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Design and synthesis of novel spirocyclopropyl cyclohexane-1,3-diones and -1,3,5-triones for their incorporation into potent HPPD inhibitors

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ABSTRACT

We report the design and the efficient synthesis of novel spirocyclopropyl cyclohexane-1,3-dione and -1,3,5-trione units to be incorporated into potent HPPD inhibitors. New routes involving original combinations of synthetic equivalents of α-cyclopropyl ketone-α-anion and α-cyclopropyl ester-β-cation are described.

Inhibitors of plant 4-hydroxyphenylpyruvate dioxygenase (HPPD) are potent herbicides.[1] The most promising sub-class of HPPD inhibitors in plant displays a generic structure with an arylketone linked to a cyclohexane-1,3-dione[2,3] (Fig. 1). Several representatives of this class of HPPD inhibitors have already found commercial applications in field crops.[2–4] In particular, Mesotrione **1** was introduced by Syngenta as a highly efficient selective herbicide in corn, controlling a broad spectrum of weeds, in particular broad leaf weeds. In an attempt to further increase the activity of Mesotrione, especially on grass weeds, substituted cyclohexane-1,3-diones were investigated. One major metabolic pathway of Mesotrione in corn and in other monocotyledon plants is hydroxylation, by cytochrome P-450 enzymes, of the cyclohexane-1,3-dione moiety at C-4 position adjacent to the carbonyl (Fig. 1). This hydroxylation leads to detoxification of corn and, unfortunately, of various grass weeds from Mesotrione. Substitution of one or both methylene groups in cyclohexane-1,3-diones by methyl groups (Fig. 1, **2**–**4**) prevents their oxidation and increases the activity of the corresponding triketones as herbicides. In particular, tetraketone **4** displays a very high activity on a very broad range of mono- and di-cotyledon weeds. However, this stabilization of derivatives **2**–**4** against cytochrome P-450 metabolism also leads to a decrease in selectivity and an increase in their soil persistence. Consequently, the corresponding triketones obtained after coupling with the arylketone moiety of Mesotrione are not tolerated anymore by corn and are much less readily metabolized in soil, increasing the risk of carry-over.[5] In addition, not much space is available in the HPPD binding site around the cyclohexane dione moiety.[6] Substituents larger than methyl are not tolerated. The bicyclic dione scaffold in **5** (Fig. 1) was identified as an excellent pattern which confers the corresponding triketones an increased stability against cytochrome P-450 metabolism and, as a consequence, an improved activity against grass weeds retaining, however, excellent selectivity for corn.[7]

We then designed novel spirocyclopropyl derivatives **6**–**8** (Fig. 1) which display less sterically demanding cyclopropyl units as opposed to the original gem-dimethyl substitution.[8] We also hoped that this feature would decrease cytochrome P-450 metabolism. In contrast, we postulated that the spirocyclopropyl moiety should be activated towards nucleophilic addition by the adjacent carbonyl group in **6**, **7**, and even more by two adjacent carbonyl functions in **8**, ideally preorganized by the cyclohexyl ring for synergistic activation of the 3-membered ring.[9,10] Therefore, one could expect that triketones **6**, **7** and tetraketones **8** should be susceptible to Glutathione S-transferase metabolism in corn and not in grass weeds. Indeed, we have shown that triketones **6**, **7** are very potent selective herbicides in corn. However, tetraketones **8** are too activated towards nucleophilic ring opening to be used as herbicides.

We postulated that spirocyclopropyl cyclohexane-1,3-diones **9** and **10** could be accessible from unstable synthons **13**–**15** generated in situ from their corresponding synthetic equivalents (Scheme 1).

Spirocyclopropyl dione **9** was readily obtained in three steps from the anion of 2-acetyl-γ-butyrolactone **16** as an equivalent of the α-cyclopropyl ketone-α-anion **15** (Scheme 2). The Michael addition of the anion **16** on methyl acrylate **17** gave the adduct **18** in 96% isolated yield.[11,12] Lactone **18** then undergoes a decarboxylative ring contraction upon treatment with sodium iodide at high temperature in a dipolar solvent[13] to provide the corresponding cyclopropane

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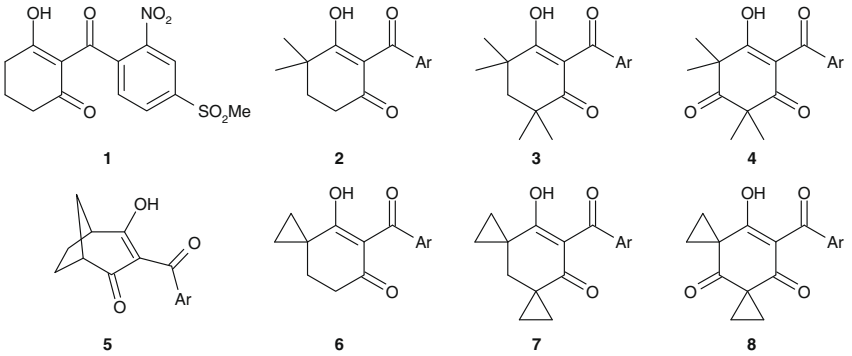
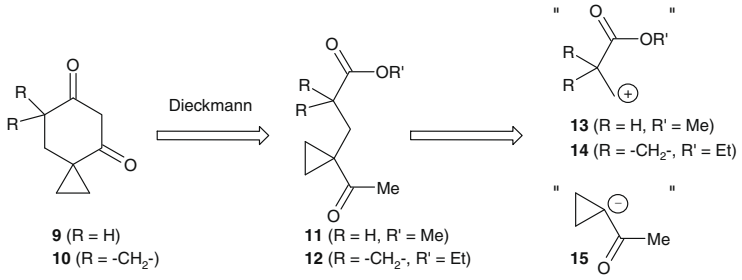


Figure 1. Triketones and tetraketones as HPPD inhibitors.



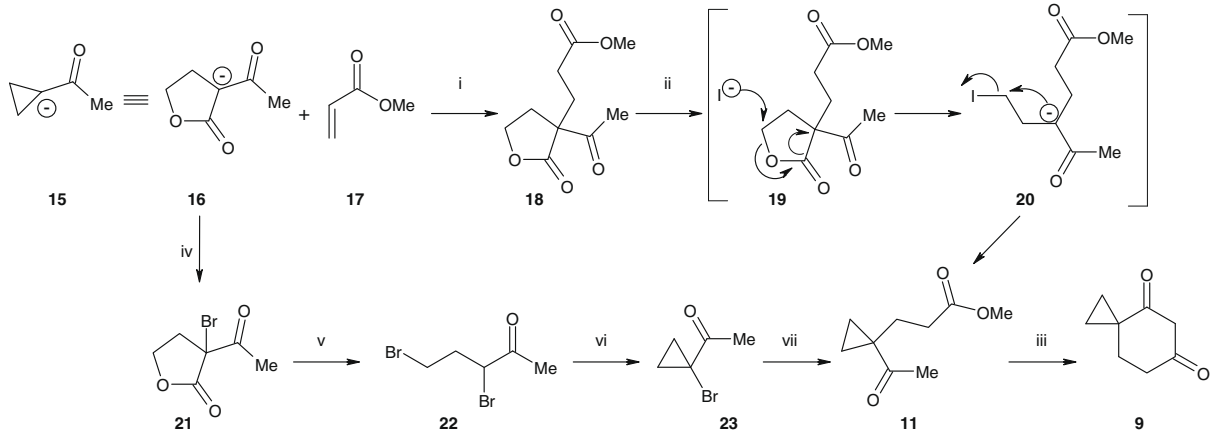
Scheme 1. Proposed retrosynthetic approach towards spirocyclopropyl cyclohexane-1,3-diones.

intermediate **11** in 63% yield. Treatment of ketoester **11** with NaH leads to the desired spirocyclohexane-1,3-dione **9** in 50% yield. This sequence was readily scaled up for the synthesis of a few hundred grams of **9** with similar overall yield.

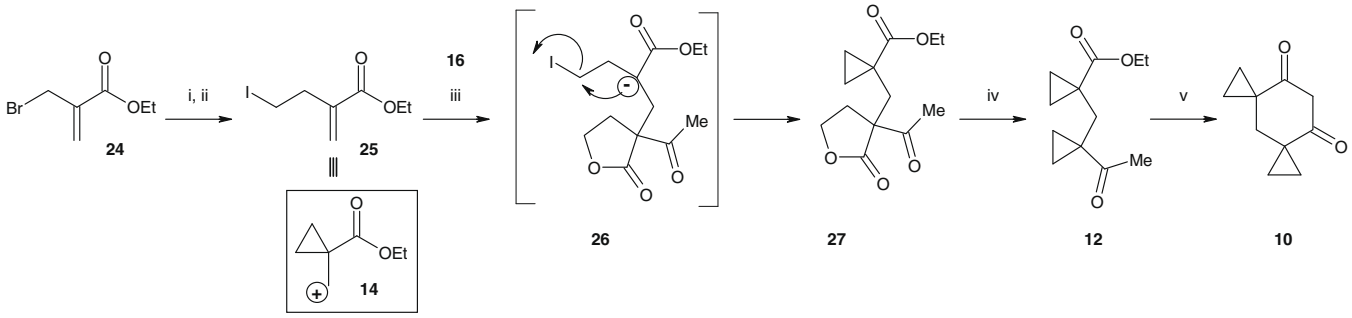
Noteworthy is an alternative synthesis which involves a radical addition reaction of the destabilized cyclopropyl radical[14] to methyl acrylate (**23**→**11**, Scheme 2). However, the desired product **11** was isolated in very modest yield due to extensive polymerization of methyl acrylate.

An efficient synthesis of the novel bis-spirocyclopropyl cyclohexane-1,3-dione **10** was established using homoallylic iodide **25** as a precursor of the unprecedented β-cationic-α-cyclopropyl ketoester **14**, readily obtained from the corresponding allylic bromide **24**[15] (Scheme 3). We postulated that the homoallylic iodide **25** should preferentially react through Michael addition with a soft nucleophile as the anion **16**, followed by cyclization of the incipient ester enolate to the corresponding cyclopropane intermediate **27**, rather than undergo elimination and/or substitution. Indeed, the primary Michael adduct is not isolated, as the corresponding anionic intermediate **26** cyclizes spontaneously to give **27** in 77% yield. Lactone **27** was further submitted to the previously described decarboxylative ring contraction conditions to give the highly volatile intermediate **12** which was directly treated under Dieckmann conditions to provide the desired bis-spirocyclopropyl cyclohexane-1,3-dione **10** in 53% yield.

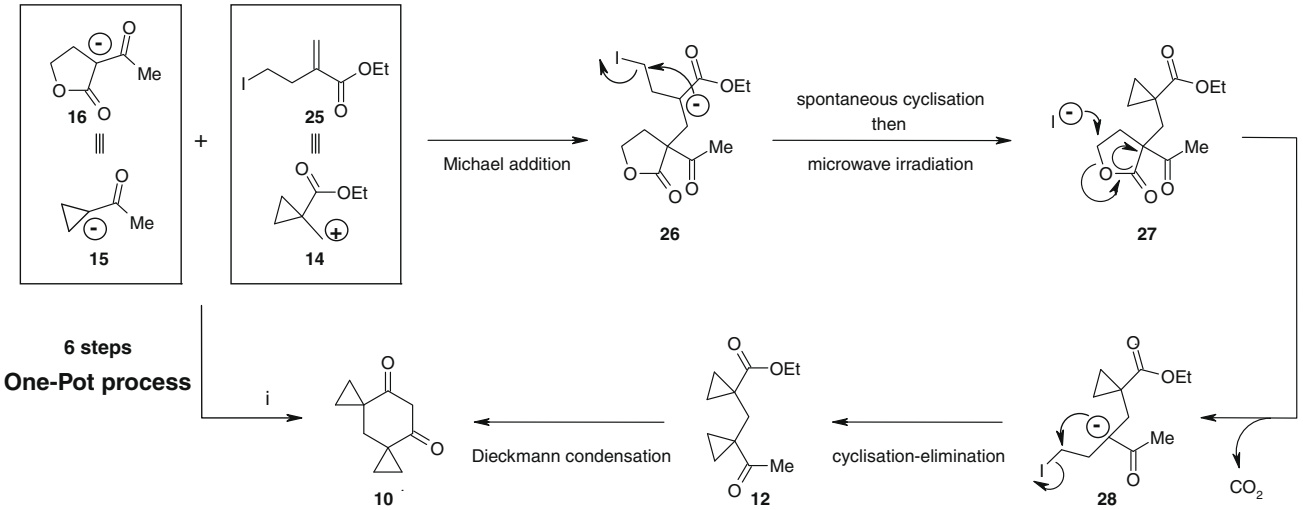
The convergence of the reaction conditions allows to envisage a one-pot process for this sequence. The iodide released from the first cyclopropanation step might act as the required nucleophile able to initiate the decarboxylative ring contraction, leading to the formation of the second cyclopropane ring. Indeed, the one-pot



Scheme 2. Reagents and conditions: (i) 2-acetyl-γ-butyrolactone (1.0 equiv), NaH (1.0 equiv), methyl acrylate **17** (1.0 equiv), *tert*-BuOH, 35 °C, 4 h, 96%; (ii) NaI (1.5 equiv), NMP, 190 °C, 2 h, 63%; (iii) NaH (1.0 equiv), DMF/THF (1:5), 70 °C, 6 h, 50%; (iv) 2-acetyl-γ-butyrolactone (1.0 equiv), NaH (1.0 equiv), Br_2 (1.0 equiv), THF, −30 °C to rt, 3 h, 90%; (v) HBr aq. (33%), 60 °C, 2 h, 40%; (vi) NaH (1.0 equiv), THF, rt, 3 h, 50%; (vii) *n*-Bu_3SnH (1.1 equiv), methyl acrylate (5.0 equiv), AIBN (0.1 equiv), benzene (0.1 M), reflux, 12 h, 15%.



Scheme 3. Reagents and conditions: (i) Zn (1.0 equiv), 1,2-dibromoethane (0.04 equiv), trimethylchlorosilane (0.03 equiv), diiodomethane (1.0 equiv), THF, rt, 5 h; (ii) ethyl α-bromomethacrylate **24** (1.0 equiv), LiI (2.3 equiv), CuI (1.2 equiv), THF, rt, 16 h, 80% (over two steps); (iii) 2-acetyl-γ-butyrolactone (1.0 equiv), NaH (1.1 equiv), DMF, 0 °C to rt, 20 h, 77%; (iv) NaI (1.5 equiv), NMP, microwaves, 240 °C, 2 × 10 min; (v) MeONa (1.5 equiv), rt, 2 h, 53% (over two steps).



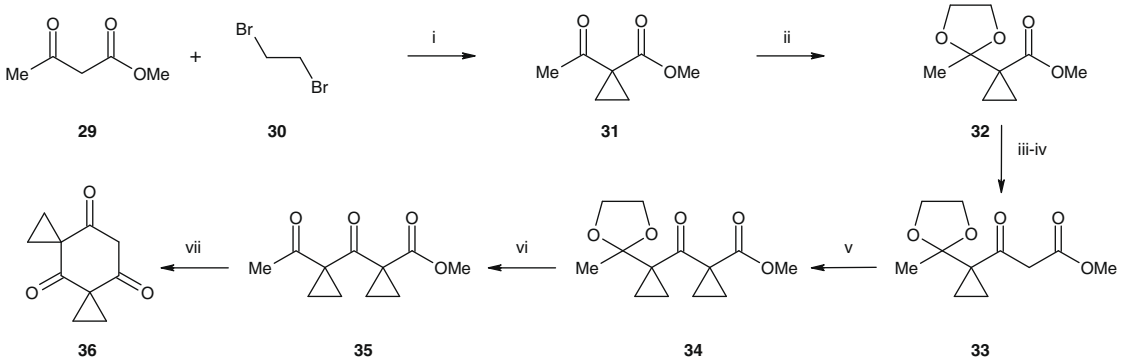
Scheme 4. Reagents and conditions: (i) 2-acetyl-γ-butyrolactone (1.0 equiv), NaH (1.1 equiv), homoallylic iodide **25** (1.0 equiv), NMP, 0 °C to rt, 20 h then microwave irradiation, 240 °C, 10 min then NaH (2.6 equiv), rt, 6 h, 28%.

sequence allowed us to isolate the desired bis-spirocyclopropyl cyclohexane-1,3-dione **10** in 28% overall yield (Scheme 4).

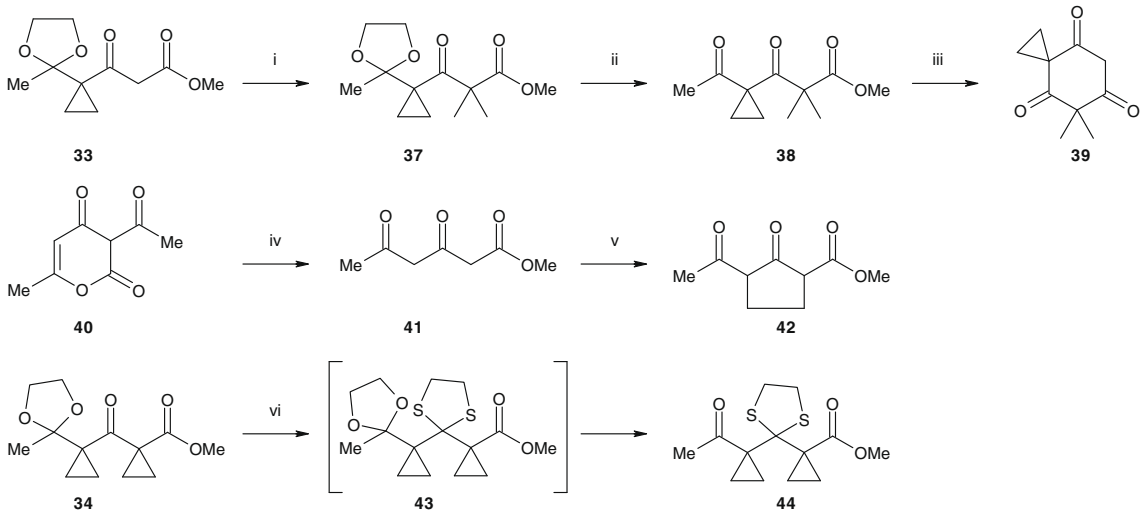
We have thus demonstrated that the homoallyliodide **25** is a synthon equivalent to the unstable α-cyclopropyl ester-β-cation **14**. We have also generalized the use of **25** with various soft nucleophiles. These results will be reported in due course.

The synthesis of the bis-cyclopropyl trione **36** requires the sequential cyclopropanation of **29** and **33** (Scheme 5). The methyl ketone in **31** has to be protected as ketal **32** to allow selective introduction of the methyl acetate moiety as well as the second selective cyclopropanation of **33** into **34**. Indeed, when this reaction was attempted on unprotected **41**,[16] only the undesired cyclopentane derivative **42** was detected (Scheme 6). After deprotection of ketal **34**, the resulting diketo ester **35** was cyclized into the rather strained triketone **36** (Scheme 5).

Various analogs of triketone **36** can be obtained using other electrophiles than 1,2-dibromoethane (Scheme 6). For example, the gem-dimethyl group can be introduced by treatment of **33**



Scheme 5. Reagents and conditions: (i) 1,2-dibromoethane (2.0 equiv), K_2CO_3 (2.5 equiv), acetone, 16 h, reflux, 80%; (ii) ethylene glycol (3.0 equiv), pyridinium toluene-4-sulfonate (0.1 equiv), toluene, 22 h, 81%; (iii) NaOH (2.2 equiv), H_2O/EtOH, rt, 18 h, 67%; (iv) $SOCl_2$ (1.5 equiv), CH_2Cl_2, rt, 1 h, then methyl acetate (1 equiv), LiHMDS (2.1 equiv), THF, −75 °C, 2 h, 83%; (v) 1,2-dibromoethane (2.0 equiv), K_2CO_3 (2.5 equiv), acetone, reflux, 20 h, 84%; (vi) pyridinium toluene-4-sulfonate (0.3 equiv), acetone/H_2O (2:1), reflux, 3 h, 76%; (vii) NaOMe (1.5 equiv), toluene/DMF (19:1), reflux, 2 h, 85%.



Scheme 6. Reagents and conditions: (i) NaH (3.0 equiv), MeI (3.0 equiv), THF, rt, 72 h, 61%; (ii) pyridinium toluene-4-sulfonate (0.3 equiv), acetone/H_2O (2:1), reflux, 3 h, 99%; (iii) MeONa (1.5 equiv), toluene/DMF (19:1), reflux, 2 h, 87%; (iv) Mg (1.5 equiv), MeOH, reflux, 16 h, 81%; (v) 1,2-dibromoethane (4.0 equiv), K_2CO_3 (5.0 equiv), acetone, reflux, 17 h, 99%; (vi) 1,2-ethanedithiol (1.5 equiv), $BF_3{\cdot}Et_2O$ (0.2 equiv), CH_2Cl_2, rt, 18 h, 58%.

with MeI in the presence of NaH, the desired trione **39** being obtained after deprotection and cyclization (Scheme 6).

The modified building-block **44**, having the central ketone protected as dithiane, can be readily obtained from **34** (Scheme 6).

The novel spirocyclopropyl diones **9**, **10** and **39** were successfully coupled to a variety of aromatic carboxylic acids, leading to very active and corn selective herbicides. Although triketone **36** could be coupled with aromatic acids, the resulting tetraketones were too susceptible to nucleophilic ring opening to be of use as herbicides.

In conclusion, we have developed simple and efficient syntheses towards novel spirocyclopropyl cyclohexane-1,3-diones and 1,3,5-triones to be incorporated into potent HPPD inhibitors. The new routes involve the combination of synthetic equivalents of the α-cyclopropyl ketone-α-anion and α-cyclopropyl ester-β-cation. The generalization of the use of the homoallyliodide **25** as a synthon equivalent to the α-cyclopropyl ester-β-cation **14** will be reported in the near future.

References and notes

1. Hawkes, T. R. In *Modern Crop Protection Compounds*; Kramer, W., Schirmer, U., Eds.; Wiley-VCH, Verlag GmbH&Co KGaA: Weinheim, 2007; pp 211–221.
2. Edmunds, A. J. F. In *Modern Crop Protection Compounds*; Kramer, W., Schirmer, U., Eds.; Wiley-VCH, Verlag GmbH&Co KGaA: Weinheim, 2007; pp 221–243.
3. Beaudegnies, R.; Edmunds, J. F.; Fraser, T. E. M.; Hall, R. G.; Hawkes, T. R.; Mitchell, G.; Schaetzer, J.; Wendeborn, S.; Wibley, J. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 4134–4152.
4. Van Almsick, A. In *Modern Crop Protection Compounds*; Kramer, W., Schirmer, U., Eds.; Wiley-VCH, Verlag GmbH&Co KGaA: Weinheim, 2007; pp 243–257.
5. Mitchell, G.; Bartlett, D. W.; Fraser, T. E.; Hawkes, T. R.; Holt, D. C.; Townson, J. K.; Wichert, R. A. *Pest. Manag. Sci.* **2001**, *57*, 120–128.
6. Brownlee, J. M.; Johnson-Winters, D. H. T.; Harrison, G. R.; Moran, G. *Biochemistry* **2004**, *43*, 6370–6377.
7. Schneider, H.; Luethy, C.; Edmunds, A. J. F. (Syngenta AG), **2003**, EP 1352901.
8. Edmunds, A. J. F.; Luthy, C.; Seckinger, K.; De Mesmaeker, A.; Kunz, W.; Schaetzer, J. **2000**, WO 2000039094.
9. Danishefsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239–3241.
10. Danishefsky, S.; Singh, R. K. *J. Org. Chem.* **1975**, *40*, 2969–2970.
11. For the stereoselective synthesis of **18** using chiral enamines see: Felk, A.; Revial, G.; Viossat, B.; Lemoine, P.; Pfau, M. *Tetrahedron: Asymmetry* **1994**, *5*, 1459–1462.
12. For the synthesis of **18** under different reaction conditions see: Bensa, D.; Rodriguez, J. *Synth. Commun.* **2004**, *34*, 1515–1533.
13. For the synthesis of methylcyclopropylketone by ring opening of the corresponding lactone with NaI see: Weber, W.; De Meijere, A. *Synth. Commun.* **1986**, *16*, 837–845.
14. For the generation of cyclopropyl radicals, see for example: Heinrich, M. R.; Zard, S. Z. *Org. Lett.* **2004**, *6*, 4969–4972.
15. Knochel, P.; Chou, T.; Chen, G. H.; Yeh, M. C. P.; Rozema, M. J. *J. Org. Chem.* **1989**, *54*, 5202–5204.
16. For the synthesis of **41**, see: Shao, L.; Kawano, H.; Saburi, M.; Uchida, Y. *Tetrahedron* **1993**, *49*, 1997–2010.