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Total Synthesis of (+)-Granatumine A and Related Bislactone Limonoid Alkaloids via a Pyran to Pyridine Interconversion

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Abstract

We report the first total synthesis of (+)-granatumine A, a limonoid alkaloid with PTP1B inhibitory activity, in ten steps. Over the course of this study, two key methodological advances were made: a cost-effective procedure for ketone α,β-dehydrogenation using allyl-Pd catalysis, and a Pd-catalyzed protocol to convert epoxyketones to 1,3-diketones. The central tetrasubstituted pyridine is formed by a convergent Knoevenagel condensation and carbonyl-selective electrocyclization cascade, which was followed by a direct transformation of a 2*H*-pyran to a pyridine. These studies have led to the structural revision of two members of this family.

Protein tyrosine phosphatase 1B (PTP1B) has emerged as an exciting target for the treatment of many ailments, such as diabetes, cancer, and neurodegenerative diseases.[1] Granatumine A (**6**), a bislactone limonoid alkaloid isolated from the Chinese mangrove (*Xylocarpus granatum*), has shown moderate inhibitory activity against PTP1B, while the related limonoid alkaloid xylogranatopyridine B (**1**) was found to be inactive.[2] This increased potency may arise due to the synthetically demanding structural differences, namely the presence of an acid-labile C3 benzylic ether substituent and a reorganized A-ring with a fused lactone.

The C3 substituent present in the bislactone limonoid alkaloids is a point of diversity in this class of natural products (**4–6**), as depicted in Figure 1B.[3] The differing reported stereochemistries at C3 across this series of limonoid natural products prompted the question of whether some of these members had been structurally misassigned.[3] In order to resolve the stereochemical assignment and provide a means to modulate structurally the pharmacologically relevant compounds, we undertook the total synthesis of the bislactone limonoid alkaloids.[4]

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b04508.

Experimental procedures, X-ray diffraction, spectroscopic data for all new compounds including ^{1}H- and ^{13}C NMR spectra (PDF)

Crystallographic data for $C_{26}H_{27}NO_6$ (CIF)

Crystallographic data for $C_{11}H_{14}O_4$, 0.5($CHCl_3$), 0.5(H_2O) (CIF)

Crystallographic data for $C_{15}H_{16}O_3$ (CIF)

Previously, our laboratory disclosed a strategy to assemble the tetrasubstituted pyridine ring present in xylogranatopyridine B (**1**) by employing a stannyl-Liebeskind pyridine synthesis followed by a late-stage selective benzylic oxidation at C1 (Figure 1A).[5] In the context of the more structurally complex bislactone alkaloids, this approach was unsuccessful, which suggested the introduction of the necessary oxidation state at an earlier stage and subsequent functional group interchange to access the variance at C3 of the bislactone limonoid alkaloids. The obstructing pyridine was retrosynthetically reduced to a 2*H*-pyran (**7**), which would serve as a cyclic equivalent to a Knoevenagel condensation product via a carbonyl-selective oxa-6π electrocyclization.[6,7] This tactical combination would simultaneously enable a convergent approach using fragments **8** and **9**, and differentiate the two ketones present in compound **8**.

The synthesis of aldehyde **9** began with the dehydrogenation of ketone **10** (Scheme 1A). Attempts to reproduce known literature procedures for the production of 2,6-dimethylcyclohex-2-en-1-one (**11**), such as Birch reduction[8a] or bromination/elimination protocols,[8b] resulted in variable results and purification challenges on large scale. Utilizing our laboratory's palladium-catalyzed ketone dehydrogenation methodology,[9] ketone **10** was converted to the corresponding enone (**11**) in 76% yield. Importantly, the conditions were modified to be more cost-effective by employing inexpensive allyl acetate as oxidant, LDA as base, and 1 mol % palladium loading; and thus might be broadly applied in the scalable synthesis of synthetic building blocks.

A diastereoselective aldol reaction was performed with 3-furaldehyde and enone **11** to afford the alcohol product in 82% yield.[10] An acylative kinetic resolution with (+)-tetramisole (**12**)[11] was conducted on the resulting alcohol to form acetate (+)-**13** in 41% yield and 91:9 er with 46% recovered starting material. The unreacted enantiomer could be recycled to **11** by a retro-aldol reaction in the presence of K_2CO_3 and MeOH in 85% yield, and a total yield of 57% of (+)-**13** could be obtained after one round of recycling (see Supporting Information). An intramolecular aldol reaction occurred upon treatment of (+)-**13** with LiHMDS, and dehydration of the resulting alkoxide with Burgess reagent formed the degraded limonoid (+)-pyroangolensolide (**14**) in 80% yield.[10] This marks the first enantioselective synthesis of (+)-**14** and the absolute configuration of (+)-**14** was confirmed by X-ray diffraction.

The interconversion of (+)-pyroangolensolide (**14**) to (+)-azedaralide (**15**) by site-selective allylic oxidation of the methyl group has been a previously described synthetic challenge.[12] After examining a wide range of allylic oxidation conditions, we discovered that (+)-azedaralide and aldehyde **9** were formed smoothly upon treatment of **14** with SeO_2 and Na_2HPO_4. Treatment of the resulting alcohol with Dess–Martin periodinane (DMP) furnished **9** in 52% yield over two steps, and **14** could be recovered in 27% yield.

For the synthetic route to the 1,3-diketone **8**, we identified (±)-α-ionone (**16**), a widely available terpene building block, as a starting material goal because they are a near structural match. Modification of **16** would require oxidative cleavage, lactone formation, and installation of the carbonyl oxidation state at C3. Although there are many stepwise approaches to synthesize enantioenriched α-ionone,[13] we viewed a direct resolution of the

commercially available material as ideal for an efficient synthesis of **17**. In fact, the previously reported synthesis of (−)-epoxy-α-ionone (**17**) via lipase-resolution proceeded via a low-yielding five-step sequence.[14]

The direct kinetic resolution of (±)-α-ionone (**16**) was realized using Jacobsen's commercially available (*S,S*)-Mn-salen epoxidation catalyst,[15] 4-PPNO, and buffered bleach as the terminal oxidant to provide (−)-**17** in 43% yield, 86:14 er, and an inconsequential mixture of diastereomers (10:1 dr), Scheme 1B. Hydrosilylation of the enone functionality with $[Rh(cod)(OH)]_2$ and phenyldimethylsilane[16] furnished enoxysilane **18** in an excellent isolated yield on decagram scale (89%). Subjection of enoxysilane **18** to ozonolytic oxidative cleavage followed by addition of Jones reagent provided ketone **20** in 51% yield. This presumably occurs via the intermediacy of carboxylic acid (**19**), which cyclizes onto the tertiary carbocation formed by acid-mediated epoxide opening. The resulting secondary alcohol would then undergo additional oxidation to form ketone **20**.

Employing Stahl's ketone α,β-dehydrogenation conditions,[17] **20** was selectively converted to enone **21**. Utilizing alternative ketone dehydrogenation conditions, including our laboratory's allyl-Pd-mediated method,[9] resulted in unselective product formation or incomplete conversion of **20**. Likewise, other methods were found to be ineffective. Nucleophilic epoxidation of enone **21** resulted in epoxide **22** in 67% yield and an inconsequential 1:1 mixture of diastereomers.

Treatment of the mixture of diastereomeric epoxides (**22**) with the previously described Pd-mediated α,β-epoxyketone opening conditions[18] did not result in the formation of diketone **8**. A broad examination of phosphine ligands, including those developed by Buchwald and co-workers,[19] revealed that XPhos could effectively promote the transformation of **22** to **8** in 90% yield. These newly discovered conditions for synthesis of 1,3-diketones from α,β-epoxyketones may find use in other challenging contexts in which traditional epoxide opening conditions are unsuccessful. More generally, this approach for 1,3-diketone synthesis may be a useful tactic in other settings, as we have found here.

With a scalable route to **8** and **9**, the convergent fragment coupling through a Knoevenagel condensation was investigated (Scheme 2A). Treatment of **8** and aldehyde **9** with ethylenediammonium diacetate (EDDA)[20,21] formed presumed enedione intermediate **23**, which under thermal conditions spontaneously underwent an oxa-6π electrocyclization to give 2*H*-pyran **7** as the only product on a gram scale in 47% yield from **9**. The oxa-6π electrocyclization allowed for a regioselective C1 ketone protection in the presence of the C3 ketone.[7e]

Intrigued by this selective pyran formation, we conducted computational investigations to determine the origins of regioselectivity, and these studies suggest that the observed product is both kinetically and thermodynamically favored.[22] At the ωB97x-D/6–311+G(2d,p)// ωB97x-D/6–31+G(d,p) level of theory,[23] the transition states for the two 6π electrocyclizations differ by only 1.0 kcal/mol, slightly favoring the pathway leading to the observed pyran product **7** (Figure 2A). Additionally, the ground state energy of pyran **7** is significantly lower in energy than its regioisomer *regio*-**7** (2.8 kcal/mol). In order to obtain

experimental evidence for the thermodynamic preference for the observed pyran **7**, *regio*-**7** was subjected to the reaction conditions used for condensation and electrocyclization, which resulted in full conversion to the pyran **7** in 69% isolated yield (Figure 2B). Interestingly, treatment of the pyran **7** with $TiCl_4$ resulted in formation of ***regio*-7** in 30% yield, and pyran **7** was recovered in 60% yield.[21] A related curiosity is that similar regioisomeric limonoid natural products have been isolated recently.[24] For both the synthetically relevant electrocyclization and for experiments conducted as part of the mechanistic investigations, high torquoselectivity was observed—in each instance, a single diastereomer was observed by ^1H NMR (see Supporting Information for computational evaluation of the torquoselectivity).

The selective differentiation of the ketone functionalities through pyran formation allowed for installation of the necessary C3 functionality present in the bislactone limonoids. Luche reduction of the C3 ketone resulted in allylic alcohol **24** in 61% yield as a single diastereomer. The use of CF_3CH_2OH as solvent prevented decomposition pathways when more nucleophilic solvents were employed, such as MeOH. Treatment of alcohol (**24**) with hydroxylamine in refluxing methanol resulted in the formation of the compound with the originally proposed structure of (+)-xylogranatin F (**4**) in 34% yield and the pyridine *N*-oxide **26** in 35% yield.[6,7] These products presumably arise via elimination of water from the intermediate **25** by two different pathways as shown in Scheme 2A. Intermediate **25** in turn likely arises via a retro-6π electrocyclization,[25] followed by oxime formation, and 6π electrocyclization.[26,27] The structure of **4** was confirmed by X-ray diffraction, conclusively demonstrating that the structure of (+)-xylogranatin F was misassigned.

In order to complete the synthesis of (+)-granatumine A, numerous derivatives of **4** were synthesized, including a tosylate, mesylate and phosphate, and an S_N2 displacement with methoxide was attempted. However, the undesired stereochemical outcome was obtained, namely the retention of configuration, which we attributed to an S_N1 solvolysis pathway. Fortunately, chlorination of the benzylic alcohol (**4**) with thionyl chloride, and in situ methanolysis resulted in formation of (+)-granatumine A (**6**) as a separable 1:1 mixture of diastereomers. The structure of (+)-granatumine A (**6**) had previously been reported by X-ray crystallography.[2]

The other major product of the pyridine synthesis cascade, the pyridine *N*-oxide (**26**), was reduced to the corresponding pyridine using Zn and $CeCl_3$[28] to form 3-deoxy-xylogranatin F (**27**), which may itself be a natural product that has not yet been isolated. To demonstrate the failure of our previously described synthetic strategy for limonoid alkaloid synthesis for the bislactone limonoid alkaloids, conversion of **27** to (+)-xylogranatin F by benzylic oxidation was attempted without success. This result is consistent with our expectation that the bislactone alkaloids are more challenging substrates for benzylic oxidation due to the increased steric hindrance and heightened deactivation by inductive effects.

In the view that NMR structure prediction calculations may not define the correct structure of xylogranatin F, we planned to use chemical synthesis to resolve this ambiguity. Given the putative biosynthesis, we hypothesized that the correct structure of xylogranatin F is the C3 epimer **29**.[29] Hence, chlorination of alcohol **4** and displacement of the resulting chloride

with $Zn(OAc)_2$ resulted in the formation of (+)-xylogranatin G (**28**) and C3-*epi*-**28** with a 1:1 dr. Hydrolysis of the acetate **28** provided **29**, whose spectral data matched those reported for (+)-xylogranatin F; hydrolysis of C3-*epi*-**28** provided **4**. As an alternative approach to directly access (+)-xylogranatin F, reduction of ketone **7** to C3-*epi*-**24** was attempted, but unsuccessful.

In summary, we have demonstrated the first asymmetric synthesis of (+)-granatumine A in 10 steps from commercially available 2,6-dimethylcyclohexanone and α-ionone, and revised the structures of (+)-xylogranatin F and (+)-xylogranatin G by the reassignment of the C3 stereocenter. Over the course of this work, we discovered new Pd-catalyzed ketone α,β-dehydrogenation and α,β-epoxy ketone opening conditions. The convergent synthesis employing a key pyran to pyridine conversion provided efficient access to bislactone limonoid alkaloids and may facilitate the biological study of these and related compounds.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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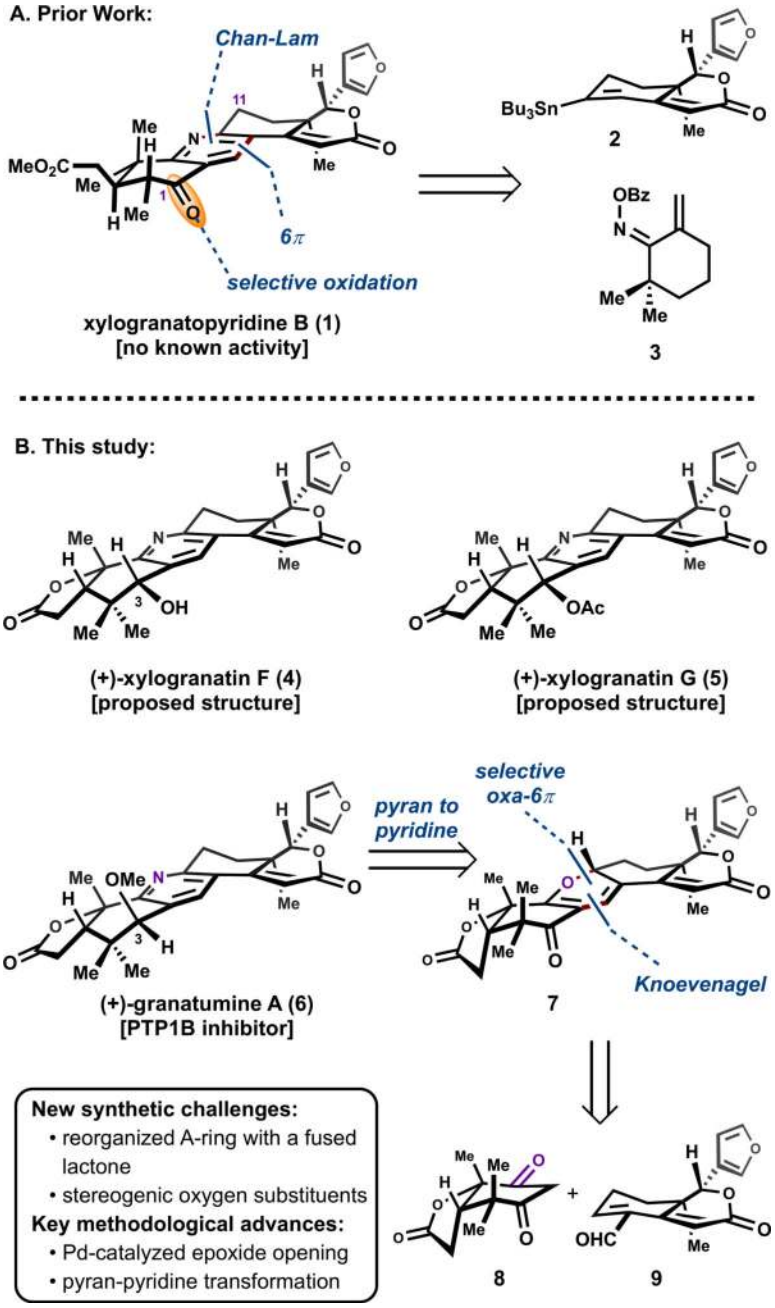


Figure 1.

(A) Previous work on the limonoid alkaloids. (B) Retrosynthetic analysis toward bislactone limonoid alkaloids.

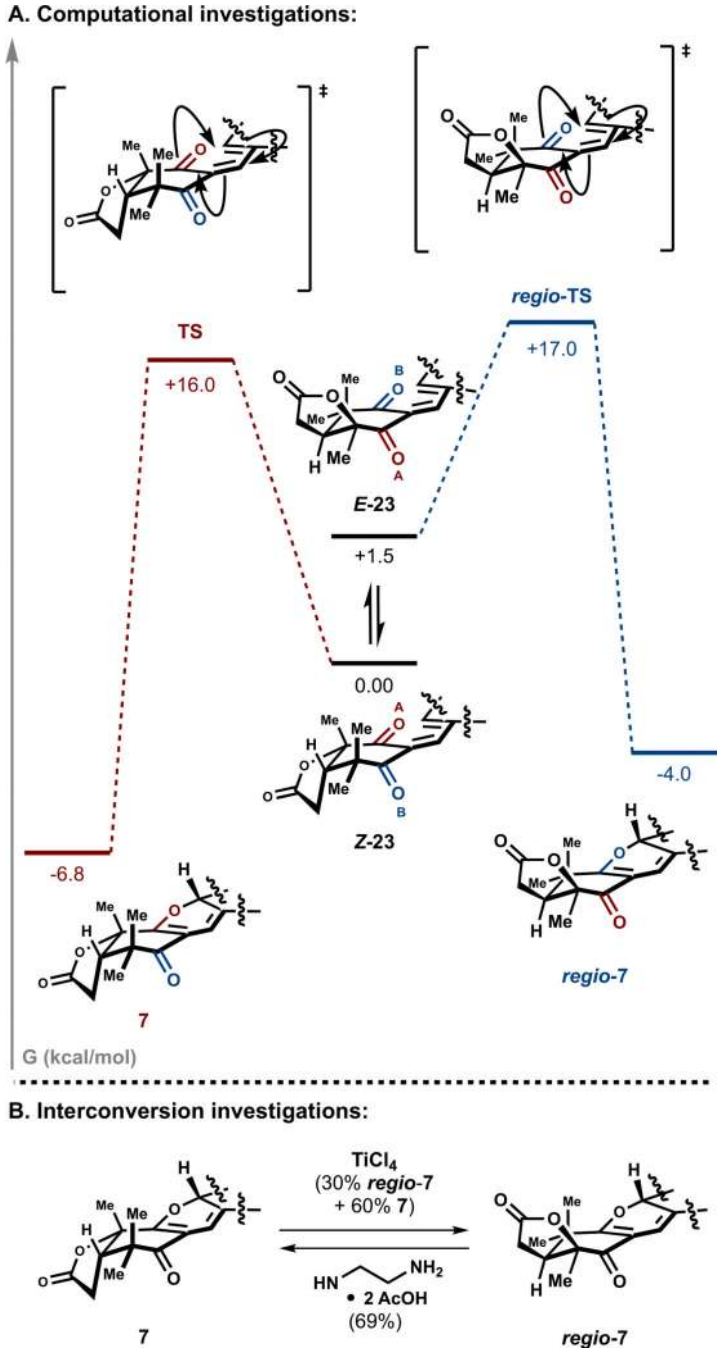
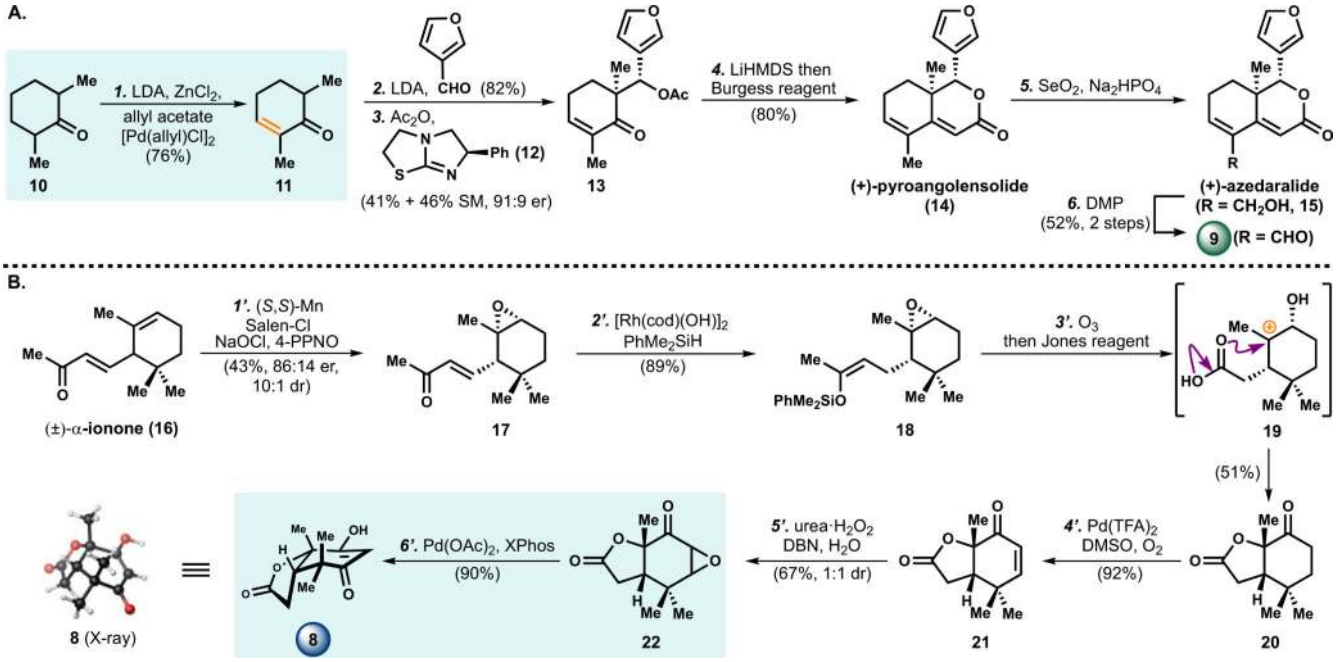


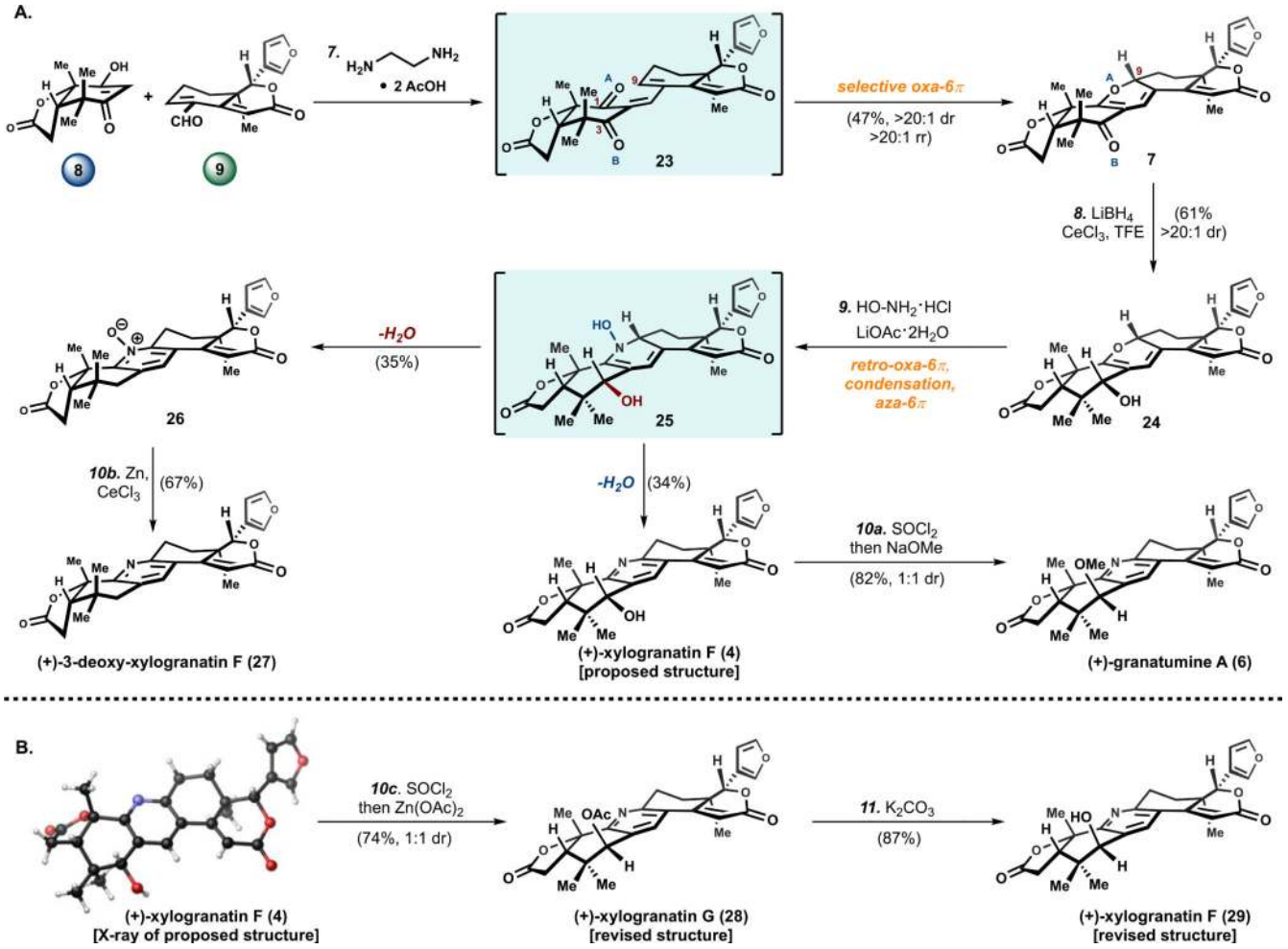
Figure 2.

(A) Computational investigations toward the regioselective pyran formation. Free energies (in kcal/mol) and structures were determined using ωB97x-D/6–311+G(2d,p)//ωB97x-D/6–31+G(d,p). (B) Interconversion investigations between pyran regioisomers.



Scheme 1. (A) Total Synthesis of Pyroangolensolide (14) and Azedaralide (15); (B) Synthesis of A-Ring Diketone (8)[a]

[a] Reagents and conditions: (1) LDA (1.5 equiv), $ZnCl_2$ (2.0 equiv), −40 °C, THF, 0.5 h, then allyl acetate (1.2 equiv), 1 mol % [Pd(allyl)Cl]2, 60 °C, 5 h, 76%; (2) LDA (1.2 equiv), 3-furaldehyde (1.2 equiv), −78 °C, THF, 0.5 h, 82%; (3) 10 mol % (+)-tetramisole, Ac_2O (0.5 equiv), PhMe, 0 °C, 10 h, 41%, 91:9 er, 46% SM; (4) LiHMDS (4.0 equiv), −78 to 23 °C, 4 h, then Burgess reagent (4.0 equiv), 60 °C, 3 h, 80%; (5) SeO_2 (2.5 equiv), Na_2HPO_4 (5.0 equiv), 1,4-dioxane, 100 °C, 14 h; (6) Dess–Martin periodinane (1.5 equiv), CH_2Cl_2, 23 °C, 1 h, 52% over 2 steps; (1′) 5 mol % (*S,S*)-(+)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride, 4-phenylpyridine-N-oxide (5 mol %), aq. NaOCl (1.0 equiv), CH_2Cl_2, 0 to 23 °C, 4 h, 43%, 86:14 er, 10:1 dr; (2′) 1 mol % [Rh(cod)(OH)]$_2$, $PhMe_2SiH$ (1.3 equiv), THF, 23 to 60 °C, 4 h, 89%; (3′) O_3, acetone, −78 °C, 0.5 h, then Jones reagent (2.0 equiv), 0 to 23 °C, 2 h, 51%; (4′) O_2 balloon, $Pd(TFA)_2$ (5 mol %), DMSO (10 mol %), AcOH, 80 °C, 12 h, 92%; (5′) urea·H_2O_2 (3.0 equiv), DBN (3.0 equiv), H_2O (9.0 equiv), THF, 0 to 23 °C, 5 h, 67%, 1:1 dr; (6′) $Pd(OAc)_2$ (5 mol %), XPhos (5 mol %), toluene, 120 °C, 15 h, 90%.



Scheme 2. (A) Total Synthesis of (+)-Granatumine A (6); (B) Structural Revision of (+)-Xylogranatin F (29) and (+)-Xylogranantin G (28)[a]

[a]Reagents and conditions: (7) ethylenediammonium diacetate (0.7 equiv), **9** (1.5 equiv), $(CH_2Cl)_2$, 65 °C, 4 h, 47%; (8) $LiBH_4$ (4.5 equiv), $CeCl_3 \cdot 7H_2O$ (4.5 equiv), CF_3CH_2OH/THF (1:1), 0 to 23 °C, 3 h, 61%; (9) HO-NH_2·HCl (5.0 equiv), LiOAc·H_2O (6.0 equiv), MeOH, 80 °C, 12 h, 34% **4** + 35% **26**; (10a) $SOCl_2$ (7.0 equiv), CH_2Cl_2, 40 °C, 12 h, then NaOMe (10.0 equiv), MeOH, 70 °C, 5 h, 82%, 1:1 dr; (10b) Zn (4.0 equiv), $CeCl_3 \cdot 7H_2O$ (2.0 equiv), MeOH, 23 °C, 6 h, 67%; (10c) $SOCl_2$ (7.0 equiv), CH_2Cl_2, 40 °C, 12 h, then $Zn(OAc)_2$ (10.0 equiv), AcOH, 100 °C, 12 h, 74%, 1:1 dr; (11) K_2CO_3 (7.0 equiv), MeOH, 60 °C, 5 h, 87%.