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Total Synthesis

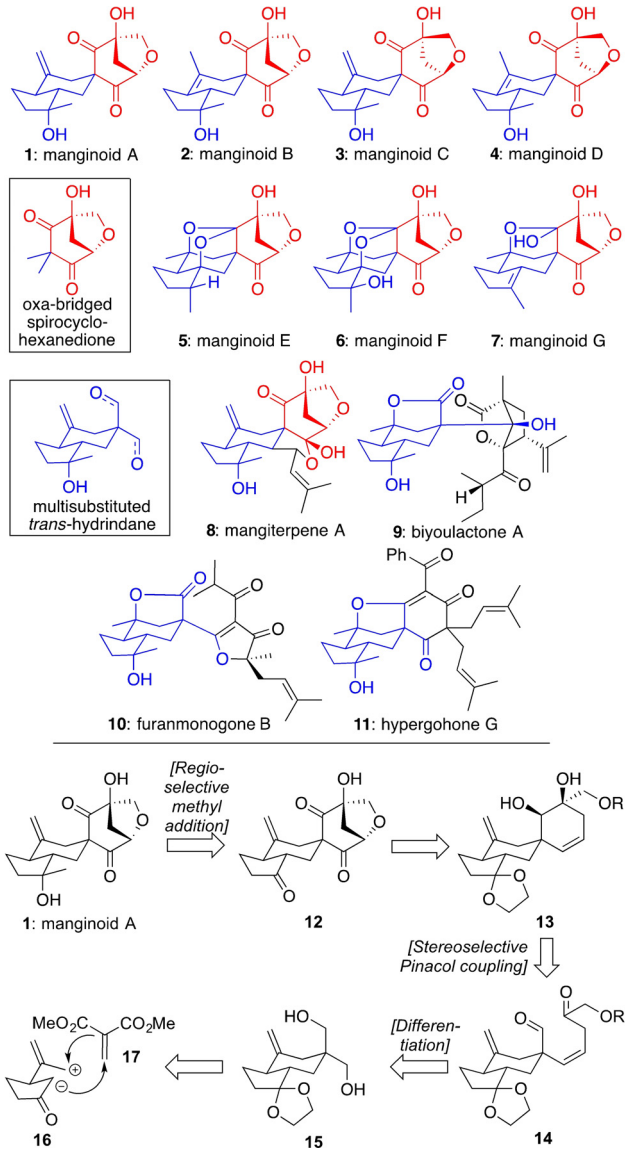
Total Synthesis of the Meroterpenoid Manginoid A as Fueled by a Challenging Pinacol Coupling and Bicycle-forming Etherification

*Yu-An Zhang, Amanda Milkovits, Valay Agarawal, Cooper A. Taylor, and Scott A. Snyder**

Abstract: *The manginoids are a unique collection of bioactive natural products whose structures fuse an oxa-bridged spirocyclohexanedione with a heavily substituted trans-hydrindane framework. Herein, we show that such architectures can be accessed through a strategy combining a challenging pinacol coupling and bicycle-forming etherification with several additional chemo- and regioselective reactions. The success of these key events proved to be highly substrate and condition specific, affording insights for their application to other targets. As a result, not only has a 19-step total synthesis of manginoid A been achieved, but a potential roadmap to access other members of the family and related natural products has also been identified.*

The manginoids (**1**–**7**, Scheme 1) are a recently isolated family of monoterpene shikimic acid-conjugated meroterpenoids obtained from the plant pathogen *Guignardia mangiferae*.[1] Of note, the lead member of this collection, manginoid A (**1**), can affect potent inhibition ($IC_{50} = 0.84 \pm 0.07$ μM) of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), an enzyme which catalyzes the intracellular conversion of cortisone to bioactive glucocorticoid cortisol; such modulation could provide a novel therapeutic pathway against metabolic diseases such as obesity, osteoporosis, and diabetes.[2] Structurally, **1** and its cousins represent the first examples of natural products that contain not only a highly substituted *trans*-hydrindane framework (colored in blue), but also a unique oxa-bridged spirocyclohexanedione moiety (colored in red). Indeed, related molecules (such as **9**–**11**)[3] are known to possess the first domain, but none have the second except for allied family members such as **8**.[4] Yet, despite their uniqueness and overall chemical complexity, only a modest number of synthetic studies toward these systems and any structurally related natural products have been reported to date.[5] Herein, we present a synthetic route, designed around several challenging and chemo- and regioselective operations, which can afford access to these frameworks. These efforts have culminated in a 19-step total synthesis of manginoid A (**1**) and provide a blueprint suitable for addressing related natural product architectures.

Our overall approach to tackling the six stereocenters, functional group array, and overall level of steric congestion found within the manginoids is shown retrosynthetically at the bottom of Scheme 1, using **1** as our inaugural target. Seeking to take advantage of its steric encumbrance, our final operation sought to add a lone methyl group with both facial



Scheme 1. Structures of selected members of the manginoid family and natural products containing the multi-substituted *trans*-hydrindane core (**1**–**11**) and a proposed retrosynthetic analysis of manginoid A (**1**) based on a critical pinacol coupling and key regioselective transformations.

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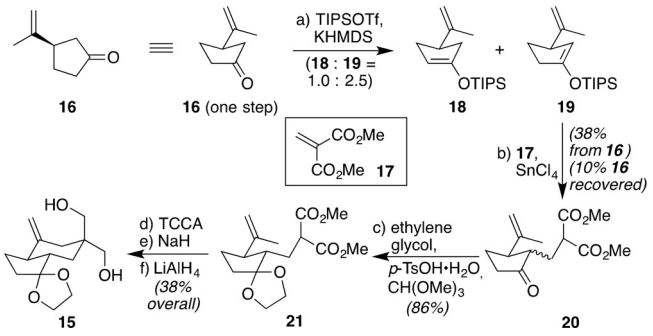
and regioselectivity onto a precursor (**12**) possessing three ketones. We assumed that the hindrance provided by both the adjacent spirocyclic quaternary carbon and the oxa-bridge framework in general would appropriately shield the other two ketones from attack.[6] In turn, following some changes in oxidation state and cleavage of the ether bond within the bicyclic unit, we arrived at compound **13**, a material whose *syn*-disposed 1,2-diol suggested its potential construction via a pinacol coupling from keto-aldehyde **14**.[7,8] In practice, however, we expected this reaction to be difficult to execute for several reasons. Namely, 1) the substrate **14** might be unstable either on its own accord or under typical pinacol reaction conditions due to its combination of three potentially sensitive functional groups: an aldehyde, a β,γ-unsaturated ketone, and an α-oxygenated ketone; 2) given the potential for the α-oxygenated ketone to undergo β-scission if initiation began at the neighboring ketone,[9] the SET process would ideally need to begin from the more reactive, but also more hindered aldehyde; 3) if the coupling was successful, it was unclear if the needed stereochemical disposition of the newly formed diol within **13** would result.

Despite such concerns, we believed such a test was worthwhile since its success would afford efficient access to the near-complete architecture of the manginoids. Moreover, we believed that the overall constraint of the system might enable its achievement when it would be likely to fail for far more flexible precursors, thus advancing knowledge regarding challenging pinacol cyclization events. Critically, the idea would be fairly easy to test since we anticipated that **14** could be readily prepared from **15** via effective differentiation of its two primary alcohols, with that intermediate deriving from the merger of **16** and **17** through a Michael reaction and subsequent intramolecular allylation using **16** as both a nucleophile and electrophile based on the formal charges shown (Scheme 1). Ultimately, while this plan was successful, it also drew on the strategic use of the alkene within the core *trans*-hydrindane framework on multiple occasions, both to shield reactive functional groups, as well as to facilitate the formation of the final ether linkage leading to **12** through conformational locking.

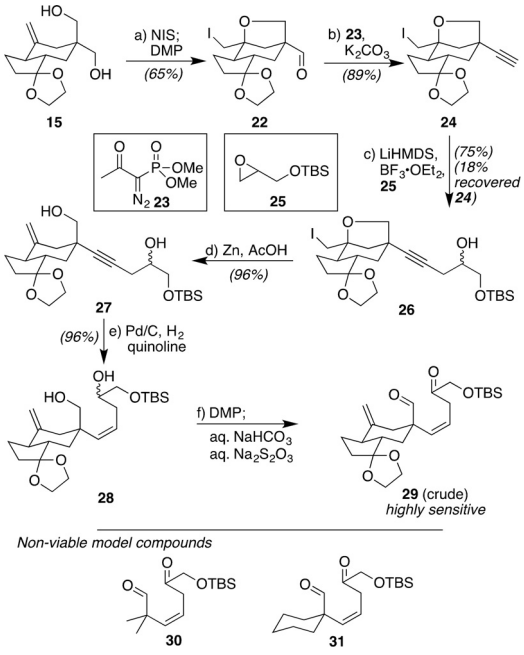
As shown in Scheme 2, our efforts commenced with the preparation of the *trans*-hydrindane skeleton as expressed by diol **15**. Thus, following isopropenyl addition to commercially available cyclopentenone to afford **16**, subsequent treatment with KHMDS and TIPSOTf at −78 °C in THF afforded a 2.5:1 mixture of regioisomeric silyl enol ethers, favoring **19**.[6] Subsequent exposure to $SnCl_4$ in the presence of methylene dimethyl malonate (**17**) then afforded compound **20** in 38% yield and undetermined d.r. over two steps.[10] Significant efforts to improve the yield and regioselectivity of this sequence were undertaken, but none proved successful; nevertheless, material processing on scale did not prove problematic. Pressing forward, the ketone within **20** was then protected as a ketal using ethylene glycol, trimethyl orthoformate, and *p*-TsOH·H_2O in hot toluene (90 °C); pleasingly, these conditions also induced epimerization of the α-carbon to afford **21** as a single diastereomer in 86% yield.[11] With the *trans*-disposition of the two sidechains established, our focus shifted to closing the final six-membered ring needed to



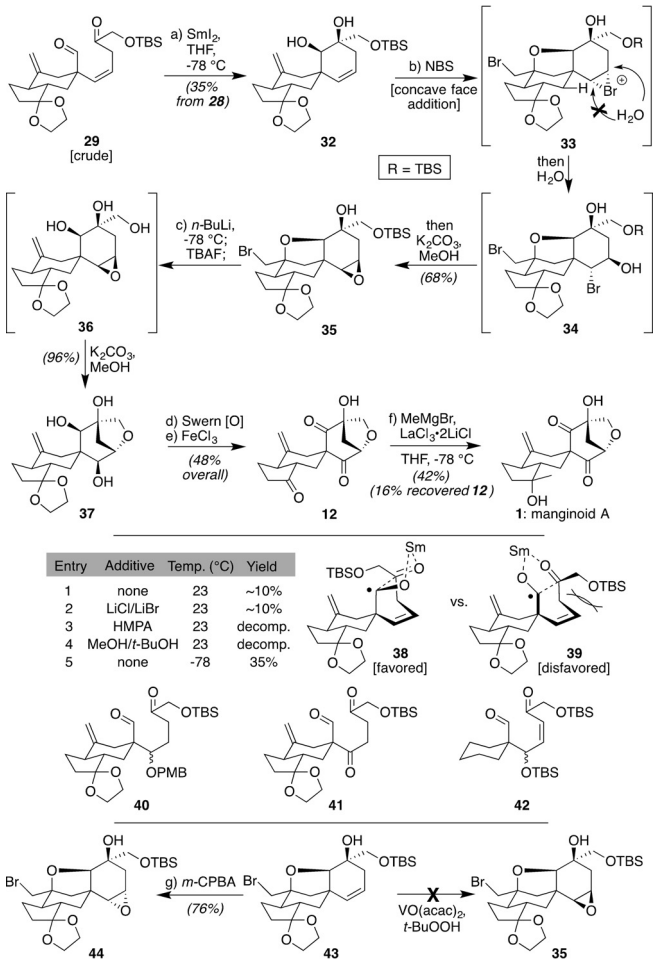
Scheme 2. Synthesis of key diol **15**: a) KHMDS (1.4 equiv), TIPSOTf (1.2 equiv), THF, −78 to 23 °C, 3 h; b) **17** (1.5 equiv), $SnCl_4$ (0.20 equiv), CH_2Cl_2, −78 to 23 °C 1.5 h, 38% from **16**, 10% recovered **16**; c) ethylene glycol (5.0 equiv), $CH(OMe)_3$ (5.0 equiv), *p*-TsOH·H_2O (0.10 equiv), toluene, 90 °C, 12 h, 86%; d) TCCA (1.1 equiv), EtOAc, −78 °C, 45 min, 64%; e) NaH (3.0 equiv), DMF, 0 to 23 °C, 3 h, 81%; f) $LiAlH_4$, (2.0 equiv), THF, 0 °C, 15 min, 73%. TCCA = trichloroisocyanuric acid.

complete the hydrindane framework. Initial investigations seeking a direct cyclization using both the White allylic oxidation protocol[12] as well as Snider's radical-based oxidative coupling[13] did not afford any desired products; only slow decomposition of the starting material was observed.[14] Pleasingly, a two-step alternative rose to the occasion by using trichloroisocyanuric acid (TCCA) to effect an allylic chlorination[8d,15] followed by NaH-induced intramolecular cyclization. Global reduction of both esters with $LiAlH_4$[16] then delivered **15** in 7 steps overall.[17] While we note that our synthesis of **15** was performed racemically for material processing, it is formally asymmetric given that several enantioselective syntheses of **16** are known, with one repeated in comparable yield and enantioselectivity in our hands.[18]

With this material synthesized, we sought next to advance it to intermediate **29** (cf. Scheme 3), the anticipated precursor for the key pinacol cyclization. The first critical operation in that regard was selective functionalization of the equatorially disposed primary alcohol, noting that such differentiation simply by reagent control was unlikely to be successful given the similar steric environments around both of the alcohols.[19] Indeed, initial probes for mono-oxidation using Dess–Martin periodinane and CrO_3 showed poor selectivity. Thus, we elected instead to take advantage of the proximity of the axial-disposed alcohol to the neighboring alkene to forge a conformationally locked iodoether protecting group through the action of NIS.[20] Following the in situ addition of Dess–Martin periodinane at the end of the sequence,[21] aldehyde **22** was obtained in 65% overall yield. Then, after use of the Bestmann modification of the Seyferth–Gilbert homologation, followed by deprotonation of the newly formed terminal alkyne and the addition of electrophile **25**, compound **26** resulted as an inconsequential mixture of diastereomers. Having served its role in facilitating the construction of the side-chain, the iodoether was reductively cleaved next through the action of Zn powder in the presence of AcOH.[20b] The resultant product (**27**) was then hydrogenated under the action of Pd/C poisoned by quinoline to afford the *cis*-alkene of **28** in 88% overall yield from **26**. Of



Scheme 3. Synthesis of dicarbonyl **29**: a) NIS (1.1 equiv), CH_2Cl_2, 23 °C, 1 h; then DMP (1.2 equiv), CH_2Cl_2, 23 °C, 1 h, 65%; b) Ohira–Bestmann reagent (**23**, 1.5 equiv), K_2CO_3 (2.5 equiv), MeOH, 23 °C, 2 h, 89%; c) LiHMDS (1.3 equiv), $BF_3{\cdot}Et_2O$ (1.3 equiv), **25** (3.0 equiv), THF, −78 to 23 °C, 3 h, 75%, 18% recoverd **24**; d) Zn (30 equiv), AcOH (10 equiv), MeOH/Et_2O, 40 °C, 1 h, 96%; e) H_2 (balloon), Pd/C (0.05 equiv), quinoline (0.35 equiv), EtOAc, 23 °C, 2 h, 96%; f) DMP (3.5 equiv), CH_2Cl_2, 23 °C, 2 h; then workup with aqueous $Na_2S_2O_3$, aqueous $NaHCO_3$. NIS = *N*-iodosuccinimide, HMDS = hexamethyldisilizane, DMP = Dess–Martin periodinane.



Scheme 4. Completion of the total synthesis of manginoid A (**1**) from dicarbonyl **29**: a) SmI_2 (6.6 equiv), THF, −78 °C, 1 h, 35% from **28**; b) NBS (2.1 equiv), THF, 23 °C, 15 min; then add H_2O, THF, 23 °C, 4 h; then add MeOH, K_2CO_3 (5.0 equiv), 50 °C, 4 h, 68%; c) *n*-BuLi (4.0 equiv), THF, −78 °C, 10 min; then add MeOH (8.0 equiv), TBAF (5.0 equiv), THF, 23 °C, 2 h; then add MeOH, K_2CO_3 (10 equiv), 50 °C, 4 h, 96%; d) DMSO (20 equiv), $(COCl)_2$ (10 equiv), Et_3N (30 equiv), CH_2Cl_2, −78 to 23 °C, 4 h, 58%; e) $FeCl_3$ (0.20 equiv), acetone, 23 °C, 12 h, 83%; f) MeMgBr (2.1 equiv), $LaCl_3{\cdot}2\,LiCl$ (2.1 equiv), THF, −78 to 23 °C, 2 h, 42%, 16% recovered **12**; g) *m*-CPBA (1.2 equiv), CH_2Cl_2, 23 °C, 2 h, 76%. NBS = *N*-bromosuccinimide, TBAF = tetra-*n*-butylammonium fluoride; *m*-CPBA = *meta*-chloroperoxybenzoic acid.

note, the traditional Lindlar catalyst did not effect this reduction in our hands. In addition, the order of these final two operations was critical; without the free primary alcohol within **27**, we were never able to complete any alkyne reduction without significant loss of material through degradation. Hence, this alcohol might be serving as an essential directing group.[22]

Having reached this stage, all that was needed to access the requisite 1,6-dicarbonyl of the pinacol coupling precursor **29** was a double oxidation. As originally feared, this event proved challenging to execute, as initial conditions screened (such as PCC, PDC, Swern oxidation, and Parikh–Doering oxidation) led to minimal product formation along with significant decomposition. Moreover, **29** proved to be highly unstable on silica gel (even when base-deactivated), making purification efforts nearly impossible.[9b,23] Fortunately, we found that if we used Dess–Martin periodinane followed by a conventional work-up with both saturated aqueous $NaHCO_3$ and $Na_2S_2O_3$ solutions, crude dicarbonyl **29** could be obtained directly in good yield and of sufficient purity to press forward. Notably, efforts to prepare simple model congeners of this 1,6-dicarbonyl in the form of **30** and **31** failed, including under the successful conditions developed to reach **29**.[24]

With **29** finally in hand, we were pleased to find that treatment with SmI_2 in THF at 23 °C led to the desired diol **32** (Scheme 4) as a single diastereomer alongside a collection of unidentified by-products. Although the yield was only 10%, this initial result was encouraging. Efforts at optimization,[25] some of which are shown in the inset table in the middle portion of Scheme 4, included additives such as lithium salts,[25c] alcohols,[7a] and species known to promote the reducing ability of SmI_2 (such as HMPA).[25a,b] In no case were superior results obtained. However, simply by lowering the temperature to −78 °C, we found that the yield could be improved to a reproducible and readily scalable 35%. Given the range of failures observed for this reaction in other venues, this outcome was notable.

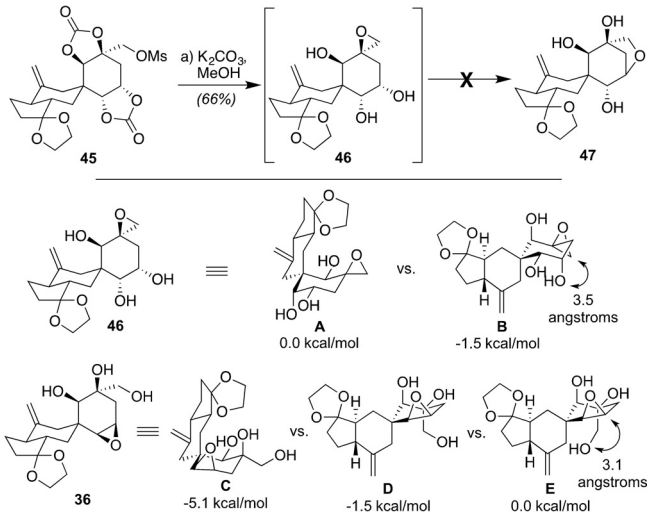
We presume that this yield enhancement may reflect greater prevention of decomposition by β-scission,[9] either by increased reaction initiation at the aldehyde or by modulated fragmentation if a non-cyclized radical formed first at the

ketone carbonyl. In addition, we rationalize the observed formation of the desired 1,2-diol stereoisomer based on the likely favorability of transition state **38** given the likely repulsions found in its alternative (**39**). Of importance, as intimated earlier the rigidity afforded by the full hydrindane framework and the alkene linking the two carbonyls appears necessary for the success of this coupling, as model compounds **40**, **41**, and **42** all failed under allied conditions.

Having completed this key operation, we next sought to construct the strained oxa-bridge of the manginoids. Success required several design iterations and careful analysis of the overall conformational properties of our intermediates. Our global approach sought to place an appropriate epoxide onto the 1,2-disubstituted alkene in hopes that it could be opened by a primary alcohol to forge the required ether linkage. To achieve that end, we first needed to engage the more reactive exocyclic alkene, again as a haloether in the form of **43** (see the bottom portion of Scheme 4). Unfortunately, upon attempted oxidation with *m*-CPBA or DMDO, compound **44** resulted in which the newly formed epoxide was generated on the undesired side; extensive efforts at a directed reaction based on the free tertiary alcohol, shown here using $VO(acac)_2$ and *t*-BuOOH, led only to recovered starting material.[26] Success was ultimately obtained via more indirect methods. Specifically, following the formation of **33** from **32** using excess NBS, the presence of water enabled a subsequent and fully stereo- and regioselective formation of bromohydrin **34**; the addition of base in the same pot then afforded the desired β-disposed epoxide of **35** in 65% yield.[27] From here, *n*-BuLi-promoted haloether ring opening[28] followed by silyl deprotection generated **36**, while subsequent base-promoted etherification completed a second single pot cascade to afford **37** in 96% yield.

With the full tetracycle in place, only a few functional group manipulations remained to generate **1**. Those operations commenced with a double Swern oxidation followed by ketal cleavage to afford **12** in 48% overall yield. The first of these steps was the lower yielding event (58%), as an unknown major side product was formed. Nevertheless, no other condition set tested (including Dess–Martin periodinane and PCC) proved capable of effecting both oxidations efficiently. For the second, the use of $FeCl_3$ was essential to avoid racemization of the α-stereocenter, an event that was observed when the deprotection was conducted with heating in the presence of *p*-TsOH·H_2O. Finally, a regioselective addition of a methyl group was successful using a combination of MeMgBr (2.1 equiv) and $LaCl_3$·2 LiCl (2.1 equiv) in THF at −78 °C.[29] This process afforded manginoid A (**1**) as a single diastereomer (in terms of the methyl addition) in 42% yield, with all spectral data matching that of Zhu, Zhang, and coworkers,[1] along with 16% recovered **12** and a complex mixture of over-addition products. This result confirmed our original hypothesis that the cyclopentanone was more reactive than the other two ketones, though not perfectly so in advance of full starting material consumption.

Finally, to put the success of the critical etherification event in further context, alternate strategies to forge the oxa-bridged ring were also explored but failed (Scheme 5). In one of those initial efforts, epoxide **46** was successfully prepared



Scheme 5. Exploration of the factors determining success in the final cyclization leading to **37**: a) K_2CO_3 (5.0 equiv), MeOH, 50 °C, 12 h.

from **45** (see SI for full details on synthesis) and tested for its capability to undergo the ring closure to afford **47**. While we anticipated that such a proposed 5-*endo*-tet cyclization would be challenging to effect, as it is formally Baldwin forbidden,[30,31] computational analysis of the structure conformations demonstrated a potential to achieve the desired cyclization. Calculations at the B3LYP/cc-pVTZ level of theory indicated that of the two possible conformers of **46**, **B**, where both reactive sites were axially positioned, was favored over **A**; such a preference suggested that suitable proximity might exist to promote the anticipated 5-*endo*-tet cyclization. Nevertheless, in the end we were not able to affect the desired transformation with this substrate. By contrast, in **36** (the material formed just prior to successful cyclization), although the necessary conformers for cyclization (**D** and **E**) are higher in energy than conformer **C**, the ring closure still occurred, likely because a 5-*exo*-tet cyclization is a generally more favorable process and the two reactive domains within **E** are fairly close (3.1 Å).

In conclusion, we have achieved the first total synthesis of manginoid A (**1**) in 19 steps via a series of unique and highly regio- and chemoselective transformations. Most critical among these were the use of 1) reversible haloetherifications to differentiate both alcohols and alkenes at critical junctures, 2) a facially specific pinacol coupling with a highly sensitive keto-aldehyde to generate the key spirocyclic system, 3) two highly orchestrated, one-pot multistep cascade reactions to forge the final ether linkage of the oxa-bridged core, and 4) a stereo- and regioselective addition of a methyl group to just one of three ketones to complete the target. We believe the developed solutions highlight the power of constrained frameworks to facilitate difficult transformations and define a roadmap for the efficient synthesis of other members of the manginoid collection.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloetherification · manginoid · pinacol coupling · regioselective · total synthesis

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