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[2.2.2]- to [3.2.1]-Bicycle Skeletal Rearrangement Approach to the Gibberellin Family of Natural Products

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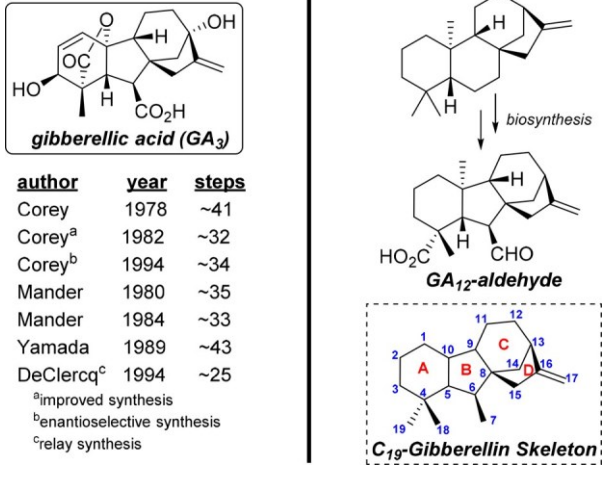
Supporting Information

ABSTRACT: Synthetic studies toward the gibberellin family of natural products are reported. An oxidative dearomatization/Diels−Alder cascade assembles the carbon skeleton as a [2.2.2]-bicycle, which is then transformed to the [3.2.1]-bicyclic gibberellin core via a novel Lewis acid catalyzed rearrangement. Strategic synthetic handles allow for late-stage modification of the gibberellin skeleton and provides efficient access to this important family of natural compounds.

Gibberellin research dates to late 19th century Japan, where their essential role in plant growth and development was first observed on rice seedlings. It was not until the 1960s that gibberellins began to enter the minds of organic chemists; upon structure elucidation by X-ray crystallography in 1963, gibberellic acid (GA_3) and other gibberellins became realistic targets for synthesis.[1,2] The gibberellin family now includes more than 130 members, named numerically in order of their date of discovery. The biosynthetic pathway is now fairly well understood; gibberellins derive from the tetracyclic diterpene ent-kaurene skeleton, with GA_{12}-aldehyde serving as a common intermediate to all gibberellins (Figure 1).[3]

E. J. Corey and co-workers were the first to complete the total synthesis of GA3.[4] Corey reported at the time of his original synthesis in 1978 there had been about 150 published papers from approximately 25 different laboratories focused on gibberellin synthesis. Despite this immense amount of effort and the nearly four decades of work since Corey's original synthesis of GA3, the feat has still only been accomplished by four research groups: Corey (three times),[3,5] Mander (twice),[6] Yamada,[7] and DeClercq.[8] Despite these extensive efforts, each synthesis is long and plagued by low overall yields. These syntheses and other efforts toward gibberellins employ a number of common strategies. The A ring is generally constructed by Diels−Alder cycloaddition, Birch reduction, or aldol chemistry. Mimicking the biological synthesis, the B ring is most frequently accessed via a ring contraction, though other approaches such as Cope rearrangement or Friedel−Crafts acylation have also been employed. The C ring commonly originates from aromatic precursors or Cope approaches, while the D ring has been synthesized via carbenoid, aldol and reductive ring closure chemistry.

Our synthetic approach toward the gibberellin family pivots on two key reactions (Scheme 1). First, leveraging our group's theme of utilizing oxidative dearomatization/Diels−Alder chemistry to rapidly assemble complex structures,[9] we sought to access the fused [2.2.2]-bicycle 4 from phenol 5, which could

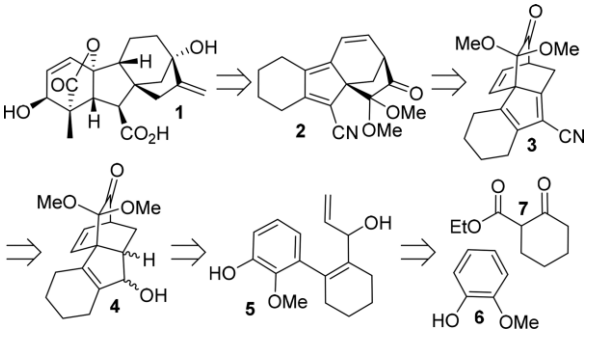


author	year	steps
Corey	1978	~41
Corey[a]	1982	~32
Corey[b]	1994	~34
Mander	1980	~35
Mander	1984	~33
Yamada	1989	~43
DeClercq[c]	1994	~25

[a]improved synthesis
[b]enantioselective synthesis
[c]relay synthesis

Figure 1. Biosynthesis and GA_3 total syntheses.

Scheme 1. Gibberellin Core Retrosynthesis



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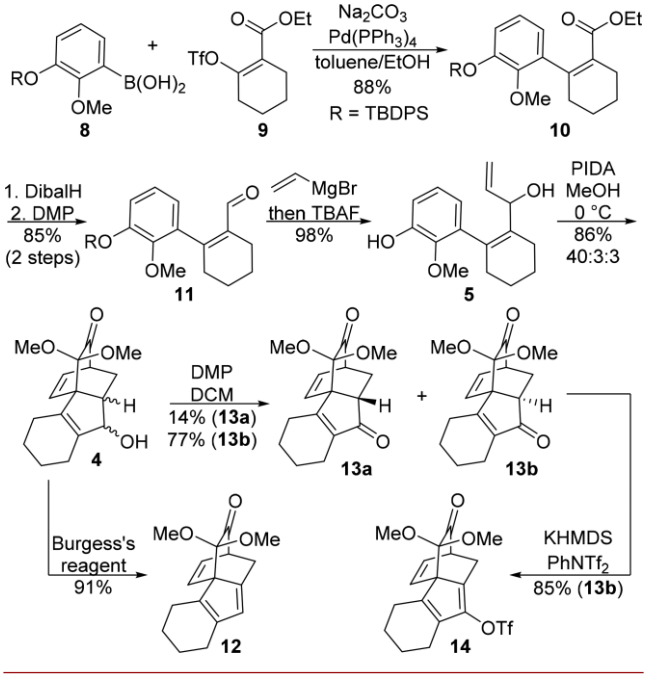
be accessed from commercially available starting materials (6 and 7) in a few steps. Following synthesis of [2.2.2]-bicycle, the C/D ring junction would be installed using a rearrangement reaction. We first encountered this new [2.2.2]- to [3.2.1]-cyclopentadiene-fused-bicycle rearrangement during our maoecrystal V synthetic efforts.[9f] Hampered by what was then undesired reactivity, we were eager to productively utilize this rearrangement toward the gibberellin family. We are not the first to approach the gibberellin C/D ring junction via a [2.2.2]- to [3.2.1]-bicycle rearrangement as Mori, Monti, and Yamada reported their efforts in the 1970s utilizing acid-based rearrangement approaches.[10] However, these prior rearrangement approaches were unable to successfully access gibberellin natural products.

We set out to synthesize a gibberellin skeleton to confirm the validity of our key dearomatization/Diels–Alder and rearrangement steps. Toward that end, Suzuki coupling of boronic acid 8, synthesized in two steps from 6, and triflate 9, synthesized in one step from 7, delivered ester 10 in excellent yield (Scheme 2). Attempts to selectively reduce ester 10 to aldehyde 11 were

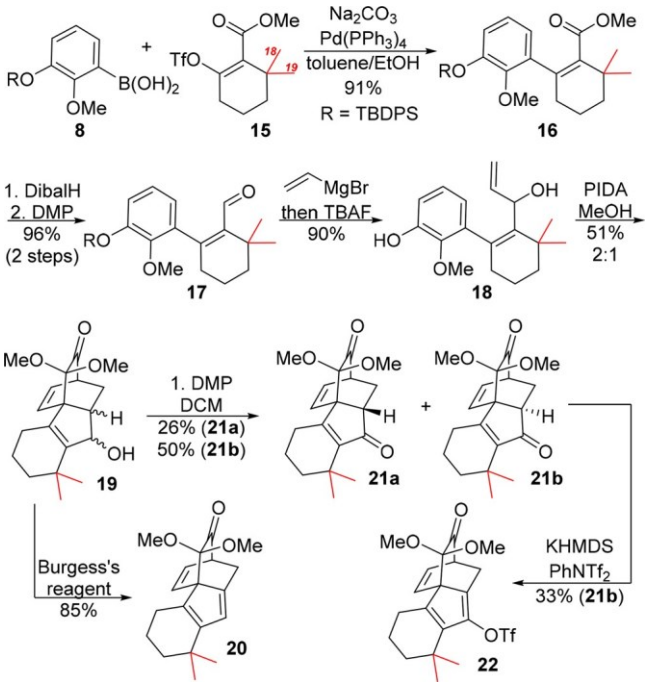
Scheme 2. Synthesis of Rearrangement Precursors



thwarted, so a two-step reduction/oxidation procedure was employed. Following a one-pot sequential addition of vinyl magnesium bromide and TBAF, phenol 5 was accessed in excellent yield. Treatment of 5 with $PhI(OAc)_2$ (PIDA) in methanol induced the desired oxidative-dearomatization/Diels–Alder cascade. The rigid cyclohexene ring enabled a facile intramolecular Diels–Alder occurring at 0 °C, delivering alcohols 4 in high selectivity (40:3:3 ratio). The alcohol mixture could be dehydrated with Burgess's reagent to deliver cyclopentadiene 12. Alternatively, 4 could be converted into triflate 14 in two steps. Only the major oxidation product, 13b, could be selectively converted into triflate 14. Efforts to convert 13a delivered a mixture of inseparable triflate products due to deprotonation of the more sterically accessible allylic hydrogens within the cyclohexene ring.

We also set out to synthesize a gibberellin construct containing the C-18 and C-19 *gem*-dimethyl groups (Scheme 3). *gem*-Dimethyl triflate 15 was synthesized in three steps employing known literature procedures.[11] In general, the

Scheme 3. Synthesis of *gem*-Dimethyl Containing Rearrangement Precursor



Suzuki cross-coupling, DIBAL reduction, DMP oxidation, and allyl installation all proceeded smoothly and in superb yield to deliver phenol 18. In contrast to the hydrogen substituted system (5), dearomatization/Diels–Alder of phenol 18 performed less efficiently, delivering cycloadduct 19 as a mixture of inseparable products. The primary competing pathway to the intramolecular Diels–Alder reaction was self-dimerization of the quinone intermediate. With cycloadduct 19 in hand, we set out to synthesize cyclopentadienes 20 and 22. Dehydration with Burgess's reagent delivered cyclopentadiene 20. Alternatively, Dess-Martin oxidation followed by enol triflation delivered cyclopentadiene 22 in poor yield. The added steric hindrance from the *gem*-dimethyl group favored isomerization of 21b to the less hindered 21a, necessitating short reaction times to achieve the desired selectivity in the triflation.

With several different cyclopentadiene-fused-[2.2.2]-bicycle constructs on hand, we first investigated the skeletal key rearrangement under thermal conditions (Table 1). While the rearrangement from a [2.2.2]- to [3.2.1]-bicycle did occur for cyclopentadienes 12 and 20, it was not nearly as clean or facile as the rearrangement that had been witnessed in our maoecrystal V synthesis.[9f] Additionally, the thermal rearrangement toward the gibberellin core was hampered by decomposition, leading to low yields and complete decomposition of the triflate substituted cyclopentadienes 14 and 21.

Having explored the thermal rearrangement, we shifted our focus to installation of the C-7 gibberellin carboxylate group. In addition to supplying a carbon necessary for the natural product, we also envisioned that this functional group might provide the opportunity to facilitate the occurrence of the desired skeletal rearrangement under catalytic conditions. With triflate substituted cyclopentadienes 14 and 22 on hand, we sought to install C-7 as a nitrile due to its lack of steric bulk and

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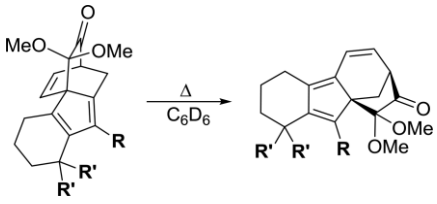
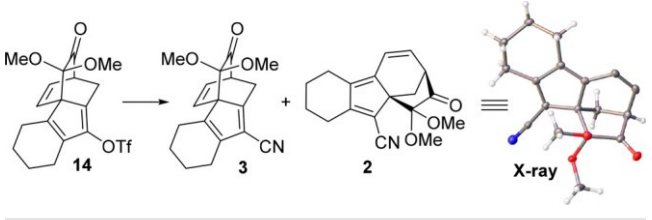
Table 1. Thermal Rearrangement Studies



substrate	R, R′	yield (%)	temp (°C)	time (h)
12	H, H	38	110	144
14	OTf, H	0	70	12
20	H, Me	36	110	168
21	OTf, Me	0	70	12

plethora of palladium-catalyzed options for its incorporation.[12] We postulated that in one pot we would be able to convert the triflate into a nitrile, which we argued would not only stabilize the intermediate cyclopentadiene anion but also serve as a handle for Lewis acids to accelerate the rearrangement. Triflate 14 was employed for these studies, which are summarized in Table 2. Rearrangement cascade explorations rapidly revealed

Table 2. Pd(0) Catalyzed Rearrangement Cascade



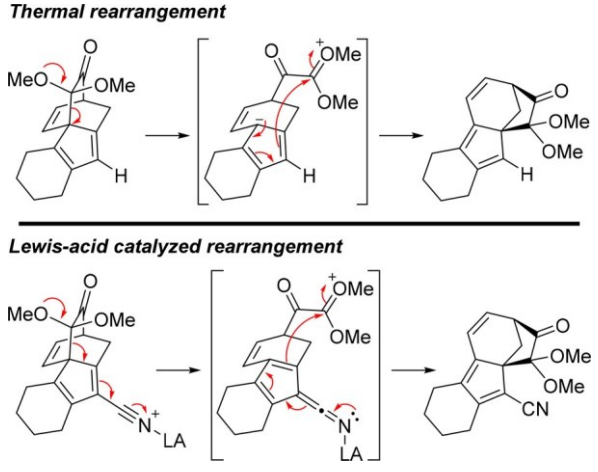
Pd source	CN source	additive	solvent	temp (°C)	yield (%)	ratio 3:2
$Pd(PPh_3)_4$	NaCN	CuI	MeCN	70	26	0.7:1.0
$Pd(PPh_3)_4$	CuCN	LiCl	DMF	80	0	
$Pd_2(dba)_3$	KCN	dppf	MeCN	60	51	7:1
$Pd(PPh_3)_4$	$Zn(CN)_2$	none	DMF	90	75	>1:20
$Pd_2(dba)_3$	$Zn(CN)_2$	none	DMF	90	0	
$Pd_2(dba)_3$	$Zn(CN)_2$	dppf	DMF	90	99	>1:20

how significant a role the cyanide counterion played. This prompted us to switch to a metal counterion better suited for nitrile coordination. Ultimately, zinc cyanide emerged as the ideal reagent. It not only facilitated installation of the nitrile but also catalyzed the desired skeletal rearrangement, cleanly delivering [3.2.1]-bicycle 2 (CCDC 1821698) in near-quantitative yield.

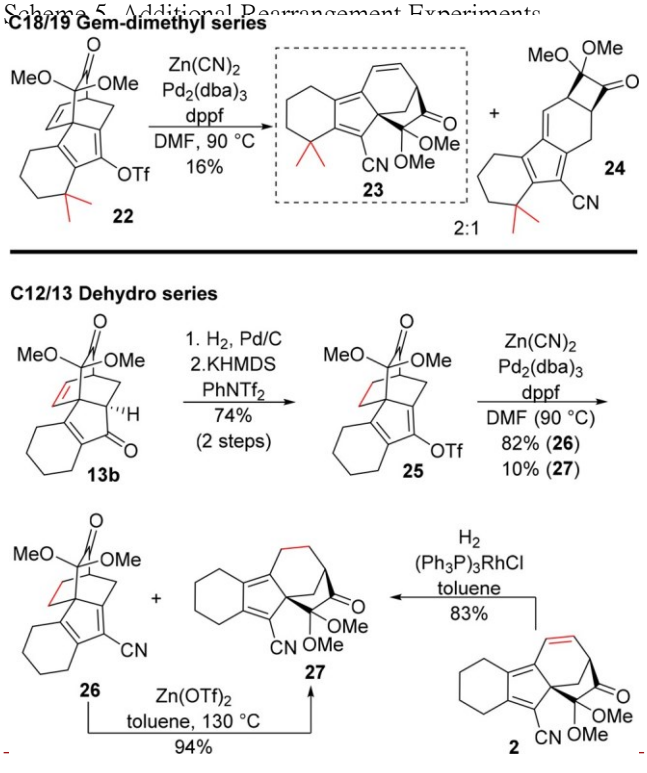
Scheme 4 illustrates the remarkable effect that the nitrile substituent has on the skeletal rearrangement. Lewis acid coordination to the nitrile not only facilitates fragmentation of the [2.2.2]-bicycle by electron donation from the ketal moiety but also stabilizes the intermediate cyclopentadienyl anion, thus suppressing the decomposition pathways that plagued the thermal rearrangement.

With the nitrile installation and rearrangement conditions determined, we sought to understand how the C18/C19 *gem*-dimethyl group and C12−C13 olefin impacted the metal-catalyzed rearrangement (Scheme 5). Application of the optimized conditions to *gem*-dimethyl substituted triflate 22 resulted in a mixture of four products in low yields delivering the desired [3.2.1]-bicycle 23 and cyclobutane 24 as an inseparable mixture, along with two unconfirmed imine

Scheme 4. Proposed Thermal vs Lewis Acid Catalyzed Rearrangement Mechanisms



Scheme 5. Additional Rearrangement Experiments



products. This result was in stark contrast to the clean reactivity observed for the unsubstituted triflate 14, suggesting that the added steric bulk hindered the recombination of the carbenium intermediate. Regardless, it is important to note that product 23 represents the completed gibberellin carbon skeleton, except carbon-17, which could be accessed by ketone olefination. We postulated that reduction of the C12−C13 olefin might eliminate these undesired pathways. Toward that end, cyclopentadiene 25 was accessed in two steps from 13b. Subjecting 25 to the optimized cross-coupling conditions delivered [2.2.2]-bicycle 26 as the major product along with a small amount of the rearranged [3.2.1]-bicycle 27, confirming that the Lewis acid catalyzed skeletal rearrangement can still proceed in the absence of the C12−C13 olefin. Furthermore, 26 could be easily converted to 27 with zinc triflate at 130 °C,

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exemplifying the utility of zinc as a Lewis acid catalyst for the rearrangement. Conjugated ketone 21b was also selectively reduced and converted to the *gem*-dimethyl containing triflate, which failed to react under the cross-coupling conditions. The added steric hindrance from the reduction of the bicycle prevented engagement with the palladium catalyst and suggests that the struggles in converting 22 to 23 were primarily due to decomposition of the triflate starting material. While removal of the C12−C13 olefin suppressed this decomposition, it could not overcome the inherent steric limitations of the *gem*-dimethyl substituted substrates.

Having thoroughly explored the skeletal rearrangement, we set out to perform postrearrangement modification of the gibberellin core. Selective reduction of 2 with Wilkinson's catalyst afforded 27, demonstrating that the C12−C13 olefin can be removed pre- or postrearrangement. Removal of the dimethoxy-ketal moiety of 27 with samarium diiodide unexpectedly enabled a retro-rearrangement, affording a mixture of [2.2.2] and [3.2.1] deketalized products in a 1:1 ratio, suggesting that the nitrile-activated cyclopentadiene must first be removed to achieve clean deketalization. Studies are ongoing to further functionalize the gibberellin core and reduce the cyclopentadiene prior to ketal cleavage and olefination.

Looking toward the future, we envision that adduct 2, which is available in 9 steps and 38% overall yield from commercially available materials, represents an ideal oxidase phase starting point for implementation of a two-phase synthesis[13] of the gibberellin family of natural products. The dimethoxy ketal moiety not only enables the IMDA and skeletal rearrangement but also serves as a convenient blocking group; the olefin and carbonyl groups will enable the application of various oxidation protocols, providing access to higher order gibberellins, such as GA3. Additionally, this will allow for the generation of unnatural gibberellins that may possess interesting biological properties.

In summary, we have implemented a concise synthesis of the gibberellin core. The synthesis hinges on an oxidative dearomatization/Diels−Alder cascade and Lewis acid catalyzed skeletal rearrangement to forge the cyclopentane-fused [3.2.1]-bicycle and provides efficient access to this biologically important scaffold. This novel Lewis acid catalyzed rearrangement is robust and may prove broadly useful for the synthesis of complex natural products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01031.

Experimental procedures; spectral and X-ray crystallography data (PDF)

Accession Codes

CCDC 1821698 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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