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Synthesis and Applications of *iso*-Hajos–Parrish Ketones**

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Abstract

Although numerous natural products possess ring systems and functionality for which “*iso*-Hajos–Parrish” ketones would be of value, such building blocks have not been exploited to the same degree as the more typical Hajos–Parrish hydrindane. Herein we outline an efficient three-step synthesis of such materials 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. We then show how one *iso*-Hajos–Parrish ketone can be converted into two distinct natural product analogs as well as 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.

Keywords

cascade reaction; cyclopentenone; natural product; Diels; Alder reaction; total synthesis; 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 ketone (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 solution for 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 sarcandra lactone A (**12**).^[3] We envisioned, however, that a more

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expedient and general strategy for the synthesis of natural products like **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 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 metallation 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 3 steps overall. Finally, we illustrate that one of these ketones can be advanced into two natural product analogs 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 made in 18 total 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 a new ketone (**18**), and then undergo a Knoevenagel condensation and generate **14**.^[11] Although all these steps individually 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 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 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 45–70% range, that outcome correlates to >80% yield per operation within the 4 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** (cf. Scheme 2) with the desired nucleophile could ultimately afford cyclopentenones of type **14**, these processes sometimes failed and overall yields when they were successful were significantly diminished. 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 non-symmetric 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 the desired intermediate.^[15] The resultant compound (**33**) was then advanced in 2 additional and standard transformations via 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** (cf. Table 1) to afford a cyclopentenone (**35**) that could be directly converted into the more complex polycycle **36** in 32% yield overall 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, its occurrence 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 *t*-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 double bond isomerization 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 3 steps by attaching a furan ring system onto the core and rupturing the cyclopropane into a β -methyl group through the reductive action of SmI₂.^[21] We also were able, after the formation of intermediate **41**, to convert the cyclopropane and its adjoining ring system into a functionalized 6-membered ring (**42**) reflective of the core of the eudesmanolides following treatment with *p*-TsOH in toluene at 100 °C.^[22] We could also convert **41** in 6 additional steps into sarcandrolide A (**12**).^[23,24] That sequence completed a 10 step route to this target overall from commercial materials, noting that as shown in Scheme 1 it had previously been prepared using the Hajos–Parrish ketone (**1**) in 18 total steps (16 steps from **1**), with most of those operations involving the transposition of the core ketone group avoided here with the efficient preparation of **39** in just 3 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 >100:1 diastereopurity in a mixture of CH₂Cl₂ 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 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 analogs. Future work seeks to expand the number of these building blocks that can be made available for the synthetic chemists’ toolbox and to achieve a number of additional natural product total syntheses from them.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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 $\text{MgBr}_2 \cdot \text{OEt}_2$ 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.
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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. >180,000 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 followed decarboxylation.
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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 NaBH₄; the final SeO₂ 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:) Lee RA, McAndrews C, Patel KM, Reusch W. Tetrahedron Lett. 1973; 14:965–968.Stork G, Benaim J. J Am Chem Soc. 1971; 93:5938–5939.
25. Several other auxiliaries were attempted, but none proved superior.

Scheme 1.

The value of the Hajos-Parrish ketone 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.

Scheme 2.

Proposed method for broad cyclopentenone synthesis.

Scheme 3.

Selected examples of advanced cyclopentenones and their use in additional applications, including a total synthesis of merrekentrone D (**34**): a) *p*-TsOH•H₂O (1.0 equiv), HCO₂H, 90 °C, 4 h, 91%; b) oxalyl chloride (2.0 equiv), DMF (cat.), CH₂Cl₂, 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%. Ts = tosyl.

Scheme 4.

Synthesis of 2 different *iso*-Hajos-Parrish ketones, the use of one of them for the generation of 2 different natural product frameworks (**40** and **42**) and 1 natural product (**12**), and a method to prepare enantiopure **29**: a) dienophile (1.5 equiv), LiHMDS (1.8 equiv), THF, -45°C , 45 min, then **37** (1.0 equiv), $-78 \rightarrow 25^{\circ}\text{C}$, 3 h; b) *p*-TsOH•H₂O (2.0 equiv), CHCl₃, 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•H₂O (1.14 equiv), toluene, 25°C , 13 h, 32%; f) Me₂CuLi₂CN (20 equiv), TMSCl (4.0 equiv), DMPU, THF, $-40 \rightarrow 25^{\circ}\text{C}$, 1 h, 83%; g) 1 M HCl, CH₂Cl₂, 25°C , 95%; h) SmI₂ (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•H₂O (1.9 equiv), toluene, 100°C , 16 h, 66%; k) H₂, Pd/C (10%, 0.1 equiv), EtOAc, 25°C , 2.5 h; filter and concentrate; Ac₂O, *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, $-78 \rightarrow -40^{\circ}\text{C}$, 3 h, 81%; n) NaOH (5 equiv), THF, pyridine, H₂O, 25°C , 24 h, 55%; o) NaBH₄ (6.1 equiv), MeOH, $0 \rightarrow 25^{\circ}\text{C}$, 4 h, 86%; p) SeO₂ (4.5 equiv), 1,4-dioxane, 80

°C, 1 h, 85%; q) standard procedure cf. Table 1, 66%; r) MeOH, 4-DMAP, toluene, , 64–83%. HMDS = hexamethyldisilazane.

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

Entry	Anhydride	X	Nucleophile	Product	Yield [%]
1		Me	MeLi		68
2		Me	MeMgBr		54
3		Me	<i>n</i> -BuLi		65
4		Me	DIBAL-H		48
5		Me			46
6		Allyl	MeLi		58
7		Bn	MeLi		62
8		<i>i</i> -Bu	MeLi		71
9			MeLi		61

Entry	Anhydride	X	Nucleophile	Product	Yield [%]
10		Me	MeLi		72[b]
11		<i>t</i> -Bu	MeLi		71
12		Me	MeLi		53
	28			29–30	
	31			32	

[a] General conditions: Wittig phosphoridene (1.0 equiv), anhydride (1.0 equiv), 50 °C, 10–16 h; *N,O*-dimethyl hydroxylamine·HCl (1.3 equiv), pyridine (5.0 equiv), CH₂Cl₂, 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.