentially with three 10-mL portions of pentane (5 min of stirring followed by removal of the pentane via cannula). The resulting solid was suspended in 10 mL of THF and cooled to 0 °C while a solution of triethyl phosphonoacetate (7.34 mL, 8.30 g, 37.0 mmol) in 25 mL of THF was added over 15 min via the addition funnel. After 30 min, a solution of **12** (4.10 g, prepared by reduction[13] of 4.39 g (37.3 mmol) of 5-chlorovaleronitrile) in 5 mL of THF was added in one portion and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then quenched with 20 mL of 1 N HCl solution and diluted with 20 mL of diethyl ether. The aqueous layer was separated and washed with two 10-mL portions of diethyl ether, and the combined organic phases were washed with 25 mL of 1 N HCl solution, three 25-mL portions of saturated sodium bicarbonate solution, two 20-mL portions of water, and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 6.51 g of a pale yellow oil used in the next step without further purification: IR (film) 2983, 2942, 2867, 1718, 1655, 1451, 1310, 1270, 1188, 1044, 982 cm^{-1}; UV (hexane) λ_{max} 206 (ε = 11 600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (dt, *J* = 7.1, 15.4 Hz, 1 H), 5.84 (dt, *J* = 1.5, 15.2 Hz, 1 H), 4.19 (q, *J* = 6.7 Hz, 2 H), 3.55 (t, *J* = 6.3 Hz, 2 H), 2.25 (apparent dq, *J* = 1.5, 7.3 Hz, 2 H), 1.77–1.84 (m, 2 H), 1.61–1.68 (m, 2 H), 1.29 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.5, 148.1, 121.9, 60.1, 44.5, 31.8, 31.2, 25.2, 14.2.

(*E*)-Ethyl 7-Iodo-2-heptenoate (17). Reaction of chloro ester **16** (6.5 g, 34 mmol) with sodium iodide (57.0 g, 380 mmol) in 70 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–15% EtOAc–hexane) afforded 6.614 g (63% overall from 5-chlorovaleronitrile) of **17** as a colorless oil: IR (film) 2935, 2880, 2862, 1717, 1654, 1451, 1368, 1309, 1270, 1215, 1183, 1042, 979 cm^{-1}; UV (hexane) λ_{max} 253 (ε = 600), 204 (ε = 14 500), 197 (ε = 14 500); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (dt, *J* = 7.0, 15.5 Hz, 1 H), 5.83 (d, *J* = 15.5 Hz, 1 H), 4.18 (q, *J* = 7.3 Hz, 2 H), 3.18 (t, *J* = 6.7 Hz, 2 H), 2.23 (dq, *J* = 1.3, 7.2 Hz, 2 H), 1.80–1.89 (m, 2 H), 1.56–1.63 (m, 2 H), 1.28 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.5, 148.1, 121.9, 60.2, 32.7, 31.0, 28.8, 14.2, 6.1; HRMS *m/e* calcd for $C_9H_{15}IO_2$ 282.0117, found 282.0119.

7-Chloro-2-heptynoic acid (19). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and 25-mL pressure-equalizing addition funnel was charged with diisopropylamine (4.5 mL, 3.25 g, 32.1 mmol) and 10 mL of THF and cooled to 0 °C while a solution of *n*-butyllithium (2.62 M in hexanes, 12.2 mL, 32.0 mmol) was added dropwise via syringe over ca. 1 min. After 15 min, the flask was cooled to −40 °C and a solution of propiolic acid (0.92 mL, 1.05 g, 15.0 mmol) in 10 mL of HMPA was added dropwise over 10 min via the addition funnel. The resulting mixture was stirred at −15 °C for 2 h, the cooling bath was then removed, and 4-chloro-1-iodobutane (3.28 g, 15.0 mmol) was added in one portion via syringe. The reaction mixture was stirred for 16 h at room temperature and then quenched by the addition of 50 mL of water. The aqueous phase was separated, washed with two 20-mL portions of dichloromethane, and then acidified to pH 1 with concentrated HCl solution. The resulting solution was extracted with three 20-mL portions of diethyl ether, and the combined ether layers were washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to afford 1.70 g of a viscous oil used in the next step without further purification: IR (film) 3209, 2874, 2653, 2235, 1675, 1410, 1276, 1075, 742 cm^{-1}; UV (methanol) λ_{max} 206 (ε = 5600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.95 (bs, 1 H), 3.57 (t, *J* = 6.3 Hz, 2 H), 2.43 (t, *J* = 6.3 Hz, 2 H), 1.87–1.94 (m, 2 H), 1.75–1.82 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.9, 91.5, 73.0, 44.1, 31.3, 24.6, 18.1.

Methyl 7-Chloro-2-heptynoate (20). A 50-mL, one-necked, round-bottomed flask fitted with an argon inlet adapter was charged with **19** (1.70 g), potassium carbonate (1.54 g, 11.1 mmol), methyl iodide (3.63 mL, 8.28 g, 58.3 mmol), and 25 mL of DMF. The reaction mixture was stirred in the dark for 24 h and then was quenched with 50 mL of water and 50 mL of diethyl ether. The aqueous layer was separated and washed with two 20-mL portions of diethyl ether, and the combined organic layers were washed with 20 mL of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to give 1.85 g of a pale yellow oil used in the next step without further purification: IR (film) 3002, 2953, 2915, 2873, 2237, 1714, 1436, 1270, 1251, 1077, 753 cm^{-1}; UV (hexane) λ_{max} 213 (ε = 3800), 205 (ε = 5200), 197 (ε = 4600); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.78 (s, 3 H), 3.58 (t, *J* = 6.5 Hz, 2 H), 2.41 (t, *J* = 7.1 Hz, 2 H), 1.88–1.95 (m, 2 H), 1.74–1.82 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.1, 88.6, 73.4, 52.6, 44.2, 31.3, 24.7, 18.0.

Methyl 7-Iodo-2-heptynoate (21). Reaction of chloro ester **20** (1.83 g) with sodium iodide (7.87 g, 52.5 mmol) in 80 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–10% EtOAc–hexane) furnished 1.404 g (35% overall from propiolic acid) of **21** as a colorless oil: IR (film) 3000, 2949, 2840, 2236, 1713, 1433, 1253, 1076, 752 cm^{-1}; UV (hexane) λ_{max} 255 (ε = 500), 213 (ε = 4600), 205 (ε = 6400), 192 (ε = 9000); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.79 (s, 3 H), 3.23 (t, *J* = 6.8 Hz, 2 H), 2.41 (t, *J* = 7.0 Hz, 2 H), 1.95–1.99 (m, 2 H), 1.71–1.76 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.0, 88.5, 73.4, 52.5, 82.2, 32.1, 17.6, 5.3; HRMS *m/e* calcd for $C_8H_{11}IO_2$ 265.9804, found 265.9802.

General Procedure B for the Alkylation of 3-Ethoxy-2-cyclohexen-1-one. 6-(3-Chloropropyl)-3-ethoxy-2-cyclohexen-1-one (23). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and 25-mL pressure equalizing addition funnel was charged with diisopropylamine (4.60 mL, 3.34 g, 33.0 mmol) and 3 mL of THF and cooled at 0 °C while a solution of *n*-butyllithium (2.62 M in hexanes, 12.2 mL, 32.0 mmol) was added dropwise via syringe

over ca. 2 min. After 15 min, the flask was cooled to −78 °C and a solution of 3-ethoxy-2-cyclohexen-1-one (4.40 mL, 4.24 g, 30.2 mmol) in 7 mL of THF was added via the addition funnel over 30 min. After an additional 30 min, HMPA (13.0 mL, 13.39 g, 74.7 mmol) was added in one portion via syringe. The cooling bath was removed, and 3-chloro-1-iodopropane (3.90 mL, 7.43 g, 36.3 mmol) was added in one portion. After 2 h, the reaction mixture was quenched by the addition of ca. 50 mL of 1 N HCl solution and diluted with 20 mL of diethyl ether. The aqueous phase was separated and washed with two 25-mL portions of ether, and the combined organic phases were washed with two 20-mL portions of saturated $NaHCO_3$ solution, two 20-mL portions of water, and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Column chromatography on silica gel (elution with 0–15% EtOAc–hexane) provided 5.23 g (80%) of **23** as a pale yellow oil: IR (film) 2938, 2872, 1653, 1606, 1447, 1372, 1307, 1232, 1190, 1040, 905, 818, 733, 648 cm^{-1}; UV (hexane) λ_{max} 238 (ϵ = 17 000); ^1H NMR (300 MHz, $CDCl_3$) δ 5.32 (s, 1 H), 3.90 (q, J = 7.0 Hz, 2 H), 3.53–3.61 (m, 2 H), 2.45 (dd, J = 5.4, 7.0 Hz, 2 H), 2.18–2.27 (m, 1 H), 2.04–2.13 (m, 1 H), 1.69–2.01 (m, 4 H), 1.50–1.69 (m, 1 H), 1.37 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 200.9, 176.7, 102.2, 64.2, 45.1, 44.6, 30.3, 28.1, 27.2, 26.6, 14.1; HRMS m/e calcd for $C_{11}H_{17}ClO_2$ 216.0917, found 216.0916.

6-(4-Chlorobutyl)-3-ethoxy-2-cyclohexen-1-one (24). Reaction of 3-ethoxy-2-cyclohexen-1-one (3.27 mL, 3.15 g, 22.5 mmol) with lithium diisopropylamide (23.6 mmol) and 4-chloro-1-iodobutane (5.90 g, 27.0 mmol) in 30 mL of THF and 10 mL of HMPA was performed according to general procedure B to afford 4.14 g (80%) of **24** as yellow oil: IR (film) 2985, 2941, 2864, 1652, 1607, 1453, 1380, 1360, 1314, 1230, 1189, 1044, 818 cm^{-1}; UV (hexane) λ_{max} 237 (ϵ = 16 400); ^1H NMR (300 MHz, $CDCl_3$) δ 5.31 (s, 1 H), 3.89 (q, J = 7.0 Hz, 2 H), 3.55 (t, J = 6.7 Hz, 2 H), 2.43 (dd, J = 5.2, 7.2 Hz, 2 H), 2.03–2.23 (m, 2 H), 1.66–1.91 (m, 4 H), 1.33–1.59 (m, 3 H), 1.36 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.6, 177.1, 102.6, 64.6, 45.4, 45.3, 33.0, 29.1, 28.5, 26.6, 24.8, 14.5; HRMS m/e calcd for $C_{12}H_{19}ClO_2$ 230.1074, found 230.1075.

6-(5-Choropentyl)-3-ethoxy-2-cyclohexen-1-one (25). Reaction of 3-ethoxy-2-cyclohexen-1-one (2.90 mL, 2.79 g, 19.9 mmol) with lithium diisopropylamide (21 mmol) and 5-chloro-1-iodopentane (9.30 g, 40.0 mmol) in 15 mL of THF and 7 mL of HMPA was performed according to general procedure B to provide 4.02 g (82%) of **25** as a yellow oil: IR (film) 2930, 2866, 1656, 1609, 1456, 1367, 1228, 1189, 1030, 819 cm^{-1}; UV (hexane) λ_{max} 237 (ϵ = 15 100); ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1 H), 3.88 (q, J = 7.4 Hz, 2 H), 3.53 (t, J = 7.2 Hz, 2 H), 2.42 (m, 2 H), 2.03–2.18 (m, 2 H), 1.71–1.84 (m, 4 H), 1.33–1.55 (m, 5 H), 1.35 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.4, 176.6, 102.1, 64.1, 45.0, 32.4, 29.3, 27.9, 26.9, 26.3, 26.2, 14.1; HRMS m/e calcd for $C_{13}H_{21}ClO_2$ 244.1230, found 244.1233.

General Procedure C for the DIBAL Reduction of Substituted 3-Ethoxy-2-cyclohexenones. 4-(3-Chloropropyl)-2-cyclohexen-1-one (26). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and 60-mL pressure-equalizing addition funnel was charged with **23** (5.23 g, 24.1 mmol) and 30 mL of dichloromethane and cooled to −78 °C while a solution of DIBAL (1.0 M in hexanes, 30.0 mL, 30.0 mmol) was added dropwise via the addition funnel over 40 min. After 30 min, the reaction mixture was allowed to warm to 0 °C and then poured into 50 mL of aqueous 1 N HCl solution cooled at 0 °C. The resulting mixture was stirred vigorously and warmed to room temperature over ca. 30 min. The aqueous phase was separated and washed with two 25-mL portions of dichloromethane, and the combined organic phases were washed with two 30-mL portions of water and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to furnish 4.27 g of a pale yellow oil used in the next step without purification: IR (film) 2940, 2864, 1681, 1450, 1389, 1251, 1213, 868, 751 cm^{-1}; UV (hexane) λ_{max} 217 (ϵ = 12 900); ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (dm, J = 10.3 Hz, 1 H), 6.00 (dd, J = 2.5, 10.2 Hz, 1 H), 3.55 (t, J = 6.4 Hz, 2 H), 2.28–2.53 (m, 3 H), 2.07–2.14 (m, 1 H), 1.81–1.91 (m, 2 H), 1.49–1.75 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.4, 153.9, 129.4, 44.7, 36.8, 35.5, 31.8, 29.9, 28.5.

4-(3-Iodopropyl)-2-cyclohexen-1-one (27). Reaction of chloro enone **26** (4.15 g) with sodium iodide (16.5 g, 110 mmol) in 100 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–15% EtOAc–hexane) gave 3.652 g (59% overall yield from **23**) of **27** as a colorless oil: IR (film) 2923, 2860, 1681, 1451, 1422, 1390, 1251, 1220, 1195, 854, 757 cm^{-1}; UV (hexane) λ_{max} 252 (ϵ = 500), 217 (ϵ = 12 700); ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (dm, J = 10.2 Hz, 1 H), 6.03 (dd, J = 2.1, 10.2 Hz, 1 H), 3.26 (t, J = 6.8 Hz, 2 H), 2.35–2.60 (m, 3 H), 2.11–2.22 (m, 1 H), 1.92–2.02 (m, 2 H), 1.53–1.82 (m, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.4, 154.0, 129.4, 36.8, 35.3, 35.2, 30.7, 28.5, 6.0; HRMS m/e calcd for $C_9H_{13}IO$ 264.0011, found 264.0009.

4-(4-Chlorobutyl)-2-cyclohexen-1-one (28). Reaction of **24** (3.46 g, 15.0 mmol) with DIBAL (1.0 M in hexanes, 19.0 mL, 19.0 mmol) in 20 mL of dichloromethane was performed according to procedure B to furnish 2.73 g of a colorless oil used in the next step without further purification: IR (film) 3023, 2944, 2925, 2862, 1681, 1454, 1390, 1251, 1213, 756 cm^{-1}; UV (hexane) λ_{max} 351 (ϵ = 11 500); ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (dm, J = 10.2 Hz, 1 H), 5.99 (dt, J = 1.6, 10.2 Hz, 1 H), 3.58 (t, J = 6.5 Hz, 2 H), 2.31–2.55 (m, 3 H), 2.11–2.17 (m, 1 H), 1.47–1.86 (m, 7 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.7, 154.5, 129.2, 44.7, 36.9, 36.0, 33.8, 32.4, 28.5, 24.2.

4-(4-Iodobutyl)-2-cyclohexen-1-one (29). Reaction of chloro enone **28** (2.61 g, 14 mmol) with sodium iodide (10.5 g, 70.0 mmol) in 100 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–15% EtOAc/hexane) provided 2.503 g (63% overall yield from **24**) of **29** as a colorless oil: IR (film) 2930, 2860, 1679, 1453, 1389, 1348, 1248, 1213, 756 cm^{-1}; UV (hexane) λ_{max} 254 (ϵ = 510), 217 (ϵ = 13 360); ^1H NMR (300 MHz, C_6D_6) δ 6.11 (dm, J = 10.5 Hz, 1 H), 5.94 (dd, J = 2.7, 10.5 Hz, 1 H), 2.67 (t, J = 6.5 Hz, 2 H), 2.28 (dt, J = 4.6, 16.4 Hz, 1 H), 1.92–2.03 (m, 1 H), 1.59 (bs, 1 H), 1.36–1.46 (m, 1 H), 1.22–1.32 (m, 2 H), 1.01–1.14 (m, 1 H), 0.65–0.95 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.6, 154.5, 129.1, 36.8, 35.9, 33.4, 33.1, 28.5, 27.8, 6.6; HRMS m/e calcd for $C_{10}H_{15}IO$ 278.0168, found 278.0165.

4-(5-Chloropentyl)-2-cyclohexen-1-one (30). Reaction of **25** (4.02 g, 16.4 mmol) with DIBAL (1.0 M in hexanes, 20.0 mL, 20.0 mmol) in 40 mL of dichloromethane was performed according to procedure B to yield 3.06 g of a colorless oil used in the next step without purification: IR (film) 2935, 2860, 1681, 1453, 1389, 1250, 1210, 728, 648 cm^{-1}; UV (hexane) λ_{max} 218 (ϵ = 13 700); ^1H NMR (300 MHz, $CDCl_3$) δ 6.79 (dm, J = 10.2 Hz, 1 H), 5.91 (dm, J = 10.2 Hz, 1 H), 3.49 (t, J = 6.6 Hz, 2 H), 2.24–2.47 (m, 3 H), 2.02–2.10 (m, 1 H), 1.34–1.76 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.7, 154.8, 129.0, 44.9, 36.9, 35.9, 34.4, 32.4, 28.5, 26.8, 26.2.

4-(5-Iodopentyl)-2-cyclohexen-1-one (31). Reaction of chloro enone **30** (3.06 g, 15.2 mmol) with sodium iodide (22.5 g, 150 mmol) in 100 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–15% EtOAc–hexane) provided 2.989 g (62% overall yield from **25**) of **31** as a colorless oil: IR (film) 2928, 2857, 1681, 1453, 1389, 1249, 1209, 847 cm^{-1}; UV (hexane) λ_{max} 255 (ϵ = 420), 218 (ϵ = 11 800); ^1H NMR (300 MHz, $CDCl_3$) δ 6.84 (dm, J = 10.2 Hz, 1 H), 5.98 (dm, J = 10.2 Hz, 1 H), 3.20 (t, J = 7.0 Hz, 2 H), 2.36–2.87 (m, 3 H), 2.01–2.08 (m, 1 H), 1.83–1.88 (m, 2 H), 1.64–1.74 (m, 1 H), 1.40–1.53 (m, 6 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.6, 154.8, 128.9, 36.8, 35.8, 34.2, 33.1, 30.3, 28.4, 25.2, 6.8; HRMS m/e calcd for $C_{11}H_{17}IO$ 292.0324, found 292.0324.

3-(4-Chlorobutyl)-2-cyclohexen-1-one (33). A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, 25-mL pressure-equalizing addition funnel, and rubber septum was charged with zinc dust (5.88 g, 90.0 mmol), 1,2-dibromoethane (0.775 mL, 1.69 g, 9.00 mmol), and 5 mL of THF, and then the resulting mixture was heated (with a heat gun) until the THF just began to reflux. The reaction mixture was

allowed to cool to room temperature and then heated in the same manner three more times. Me_3SiCl (0.57 mL, 0.489 g, 4.50 mmol) was then added dropwise via syringe. After 15 min, a solution of 4-chloro-1-iodobutane (9.18 g, 42.0 mmol) in 10 mL of THF was added dropwise over 20 min via the addition funnel, while the temperature of the reaction mixture was maintained below 30 °C. The reaction mixture was stirred at room temperature for 1.5 h, and then stirring was halted and the excess zinc was allowed to settle.

A 100-mL, three-necked, round-bottomed flask equipped with an argon inlet adapter, rubber septum, and glass stopper was charged with LiCl (3.56 g, 84.0 mmol), CuCN (3.76 g, 42.0 mmol), and 40 mL of THF and then was cooled to −20 °C while the solution of organozinc reagent prepared above was added via cannula. After 5 min, the flask was cooled to −60 °C while 3-iodo-2-cyclohexen-1-one (5.10 g, 23.0 mmol) was added in one portion via syringe. The reaction mixture was allowed to warm to −30 °C, stirred at −30 °C for 1.5 h, and then allowed to warm to room temperature over 2 h. The resulting mixture was quenched by the addition of 30 mL of aqueous 1 N HCl and diluted with 30 mL of diethyl ether. The aqueous layer was separated and washed with two 25-mL portions of diethyl ether, and the combined organic layers were washed with two 50-mL portions of saturated ammonium chloride solution, 30 mL of water, and 30 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 4.3 g of a pale yellow oil used in the next step without further purification: IR (film) 2938, 2871, 1666, 1626, 1456, 1424, 1300, 1250, 1192, 1129, 889 cm^{-1}; UV (hexane) λ_{max} 223 (ϵ = 13 400); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (t, J = 1.5 Hz, 1 H), 3.56 (t, J = 6.5 Hz, 2 H), 2.24–2.39 (m, 6 H), 1.96–2.04 (m, 2 H), 1.75–1.85 (m, 2 H), 1.62–1.73 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.6, 165.3, 125.9, 44.5, 37.3, 37.1, 31.9, 29.5, 24.1, 22.7.

3-(4-Iodobutyl)-2-cyclohexen-1-one (34). Reaction of chloro enone **33** (4.3 g) with sodium iodide (34.5 g, 230 mmol) in 100 mL of acetone was performed according to general procedure A. Column chromatography on silica gel (elution with 0–15% EtOAc–hexane) provided 4.670 g (57% overall yield from 1,3-cyclohexanedione) of **34** as a colorless oil: IR (film) 2925, 2867, 2830, 1665, 1625, 1455, 1424, 1349, 1324, 1251, 1213, 1196, 890 cm^{-1}; UV (hexane) λ_{max} 224 (ϵ = 15 900); ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (t, J = 1.5 Hz, 1 H), 3.20 (t, J = 6.7 Hz, 2 H), 2.34–2.39 (m, 2 H), 2.22–2.31 (m, 4 H), 1.96–2.04 (m, 2 H), 1.79–1.88 (m, 2 H), 1.58–1.69 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 199.5, 165.2, 125.9, 37.2, 36.7, 32.6, 29.5, 27.6, 22.6, 6.1; HRMS m/e calcd for $C_{10}H_{15}IO$ 278.0168, found 278.0165.

General Procedure D for the Intramolecular Conjugate Addition Reaction. 1-Cyclopentyl-3,3-dimethyl-2-butanone (11). A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet, 10-mL pressure-equalizing addition funnel, and rubber septum was charged with lithium (0.032 g, 4.61 mmol), naphthalene (0.615 g, 4.80 mmol), and 3 mL of THF. After 2.5 h, a solution of zinc chloride (0.327 g, 2.40 mmol) in 5 mL of THF was added over 15 min via the addition funnel to the blue-green solution of lithium naphthalenide. A dark gray suspension of active zinc metal formed immediately. To this mixture was then added in one portion a solution of iodo enone **10** (0.294 g, 1.00 mmol) in 4 mL of THF. After 1 h, the reaction mixture was quenched with 10 mL of 1 N HCl solution and diluted with 10 mL of diethyl ether. The aqueous layer was separated and washed with three 20-mL portions of diethyl ether, and the combined organic layers were washed with 20 mL of saturated Na_2SO_3 solution and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (elution with 0–50% dichloromethane–hexane) provided 0.101 g (60%) of **11** as a colorless oil which exhibited spectral data consistent with those reported previously:[29] IR (film) 2955, 2869, 1704, 1469, 1401, 1366, 1147, 1060, 996 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, J = 7.0 Hz, 2 H), 2.16–2.32 (m, 1 H), 1.74–1.85 (m, 2 H), 1.46–1.63 (m, 4 H), 1.09 (s, 9 H), 0.94–1.07 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 215.8, 44.0, 42.7, 35.3, 32.7, 26.3, 25.0.

1-Cyclopentyl-2-propanone (35). Reaction of iodo enone **15** (0.806 g, 3.20 mmol) in 30 mL of THF with activated zinc (prepared from lithium (0.136 g, 19.6 mmol), naphthalene (2.83 g, 22.1 mmol), and zinc chloride (1.53 g, 11.2 mmol)) was performed according to general procedure D, except that the flask was cooled to 20 °C during the addition of zinc chloride and the reaction mixture was stirred at room temperature for 50 min before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) afforded 0.224 g (56%) of **35** as a colorless oil which exhibited spectral data consistent with those reported previously:[30] IR (film) 2952, 2863, 1709, 1457, 1418, 1357, 1242, 1165, 733 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (d, J = 7.2 Hz, 2 H), 2.13–2.31 (m, 1 H), 2.13 (s, 3 H), 1.76–1.88 (m, 2 H), 1.47–1.68 (m, 4 H), 1.01–1.15 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 209.0, 50.0, 35.5, 32.5, 30.0, 24.9.

Ethyl Cyclopentylacetate (36). Reaction of iodo ester **17** (0.564 g, 2.00 mmol) in 12 mL of THF with activated zinc (prepared from lithium (0.050 g, 7.20 mmol), naphthalene (1.03 g, 8.03 mmol), and zinc chloride (0.545 g, 4.00 mmol)) was performed according to general procedure D, except that Me_3SiCl (0.635 mL, 0.543 g, 5.0 mmol) was added after 30 min and the reaction mixture was stirred at room temperature for 24 h before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) provided 0.128 g (41%) of **36**, contaminated with ca. 4% of the corresponding reduction product. A pure sample of **36** was obtained by column chromatography on silica gel (elution with 2–3% EtOAc–hexane) as a colorless oil which exhibited spectral data consistent with those reported previously:[31] IR (film) 2949, 2866, 1735, 1451, 1374, 1332, 1289, 1255, 1185, 1132, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.12 (q, J = 7.4 Hz, 2 H), 2.17–2.32 (m, 3 H), 1.76–1.88 (m, 2 H), 1.51–1.67 (m, 4 H), 1.25 (t, J = 7.4 Hz, 3 H), 1.11–1.22 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 173.4, 60.0, 40.5, 36.5, 32.4, 25.0, 14.2.

Methyl Cyclopentylideneacetate (37). Reaction of iodo ester **21** (0.293 g, 1.10 mmol) in 10 mL of THF with zinc (prepared from lithium (0.032 g, 4.6 mmol), naphthalene (0.641 g, 5.00 mmol), and zinc chloride (0.341 g, 2.50 mmol)) was performed according to general procedure D, except that the reaction mixture was stirred at room temperature for 5 days before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) furnished 0.101 g of **37** (66%) as a colorless oil which exhibited spectral data consistent with those reported previously:[32] IR (film) 2945, 2881, 2850, 1711, 1655, 1431, 1361, 1263, 1206, 1125, 1033, 859 cm^{-1}; UV (hexane) λ_{max} 217 (ϵ = 12 100); ^1H NMR (300 MHz, $CDCl_3$) δ 5.81 (quin, J = 2.3 Hz, 1 H), 3.69 (s, 3 H), 2.77 (bt, J = 7.5 Hz, 2 H), 2.44 (bt, J = 7.2 Hz, 2 H), 1.62–1.80 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.5, 167.3, 111.2, 50.7, 35.9, 32.6, 26.4, 25.5.

***cis*-5-Hydrindanone (38).** Reaction of iodo enone **27** (0.396 g, 1.5 mmol) in 12 mL of THF with zinc (prepared from lithium (0.043 g, 6.2 mmol), naphthalene (0.833 g, 6.50 mmol), and zinc chloride (0.436 g, 3.20 mmol)) was performed according to general procedure D, except that the reaction mixture was stirred at room temperature for 1 h before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) provided 0.137 g of **38** (66%) as a colorless oil which exhibited spectral data consistent with those reported previously:[23] IR (film) 2948, 2870, 1715, 1460, 1419, 1331, 1308, 1231, 1199, 1154 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 2.14 (dd, J = 5.8, 14.2 Hz, 1 H), 2.05 (dt, J = 5.4, 16.3 Hz, 1 H), 1.80–1.96 (m, 3 H), 1.60–1.72 (m, 1 H), 1.36–1.54 (m, 4 H), 1.13–1.29 (m, 2 H), 0.95–1.12 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 214.0, 43.3, 38.4, 38.3, 37.1, 32.6,

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31.5, 27.2, 24.0. 2,4-DNP derivative (recrystallized from MeOH–$CHCl_3$): mp 173 °C (lit.[22d] mp 171 °C).

***cis*-2-Decalone (39).** Reaction of iodo enone **29** (0.348 g, 1.25 mmol) in 10 mL of THF with zinc (prepared from lithium (0.033 g, 4.75 mmol), naphthalene (0.641 g, 5.00 mmol), and zinc chloride (0.341 g, 2.50 mmol)) was performed according to general procedure D, excpet that Me_3SiCl (0.40 mL, 0.34 g, 3.15 mmol) was added after 30 min and the reaction mixture was stirred at room temperature for 48 h before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) furnished 0.097 g (51%) of **39** as a colorless oil which exhibited spectral data consistent with those reported previously:[24] IR (film) 2918, 2859, 1714, 1455, 1340, 1256, 1196, 1163, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.22–2.36 (m, 4 H), 2.06–2.14 (m, 1 H), 1.90–2.04 (m, 2 H), 1.42–1.77 (m, 9 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.7, 45.4, 39.3, 38.5, 34.8, 28.8, 28.7, 28.3, 23.6, 22.9.

Spiro[4.5]decan-7-one (40). Reaction of iodo enone **34** (1.95 g, 7.01 mmol) in 35 mL of THF with zinc (prepared with lithium (0.199 g, 28.7 mmol), naphthalene (3.97 g, 31.0 mmol), and zinc chloride (2.112 g, 15.50 mmol)) was performed according to general procedure D, except that the flask was cooled to 20 °C during the addition of zinc chloride and the reaction mixture was stirred at room temperature for 24 h before quenching. Column chromatography on silica gel (elution with 0–3% EtOAc–hexane) provided 0.725 g of **40** (68%) as a colorless oil which exhibited spectral data consistent with those reported previously:[4] IR (film) 2955, 2936, 2861, 1708, 1450, 1426, 1311, 1284, 1228, 1079 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.27–2.32 (dt, J = 1.4, 6.5 Hz, 2 H), 2.24 (s, 2 H), 1.82–1.90 (m, 2 H), 1.61–1.68 (m, 6 H), 1.40–1.45 (m, 4 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.0, 53.3, 47.4, 41.3, 38.2, 36.8, 24.3, 23.7.

***cis*-4-Methyl-5-hydrindanone (47 and 48).** A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet, 10-mL pressure-equalizing addition funnel, and rubber septum was charged with lithium (0.39 g, 5.62 mmol), naphthalene (0.769 g, 6.00 mmol), and 4 mL of THF. After 2.5 h, a solution of zinc chloride (0.409 g, 3.00 mmol) in 6 mL of THF was added via the addition funnel over 15 min to the blue-green solution. A dark gray suspension of active zinc metal formed immediately. To this mixture was added in one portion a solution of iodo enone **27** (0.396 g, 1.50 mmol) in 2 mL of THF. After 1 h, the reaction mixture was cooled to −78 °C and treated dropwise over 1 min with a solution of methyllithium (1.43 M in hexane, 2.10 mL, 3.00 mmol) followed by methyl iodide (0.467 mL, 1.07 g, 7.50 mmol). After 30 min, the cooling bath was removed and the reaction mixture was stirred at room temperature for 2.5 h. The resulting mixture was cooled to 0 °C, quenched by the addition of 10 mL of 1 N HCl solution, and diluted with 10 mL of diethyl ether. The aqueous phase was separated and washed with two 10-mL portions of diethyl ether, and the combined organic phases were washed with 20 mL of saturated Na_2SO_3 solution and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (elution with 0–2% EtOAc–hexane) provided 0.133 g of an 85:15 mixture of **47** and **48** (58%) as a colorless oil: IR (film) 2940, 2917, 2869, 1711, 1456, 1407, 1378, 1310, 1202 cm^{-1}; ^1H NMR (300 MHz, C_6D_6) δ 2.80 (quint, J = 5.8 Hz, **48**), 2.08 (dt, J = 5.0, 17.3 Hz, 1 H), 1.83–1.98 (m, 1 H), 1.78 (dq, J = 6.4, 10.9 Hz, 1 H), 1.52–1.69 (m, 3 H), 1.38–1.50 (m, 3 H), 1.17–1.34 (m, 2 H), 1.00–1.12 (m, 2 H), 1.04 (d, J = 6.4 Hz, 3 H, **47**), 1.01 (d, J = 6.8 Hz, **48**); ^{13}C NMR (75.5 MHz, $CDCl_3$) **47**, δ 215.3, 46.0, 45.0, 37.8, 37.6, 33.3, 32.7, 27.0, 25.2, and 12.8, **48**, δ 214.4, 47.6, 44.8, 38.7, 37.7, 30.8, 27.8, 26.3, 22.6, and 12.6; HRMS m/e calcd for $C_{10}H_{16}O$ 152.1201, found 152.1201.

***(E)*-4-Ethylidene-*cis*-5-hydrindanone (49).** A 50-mL, three-necked, round-bottomed flask equipped with an argon inlet, 10-mL pressure-equalizing addition funnel, and rubber septum was charged with lithium (0.057 g, 8.21 mmol), naphthalene (1.16 g, 9.00 mmol), and 4 mL of THF. After 2.5 h, a solution of zinc chloride (0.613 g, 4.50 mmol) in 6 mL of THF was added via the addition funnel over 20 min to the blue-green solution. A dark gray suspension of active zinc metal formed immediately. To this mixture was added a solution of iodo enone **27** (0.528 g, 2.00 mmol) in 2 mL of THF in one portion. After 1 h, the reaction mixture was cooled to −78 °C while a solution of methyllithium (1.43 M in hexane, 2.80 mL, 4.00 mmol) was added via syringe over ca. 1 min. After 10 min, a solution of acetaldehyde (0.880 g, 1.16 mL, 20.0 mmol) in 2 mL of THF was added in one portion via the addition funnel and the reaction mixture was stirred at −78 °C for 3 h. The reaction mixture was quenched at 0 °C with 10 mL of 1 N HCl solution and diluted with 10 mL of diethyl ether. The aqueous phase was separated and washed with two 10-mL portions of diethyl ether, and the combined organic phases were washed with 20 mL of saturated Na_2SO_3 solution and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. The residue was dissolved in 20 mL of benzene, a crystal of *p*-toluenesulfonic acid was added, and the resulting solution was stirred at room temperature for 12 h and then was quenched with 10 mL of water. The aqueous layer was separated and extracted with two 10-mL portions of diethyl ether, and the combined organic phases were washed with three 20-mL portions of water and 20 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated. Column chromatography on silica gel (elution with 0–2% EtOAc–hexane) provided 0.121 g (37%) of **49** as a colorless oil: IR (film) 2928, 2866, 1690, 1616, 1449, 1419, 1321, 1255, 1168, 1149, 891 cm^{-1}; UV (hexane) λ_{max} 238 (ϵ = 7100); ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (dq, J = 1.3, 7.3 Hz, 1 H), 3.10 (br q, J = 8.1 Hz, 1 H), 2.43–2.52 (m, 1 H), 2.23–2.40 (m, 2 H), 1.87–2.10 (m, 2 H), 1.54–1.80 (m, 5 H), 1.79 (d, J = 7.1 Hz, 3 H), 1.25–1.39 (m, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.3, 139.5, 135.3, 40.4, 38.3, 37.6, 31.9, 31.8, 25.9, 23.7, 13.7; HRMS m/e calcd for $C_{11}H_{16}O$ 164.1201, found 164.1201.

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