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Letter

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Tetrahydrobenzochromene Synthesis Enabled by a Deconjugative Alkylation/Tsuji−Saegusa−Ito Oxidation on Knoevenagel Adducts

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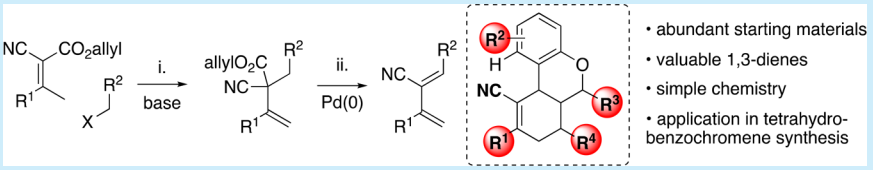
Supporting Information



ABSTRACT: A modular and practical route to versatile cyano-1,3-dienes by a sequence involving deconjugative alkylation and "Tsuji−Saegusa−Ito oxidation" is reported. In this letter, the versatility of the products is also explored, including a route to benzochromene scaffolds common to many natural products.

The tetrahydro- and hexahydrobenzochromene scaffold is common to many biologically active molecules (Figure 1). For example, the natural product Δ9-tetrahydrocannabinol[1] (THC) bears this core, as well as many other natural products, including machaeriol A,[2] conicol,[3] salvidorol,[4] sauchinone,[5] alfileramine,[6] exotiacetal A,[7] and palodesangren E.[8]

Δ9-THC and its synthetic and semisynthetic analogs (e.g., nabilone, levonantradol, and 1-desoxy-Δ9-THC) are by far the most synthetically targeted tetrahydrobenzochromenes.[1,9−16]

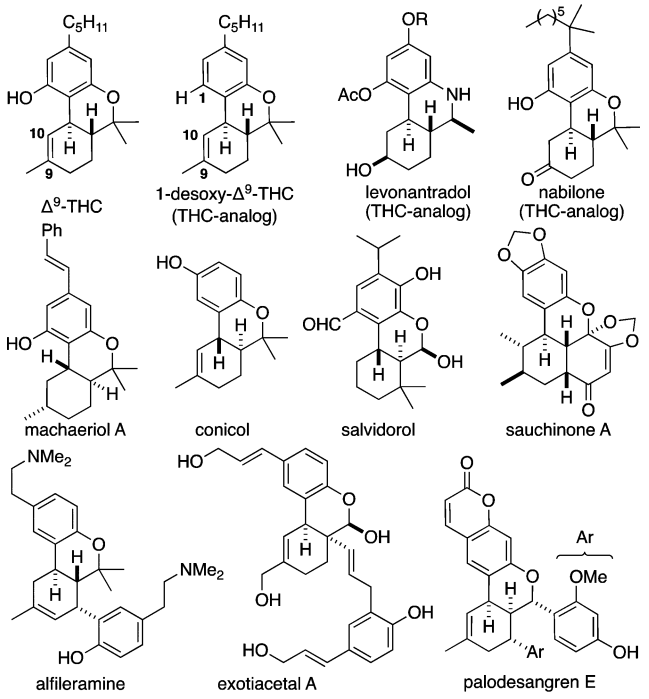


Figure 1. Representative natural and unnatural tetrahydro- and hexahydro-benzochromenes.

Though photocannabinoid synthesis has been studied since the 1960s, the routes have many similarities. It is common to prepare the tetrahydrobenzochromene by the addition of a nucleophilic arene to the monoterpene or monoterpene derivative.[10] An allylic alkylation (or Ireland−Claisen rearrangement)/ring-closing metathesis sequence has also been examined by numerous research groups.[11] Related to this report, the intramolecular Diels−Alder reaction has also been examined.[12] Regarding medicinal chemistry centered on THC and the benzochromene scaffold, the biomimetic route is most commonly utilized (Figure 2).[14]

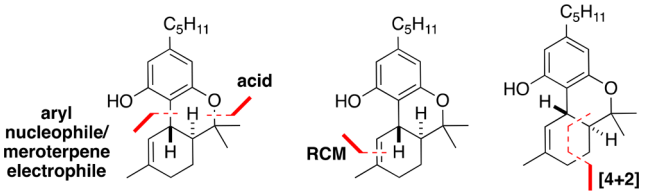


Figure 2. Summary of strategies toward tetrahydrobenzochromene scaffolds.

Inspired by cannabinoids, we wished to devise a new route to tetrahydrobenzochromene scaffolds that would be concise, operationally simple, and convergent from the abundant starting material classes.[17] This would allow for diverse target and target-analog synthesis. With this goal in mind, we proposed the following sequence: allyl cyanoacetate and ketone-derived Knoevenagel adducts **1** and 2-allyloxybenzyl electrophiles **2** can undergo (i) deconjugative alkylation to **3**,[18] (ii) the Tsuji-variant of the Saegusa−Ito oxidation ("Tsuji−Saegusa−Ito oxidation") yielding the diene/dienophile-paired substrate **4**,[19] and (iii) intramolecular [4 + 2] cycloaddition

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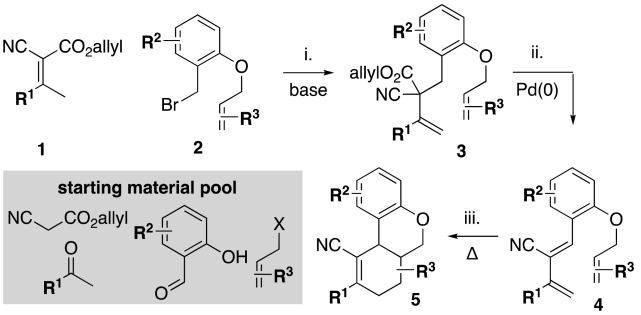
yielding the target scaffolds **5**.[20] The scaffolds can have high structural diversity considering their synthetic origins (ketones, allyl cyanoacetate, salicylaldehydes, and allylic electrophiles) and would contain a nitrile, which themselves have beneficial medicinal properties and are excellent functional handles.[21] From the perspective of cannabinoid structure−activity relationship studies, nitrile-containing analogs have never been evaluated.[1,9−16] Furthermore, the nitrile has the potential to stabilize the Δ9-alkene configuration on the tetrahydrobenzochromene, potentially improving its physical properties.

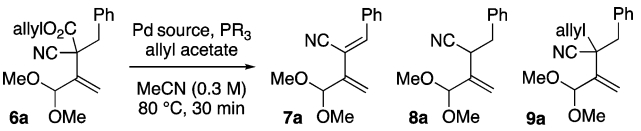
The proposed sequence has the potential to be operationally simple, as the key C−C bond forming reactions require mild bases (step i) or are thermal (step iii). The major synthetic liability was the proposed Tsuji−Saegusa−Ito oxidation to yield cyano-1,3-dienes **4** (step ii). Although ketone and nitrile dehydrogenation catalyzed by Pd(0) using allyl acetate as a stoichiometric oxidant has been known for decades,[19] it has not been explored for preparing 2-cyano-1,3-dienes. It should also be noted that Newhouse and co-workers are making related advancements to Pd-catalyzed Tsuji-type dehydrogenation.[22] It is also possible that the targeted 2-cyano-1,3-dienes could be prepared by Horner−Wadsworth−Emmons (HWE) reactions between aldehydes and α-cyano vinyl phosphonates. However, this transformation yields preferentially 1-cyano-1,3-dienes via vinylogous-HWE reaction, isomeric connectivity to our targeted 2-cyano-1,3-dienes.[23] Herein, we report the development of the sequence outlined in Scheme 1.

Scheme 1. New Diene Synthesis and Application in Benzochromene Synthesis



To begin our studies, we wished to examine the proposed Tsuji−Saegusa−Ito oxidation separately. Test substrate **6a** was prepared from pyruvaldehyde dimethyl acetate, allyl cyanoacetate, and benzyl bromide (Table 1). After some experimentation, we uncovered that high yields of the desired product **7a** could be accessed using 10 mol % $Pd(OAc)_2$, 8 mol % PPh_3, and 2 equiv of allyl acetate in acetonitrile at 80 °C. The Pd-precatalyst to PPh_3 ratio is very important. $Pd(PPh_3)_4$ and other Pd(0) precatalysts/PPh_3 yielded primarily the decarboxylative allylation product **9a**. To varying degrees, the desired product was observed with Pd(II) precatalysts and phosphine in roughly equimolar ratios. These results are in line with Tsuji's original report: the phosphine likely serves as a sacrificial reductant, and $Pd(0)\cdot PR_3$ complexes promote decarboxylative allylation.[19] Thus, it is important to ensure no additional phosphine is present.

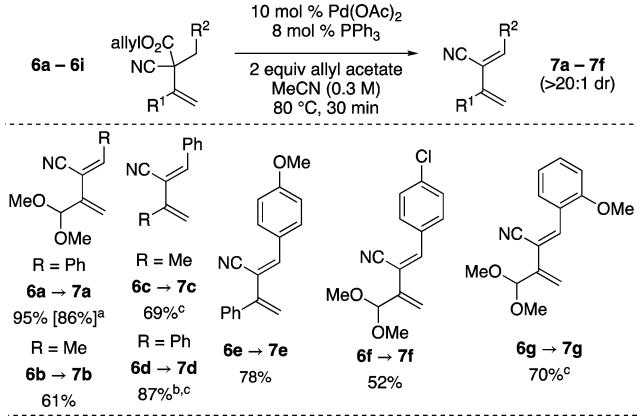
Table 1. Optimization of 2-Cyano-1,3-diene Synthesis



entry	catalyst (10 mol % Pd)	Pd/P	allyl acetate	**7a** (%)	**8a** (%)	**9a** (%)
1	$Pd(PPh_3)_4$	1:4	0 equiv	–	–	86
2	Pd_2dba_3:PPh_3	1:1	0 equiv	–	trace	41
3	$Pd(OAc)_2$:PPh_3	1:0.5	0 equiv	67	trace	–
4	$Pd(OAc)_2$:dppe	1:0.5	0 equiv	40	trace	21
5	$Pd(OAc)_2$:PPh_3	1:0.8	0 equiv	78	trace	–
6	$Pd(OAc)_2$:PPh_3	1:0.8	2 equiv	95	–	–
7	White cat.:PPh_3	1:0.8	2 equiv	95	–	–

With the optimized conditions in hand, we systematically explored the coupling partners and found that good yields of the 2-cyano-1,3-dienes **7** could be prepared when Knoevenagel adducts were derived from methyl ketones and various 1° alkyl halides (Scheme 2). Also noteworthy, in all cases, single diene

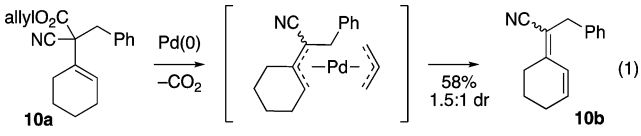
Scheme 2. Scope of 2-Cyano-1,3-diene Synthesis



[a]5 mol % $Pd(OAc)_2$, 4 mol % PPh_3 [gram scale]. [b]10 mol % White catalyst used *in lieu* of $Pd(OAc)_2$. [c]Distilled over CaH_2 MeCN used *in lieu* of commercial-anhydrous (over molecular sieves) MeCN.

diastereomers were observed. For example, products **7a** and **7b** were prepared from benzyl bromide or ethyl iodide, respectively. Products **7c** and **7d** were prepared from different ketone-derived starting materials (acetone or acetopheone, respectively). Products **7e**−**7g** have various electronic and steric patterns about the arene. The 2-cyano-1,3-diene synthesis was also scalable (up to gram-scale) without significant changes in yield (Scheme 2, footnote a). In this study, the catalyst loading was also reduced to 5 mol % $Pd(OAc)_2$. In a few cases, we observed unacceptable amounts of protonation byproducts (10−20%) that were inseparable from the desired product. We found that repurified acetonitrile (distilled of CaH_2) seemed to perform better than the commercial anhydrous solvent (obtained over molecular sieves, footnote c).

We also examined the substrate **10a** derived from cyclohexanone, allyl cyanoacetate, and benzyl bromide (eq 1). This



substrate has two potential sites for β-hydrogen elimination. In this case, the regioselectivity opposite to that observed from

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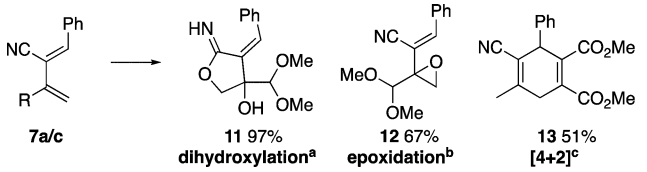
methyl ketone-derived Knoevenagel adducts was observed (eq 1 vs Scheme 2). In this case, a 1-cyano-1,3-diene **10b** was prepared.

We next examined the reactivity of these cross-conjugated 2-cyano-1,3-dienes **7** (Scheme 3). The electron-rich olefin could

Scheme 3. Reactivity of 2-Cyano-1,3-dienes 7a/b



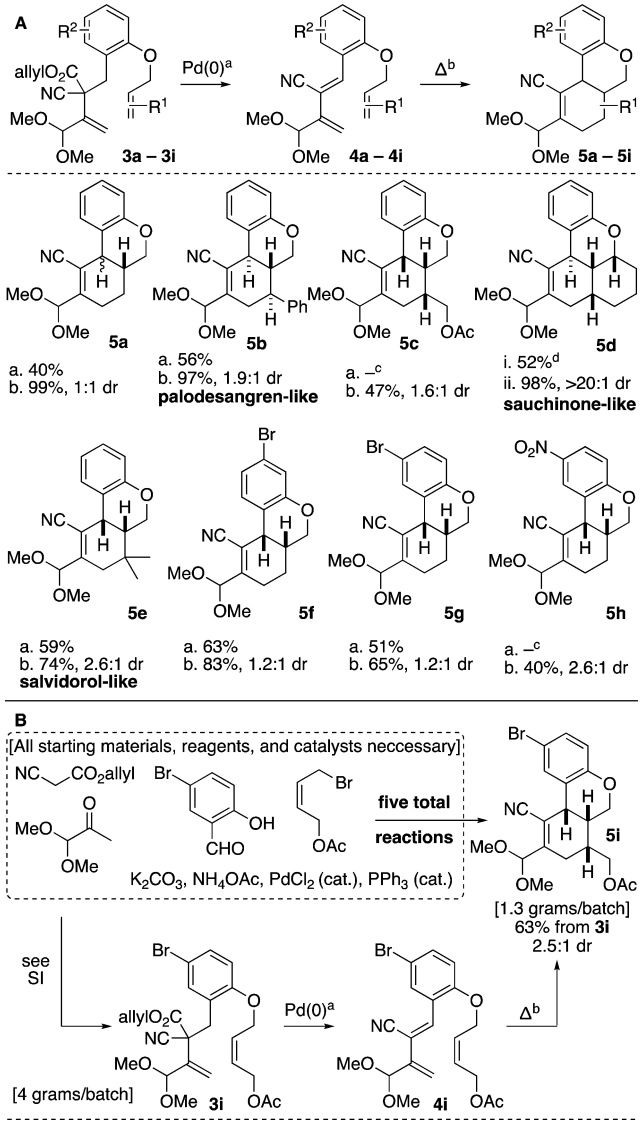
[a]3 mol % OsO_4, 1.5 equiv of NMO, acetone/H_2O (4:1). [b]1.5 equiv of *m*CPBA, 3.5 equiv of $NaHCO_3$, CH_2Cl_2. [c]10 equiv of dimethly acetylenedicarboxylate, neat, 150 °C.

be dihydroxylated with a subsequent Pinner reaction to yield an *α,β*-unsaturated cyclic imidate **11** in excellent yield. Similarly, this olefin can also be selectively epoxidized to **12** using *m*CPBA. 1,3-Dienes are commonly utilized in cycloaddition reactions. Although they bear a 2-cyano group, the 1-aryl-3-alkyl groups electronically dominate, and this diene reacts with electron-deficient dieneophiles to yield cycloadducts such as **13**.

We next turned to our original goal, targeting diverse tetrahydrobenzochromene scaffolds by a Tsuji−Saegusa−Ito oxidation/intramolecular [4 + 2] cycloaddition strategy (Scheme 4). Under the standard conditions for decarboxylative oxidation, dienes **4a−4i** could be prepared and were competent cycloaddition substrates (to **5a−5i**). Regarding the [4 + 2] cycloaddition, there was a slight preference for the *cis*-fused ring system in most cases. However, **5b** slightly favored the *trans*-fused ring system (2:1 dr), likely due to a secondary orbital overlap between the phenyl group and the diene. Surprisingly **5d** was prepared as a single diastereomer and is the result of an exo-cycloaddition. Although in most cases diastereomeric mixtures were observed due to competing endo-/exocycloadditions, stereochemistry can converge to the *trans*-product by acetal deprotection/isomerization (Scheme 5). Diversity can easily be achieved by simple modification of the starting materials; we explored a variety of allylic and arene substitution patterns. For example, scaffolds **5a−5e** are systematically diversified based on the allylic electrophile where allyl (**5a**), cinnamyl (*E*-olefin, **5b**), *cis*-buten-1−4-diol (*Z*-olefin, **5c**), cyclohexenyl (**5d**), and prenyl (**5e**) electrophiles were utilized. These changes result in benzochromenes that are "palodesangren-like (**5b**)," "sauchinone-like (**5d**)," and "salvidorol-like (**5e**)" (Scheme 4 compared to Figure 1). Scaffolds **5f−5h** were prepared respectively from 4-bromo- (**5f**), 5-bromo- (**5g**), and 5-nitro- (**5h**) salicylaldehyde. In the course of our studies, **5i** was prepared multiple times on gram scale (Scheme 4B). Scheme 4B also reiterates the significance of this route: all starting materials, reagents, and catalysts are inexpensive, the synthesis is operationally simple, and the target scaffold has orthogonal functional groups distributed about the core. This is ideal for drug discovery applications. Regarding the latter point, **5i** is decorated with bromoarene, nitrile, acetal, and protected alcohol functional groups.

In preparation for target- and target-analog synthesis, our final studies in this initial letter are potential ways **5i** can be manipulated (Scheme 4). Under standard Suzuki cross-

Scheme 4. Modular Route to Tetrahydrobenzochromene Scaffolds



[a]10 mol % Pd $(OAc)_2$, 8 mol % PPh_3, 2 equiv of allyl acetate, MeCN (0.3 M), 80 °C, 30 min. [b]Toluene (0.1 M), 12 h, reflux. [c]Inseparable from protonation byproduct. [d]10% White catalyst *in lieu* of $Pd(OAc)_2$.

coupling conditions with phenylboronic acid, **14a** was prepared. Acetal deprotection/isomerization can occur under a variety of acidic conditions to yield either **14b** or **14c** with concomitant alcohol deprotection. By design, the aldehyde incorporated on the scaffold is a useful functional handle; in this regard the imidate-containing product **14d** was prepared by a reduction/intramolecular Pinner reaction. Finally, the protected alcohol could selectively be deprotected using DIBAL−H to yield **14e**.

In conclusion, we have developed a modular two-step route to 2-cyano-1,3-dienes from Knoevenagel adducts and alkyl electrophiles. These dienes are versatile and can be converted to a variety of unique scaffolds. We also utilized this report's development in conjunction with intramolecular cycloaddition to modularly assemble benzochromene scaffolds. In addition to the pursuits of target/target-analog synthesis and biological evaluation, for which we are seeking collaborators, the

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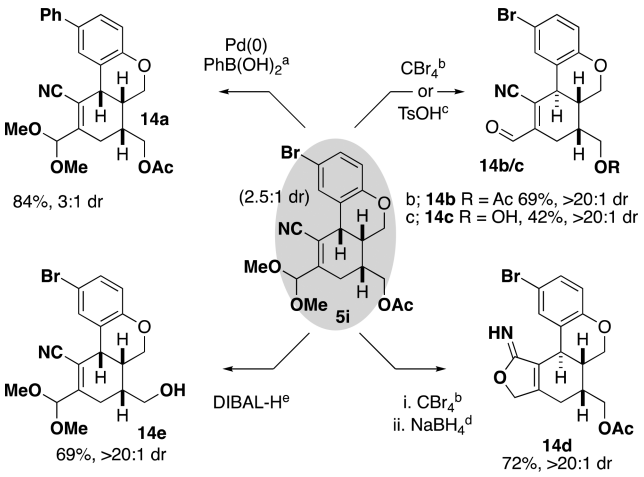
Scheme 5. Functional Group Interconversion of Tetrahydrobenzochromene Scaffold 5i



[a]10 mol % $PdCl_2(PPh_3)_2$, 3 equiv of $PhB(OH)_2$, 3 equiv of K_2CO_3 dioxane (0.5 M), 120 °C. [b]0.5 equiv of CBr_4, $MeCN/H_2O$ (1:2), 80 °C. [c]0.5 equiv of TsOH, acetone/H_2O (4:1), 40 °C. [d]$NaBH_4$, MeOH (0.5 M) 0 °C. [e]2 equiv of DIBALH, CH_2CL_2 (0.25 M), diastereomers separable by chromatography; major diasteromer reported.

discoveries reported herein will lead to significant future synthetic developments related to improving the scope and stereoselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01857.

Experimental procedures, characterization data (^1H, ^{13}C NMR and HRMS) (PDF)

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Notes

The authors declare no competing financial interest.

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