Natural Products

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Synthesis and Applications of Hajos–Parrish Ketone Isomers**

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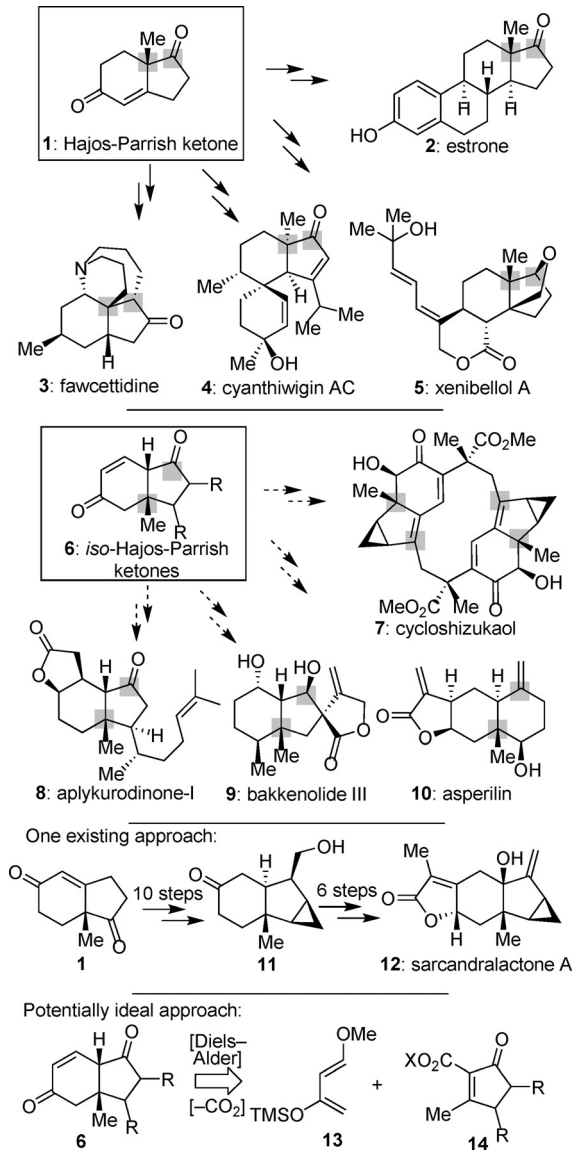
Abstract: *Numerous natural products possess ring systems and functionality for which Hajos–Parrish ketone isomers with a transposed methyl group (termed "iso-Hajos–Parrish ketones") would be of value. However, such building blocks have not been exploited to the same degree as the more typical Hajos–Parrish hydrindane. An efficient three-step synthesis of such materials was fueled by a simple method for the rapid preparation of highly functionalized cyclopentenones, several of which are new chemical entities that would be challenging to access through other approaches. Furthermore, one iso-Hajos–Parrish ketone was converted into two distinct natural product analogues and one natural product. As one indication of the value of these new building blocks, that latter target was obtained in 10 steps, having previously been accessed in 18 steps using the Hajos–Parrish ketone.*

The Hajos–Parrish ketone (**1**, Scheme 1)[1] has long been a valuable starting material for accessing natural products, given the wealth of structures containing similar 6,5-fused ring systems with a 1,2 relationship between the highlighted stereogenic center and the ketone group (or functional groups derived from it).[2] By contrast, strategies to access "iso-Hajos–Parrish" ketones of general structure **6**, materials that possess a 1,3 placement of these two key groups and a change in alkene location, are far less developed, even though numerous compounds carry one or more such domains (including **7**–**9**), sometimes in a ring-expanded format (as in **10**). One possibility to prepare these materials begins with the Hajos–Parrish ketone (**1**) itself and uses a linear array of subsequent synthetic steps to transpose its functional groups into molecules such as sarcandralactone A (**12**).[3] We envisioned, however, that a more expedient and general strategy for the synthesis of natural products such as **7**–**10** and **12**[4] could exist if one could readily prepare an array of iso-Hajos–Parrish ketones (**6**) with diversity at the sites indicated by group R. For that task, an ideal approach might be to merge varied cyclopentenones (**14**) directly with the Danishefsky diene (**13**) in a Diels–Alder reaction, followed by an in situ decarboxylation. However, while this idea is simply



Scheme 1. The value of the Hajos–Parrish ketones (**1**) in total synthesis, and a proposal that iso-Hajos–Parrish ketones of structure **6** could be of equal value if the merger of **13** and **14** can be achieved in one pot and if diverse cyclopentenones of type **14** can be prepared.

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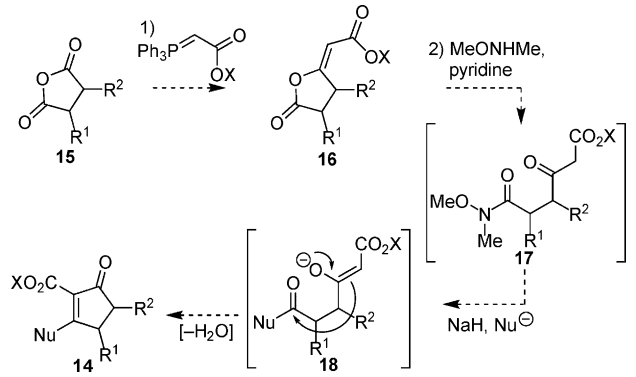
stated, such Diels–Alder reactions are rare, often needing multi-step or mechanistically distinct solutions such as double Michael additions.[5] Perhaps more critically, methods to efficiently and reliably prepare the requisite functionalized cyclopentenones (**14**) are lacking. Indeed, while cyclopentenones can be prepared by a number of different pathways, including metalation chemistry,[6] Michael additions/reoxidations,[7] metal cyclizations/Conia ene chemistry,[8] and Nazarov cyclizations,[9] general, mild, and step-economic processes have not been demonstrated for many variants of the types desired as broadly defined by R within **14**. Herein, we detail a simple, two-step solution capable of affording structurally diverse cyclopentenones. We then show how these materials can be converted into complex polycycles, serve as masked forms of cyclopentadienone, and afford several iso-Hajos–Parrish ketones (**6**) in just three steps overall. Finally, we illustrate that one of these ketones can be advanced into two natural product analogues and natural product **12**. As one measure of that new ketone′s value, the latter target was obtained in only 10 steps, having been previously prepared in a total of 18 steps using **1**.

Our overall design for achieving a rapid and broadly applicable cyclopentenone synthesis is shown in Scheme 2. Following Wittig olefination of an anhydride (**15**) with a stabilized ylide to generate **16**,[10] we hoped that subsequent ring opening as facilitated by the Weinreb amine would afford a new material (**17**) that could, in the same pot, be enolized, treated with a nucleophile (here a methyl anion) to form

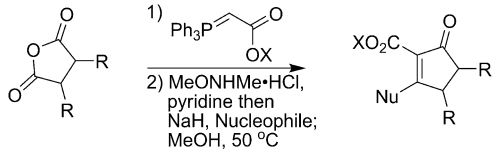


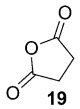
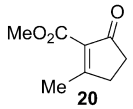
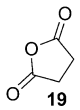
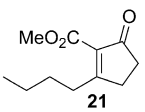
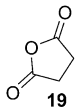
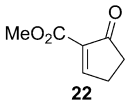
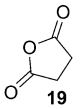
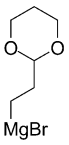
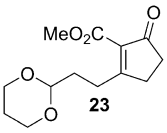
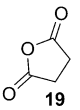
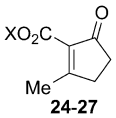
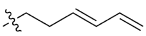
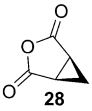
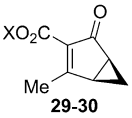
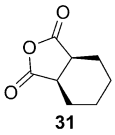
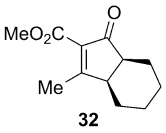
Scheme 2. Proposed method for cyclopentenone synthesis.

a new ketone (**18**), and then undergo a Knoevenagel condensation and generate **14**.[11] Although all these individual steps are known operations, their combination in this cascade is, to the best of our knowledge, without precedent.

Following significant reaction screening and optimization, particularly of the second of these two steps, this designed process could be achieved and a number of functionalized cyclopentenones were prepared in moderate to good yield as shown in Table 1. The initial Wittig reaction was conducted in toluene at 50 °C for 16 h, and afforded only a single alkene stereoisomer in all cases presented within the table. The optimized process for step two involved the initial formation of a Weinreb amide[12] under standard conditions, followed by treatment with 1.3 equivalents of NaH in THF at 0 °C for 30 min and then exposure to the desired nucleophile (1.1 equiv) at −78 °C for 1 h. Once complete, the reaction mixture was then heated at 50 °C in the presence of excess MeOH (50 equiv) for 1 h to effect the terminating Knoevenagel condensation. As indicated with the entries listed for succinic anhydride (**19**), many different nucleophiles can be used, with lithiated species generally giving superior yields over Grignard reagents (entries 1–5).[13] Various groups labelled as X can be incorporated in the olefination step as well to ultimately give different exocyclic esters (entries 6–9), with control of reaction temperature in the final Knoevenagel condensation being key to preventing transesterification with the added MeOH. Critically, anhydrides with additional substituents, and thus increased steric bulk near the key

Table 1: Initial exploration of the scope of cyclopentenone synthesis from acid anhydrides.[a]



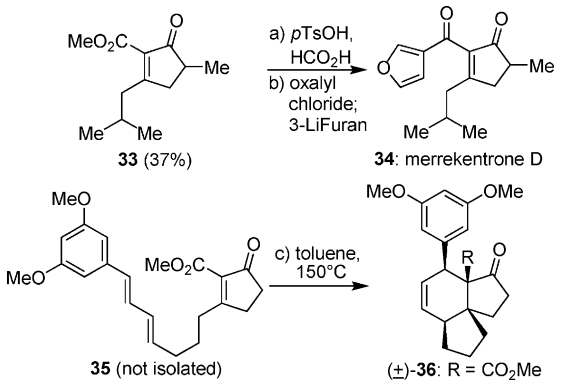
Entry	Anhydride	X	Nucleophile	Product	Yield [%]
1	 **19**	Me	MeLi	 **20**	68
2		Me	MeMgBr		54
3	 **19**	Me	*n*BuLi	 **21**	65
4	 **19**	Me	DIBAL-H	 **22**	48
5	 **19**	Me		 **23**	46
6	 **19**	Allyl	MeLi	 **24-27**	58
7		Bn	MeLi		62
8		*t*Bu	MeLi		71
9			MeLi		61
10	 **28**	Me	MeLi	 **29-30**	72[b]
11		*t*Bu	MeLi		71
12	 **31**	Me	MeLi	 **32**	53

[a] General conditions: Wittig phosphorylidine (1.0 equiv), anhydride (1.0 equiv), 50 °C, 10–16 h; *N*,*O*-dimethyl hydroxylamine·HCl (1.3 equiv), pyridine (5.0 equiv), CH_2Cl_2, 25 °C, 6 h, then THF, NaH (1.3 equiv), 0 °C, 30 min, then nucleophile (1.1 equiv), −78 °C, 1 h, then MeOH (50 equiv), 50 °C, 1 h. [b] Synthesized on gram scale.

reacting carbonyl groups, were also tolerated, affording the means to effect inaugural syntheses of cyclopentenones **29**, **30**, and **32** (entries 10–12). The reaction sequence could also be performed on gram scale (entry 10).

Globally, while the overall yield of these two-step sequences are in the range of 45–70%, that outcome correlates to more than 80% yield per operation within the four-part cascade sequence of step 2 for even the lowest-yielding entry. Key to these yields is the initial formation of a Weinreb amide. Indeed, although direct treatment of materials of type **16** (compare with Scheme 2) with the desired nucleophile could ultimately afford cyclopentenones of type **14**, these processes sometimes failed and overall yields were significantly diminished when they were successful. Of note, several of the final compounds in Table 1, such as the acetal of **23**, the allyl group of **24**, and the cyclopropane of **29** and **30**, are unlikely to result from and/or survive the conditions of available approaches, particularly Lewis acid promoted Nazarov cyclizations.[14]

Two more advanced examples of cyclopentenone synthesis are shown in Scheme 3. In the first case, a nonsymmetric anhydride could be converted into **33** in 37% overall yield. Here, the initial Wittig reaction proceeded to afford a 1:1.2 ratio of regioisomers, indicating that the neighboring bulk of the methyl group did not dramatically deter the formation of



Scheme 3. Selected examples of advanced cyclopentenones and their use in additional applications, including a total synthesis of merrekentrone D (**34**): a) *p*-TsOH·H_2O (1.0 equiv), HCO_2H, 90°C, 4 h, 91%; b) oxalyl chloride (2.0 equiv), DMF (cat.), CH_2Cl_2, 0°C, 30 min, then 25°C, 4 h; concentrate; 3-LiFuran (1.1 equiv), THF, −116°C, 1.5 h, 18%; c) toluene, 150°C, 24 h, 32%. DMF = *N*,*N*-dimethylformamide, Ts = tosyl.

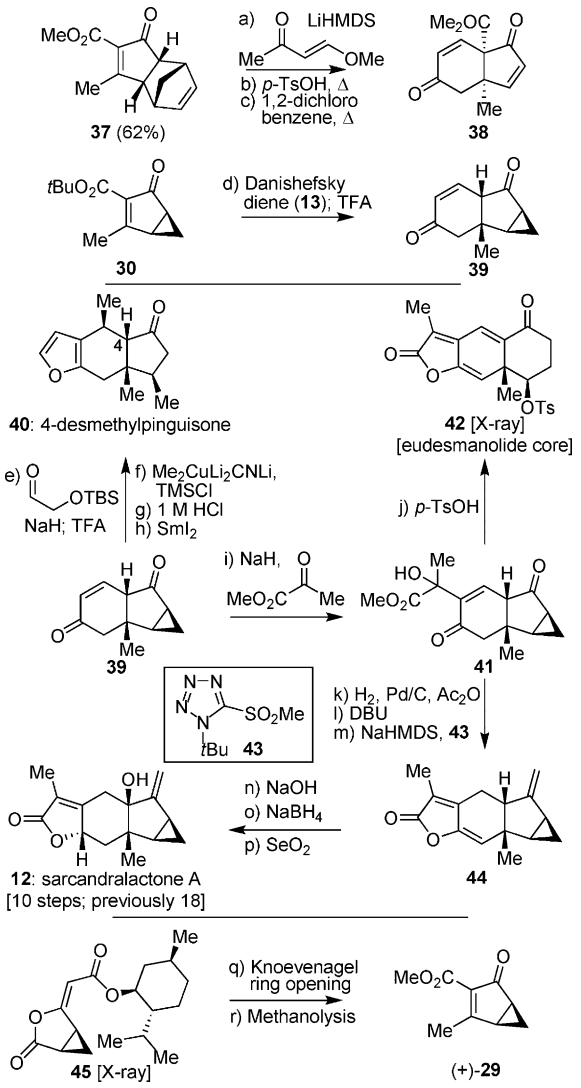
the desired intermediate.[15] The resultant compound (**33**) was then advanced in two additional and standard transformations through the intermediacy of an acid chloride into the natural product merrekentrone D (**34**).[16,17] In the second example, a nucleophile was used bearing a pendant diene system with anhydride **19** (compare with Table 1) to afford a cyclopentenone (**35**) that could be directly converted into the more complex polycycle **36** in 32% overall yield through an intramolecular Diels–Alder reaction. This result is of significance both for the complexity of the final material and as an additional example of a Diels–Alder reaction occurring under simple thermal conditions with an α,β-unsaturated system bearing a β substituent.[5,18]

We next turned our attention to generating iso-Hajos–Parrish ketones of general structure **6**. Scheme 4 presents two examples of such materials we have prepared. In the first, following the synthesis of cyclopentenone **37** in 62% yield using the standard procedures delineated above, subsequent exposure to a Danishefsky diene surrogate using LiHMDS followed by acid treatment delivered a formal equivalent of a Diels–Alder product in a double Michael addition process in 44% yield (53% based on recovered starting material). In a thermal Diels–Alder reaction between the Danishefsky diene (**13**) and **37**, the desired product was obtained in only 15% yield following treatment with TFA. While that outcome is non-optimal, the occurrence of the product in any yield is of note.[5ab,19] In any event, we were then able to take the resultant product and extrude cyclopentadiene in a retro-Diels–Alder reaction in 91% yield upon heating at reflux in 1,2-dichlorobenzene. As such, this process highlights an example of a formal cyclopentadienone equivalent. In the second case, we were able to execute an effective thermally promoted Diels–Alder reaction between **30** and **13**, finding that the *tert*-butyl ester group in the resultant product could be extruded in the same pot by heating in the presence of TFA at 75°C to generate **39** in 95% yield. No isomerization of the double bond was noted.[20]

As a final study, we sought to determine what types of frameworks could be accessed from iso-Hajos–Parrish ketone **39**. As shown in the middle portion of Scheme 4, we were able to convert it into 4-desmethylpinguisone (**40**) in three steps by attaching a furan ring system onto the core and rupturing the cyclopropane into a β-methyl group through the reductive action of SmI_2.[21] We also were able, after the formation of intermediate **41**, to convert the cyclopropane and its adjoining ring system into a functionalized six-membered ring (**42**), reflective of the core of the eudesmanolides, following treatment with *p*-TsOH in toluene at 100°C.[4d,22] We could also convert **41** in six additional steps into sarcandrolide A (**12**).[23,24]

That sequence completed a 10-step route to this target from commercial materials, noting that it had previously been prepared in a total of 18 steps using the Hajos–Parrish ketone (**1**; 16 steps from **1** itself). Most of those operations involved the transposition of the core ketone group, which was avoided here with the efficient preparation of **39** in just three steps. Lastly, although all the studies described thus far have afforded racemic materials, chiral **29** could be accessed for enantiospecific syntheses by implanting a menthol chiral auxiliary as part of the ester component in the initial Wittig coupling (generating **45** in 2.7:1 d.r.), recrystallizing **45** to more than 99:1 diastereopurity in a mixture of CH_2Cl_2 and hexanes, performing the cyclopentenone formation sequence, and then cleaving the auxiliary through methanolysis.[25]

In summary, we have developed a two-step sequence capable of delivering a number of uniquely functionalized cyclopentenones from anhydrides, several of which are unlikely to arise from other available approaches. We have then shown how these materials can be used in a number of applications, most notably as precursors that undergo thermal



Scheme 4. Synthesis of two different iso-Hajos–Parrish ketones, the use of one of them for the generation of two different natural product frameworks (**40** and **42**) and one natural product (**12**), and a method to prepare enantiopure compound **29**. a) Dienophile (1.5 equiv), LiHMDS (1.8 equiv), THF, −45 °C, 45 min, then **37** (1.0 equiv), −78→25 °C, 3 h; b) *p*-TsOH·H_2O (2.0 equiv), $CHCl_3$, reflux, 3 h, 44% over two steps, 53% b.r.s.m.; c) 1,2-dichlorobenzene, reflux, 9 h, 91%; d) Danishefsky diene (**13**, 2.5 equiv), toluene, sealed tube, 140 °C, 16 h; concentrate; TFA, 75 °C, 15 h, 95%; e) aldehyde (1.3 equiv), NaH (1.3 equiv), THF, 0 °C, 2 h; TFA, toluene; concentrate; *p*-TsOH·H_2O (1.14 equiv), toluene, 25 °C, 13 h, 32%; f) Me_2CuLi_2CN (20 equiv), TMSCl (4.0 equiv), DMPU, THF, −40→25 °C, 1 h, 83%; g) 1 M HCl, CH_2Cl_2, 25 °C, 95%; h) SmI_2 (1.0 equiv), DMPU, THF, 25 °C, 30 min, 71%; i) NaH (1.3 equiv), THF, 0 °C, 30 min; methyl pyruvate (1.3 equiv), 0 °C, 30 min, repeat 6 times, 89%; j) *p*-TsOH·H_2O (1.9 equiv), toluene, 100 °C, 16 h, 66%; k) H_2, Pd/C (10%, 0.1 equiv), EtOAc, 25 °C, 2.5 h; filter and concentrate; Ac_2O, *p*-TsOH (0.55 equiv), 25 °C, 16 h; l) DBU (10 equiv), THF, 25 °C, 16 h, 63% over two steps; m) **43** (3.0 equiv), NaHMDS (2.5 equiv), THF, −78→-40 °C, 3 h, 81%; n) NaOH (5 equiv), THF, pyridine, H_2O, 25 °C, 24 h, 55%; o) $NaBH_4$ (6.1 equiv), MeOH, 0→25 °C, 4 h, 86%; p) SeO_2 (4.5 equiv), 1,4-dioxane, 80 °C, 1 h, 85%; q) standard procedure compare with Table 1, 66%; r) MeOH, 4-DMAP, toluene, Δ, 64–83%. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, HMDS = hexamethyldisilazane, TFA = trifluoroacetic acid, TMS = trimethylsilyl.

Diels–Alder chemistry with the Danishefsky diene to deliver iso-Hajos–Parrish ketones. These materials, in turn, can afford structural diversity pertinent to several natural product classes as highlighted by syntheses of natural targets and analogues. In future work, we seek to expand the number of these building blocks and to achieve a number of additional total syntheses of natural products from them.

Keywords: cascade reactions · cyclopentenones · Diels–Alder reactions · Hajos–Parrish ketones · total synthesis

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[9] For example, the Frontier group has shown that 2-carboalkoxy cyclopentenones of the type within **6** can arise from the Nazarov reaction, but aryl substitution is required and the products are often prone to Wagner–Meerwein shifts: a) J. Huang, D. Lebœuf, A. J. Frontier, *J. Am. Chem. Soc.* **2011**, *133*, 6307 – 6317; b) T. Vaidya, R. Eisenberg, A. J. Frontier, *ChemCatChem* **2011**, *3*, 1531 – 1548. For a gold-based approach, see: c) L. Zhang, S. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442. For an early example of Nazarov chemistry, see: d) S. E. Denmark, T. K. Jones, *J. Am. Chem. Soc.* **1982**, *104*, 2642 – 2645.

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[12] a) S. Nahm, S. M. Weinreb, *Tetrahedron Lett.* **1981**, *22*, 3815 – 3818; b) M. Mentzel, H. M. R. Hoffmann, *J. Prakt. Chem.* **1997**, *339*, 517 – 524.

[13] The major side product of the sequence when Grignard reagents were used was uncondensed γ-ketoacetates (i.e. **17**), an outcome we attribute to the oxophilic chelation of magnesium and acetoacetate to form an intermediate less reactive in the Knoevenagel condensation.

[14] Attempts to extend the scope of the process to cyclohexenones have not succeeded to date, and ester-containing ylides are the best homologating reagents for the approach.

[15] **33** could also be obtained from the cyclopropane-containing cyclopentenone **29** using $MgBr_2 \cdot OEt_2$ to effect a ring opening and 1,5-hydride shift, followed by reduction with Stryker's reagent; however, the yield for this sequence was inferior. In addition, attempts to incorporate the furan ring and ketone during the cyclopentenone-forming sequence as part of the Wittig reagent afforded the needed intermediate of type **16**, but could not be advanced in the second step.

[16] K. Jenett-Siems, K. Siems, L. Witte, E. Eich, *J. Nat. Prod.* **2001**, *64*, 1471 – 1473.

[17] The low yield reflects difficulty in achieving controlled mono-addition of nucleophiles onto appropriate carbonyl coupling partners. Several routes were attempted, with the shown sequence proving optimal.

[18] The difficulty with such substrates was first noted by Acheson, and has since been observed on several additional occasions. See: a) R. M. Acheson, *J. Chem. Soc.* **1952**, 3415 – 3418; b) A. G. Ross, X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2012**, *134*, 16080 – 16084; c) H. V. Pham, R. S. Paton, A. G. Ross, S. J. Danishefsky, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 2397 – 2403.

[19] The only successful thermal example of reacting the Danishefsky diene was reported by Baker (Ref. [5c]) to proceed in the absence of solvent, affording an 18% yield of Diels–Alder adducts using 6 equivalents of **13** at 155 °C for 24 h; high-pressure conditions (13 kbar, i.e. > 180000 psi) afforded a superior yield (91%).

[20] If a substrate without the cyclopropane ring was used, a mixture of olefin isomers resulted, indicating that the substrate controls whether a single enone is produced following decarboxylation.

[21] a) V. Benesova, Z. Samek, V. Herout, F. Sorm, *Collect. Czech. Chem. Commun.* **1969**, *34*, 582 – 592; b) V. Benesova, V. Herout, F. Sorm, *Collect. Czech. Chem. Commun.* **1969**, *34*, 1810 – 1814.

[22] W. Herz, G. Hoegenauer, *J. Org. Chem.* **1962**, *27*, 905 – 910.

[23] The stereoselective reduction of **41** (step *m*) was known from early isolation efforts and proceeds by hydrolyzing the lactone to a hemi-ketal followed by axial reduction with $NaBH_4$; the final SeO_2 oxidation (step *n*) was used by Zhao in their synthesis of **42** (Ref. [3]).

[24] We hypothesize that the dienolate of **39** reversibly reacts with methyl pyruvate without regioselectivity. However, unlike the quaternized bridgehead, the cyclohexyl methine position is capable of alkene isomerization, thereby preventing the retro-aldol reaction and exclusively affording **41**. For some discussion on dienolates more generally, see: a) R. A. Lee, C. McAndrews, K. M. Patel, W. Reusch, *Tetrahedron Lett.* **1973**, *14*, 965 – 968; b) G. Stork, J. Benaim, *J. Am. Chem. Soc.* **1971**, *93*, 5938 – 5939.

[25] Several other auxiliaries were investigated, but none proved superior.

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