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Synthetic Study Aiming at the Tricyclic Core of 12-*epi*-JBIR-23/24

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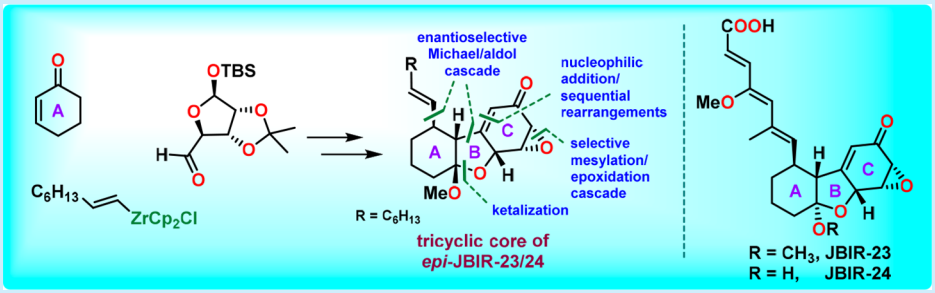
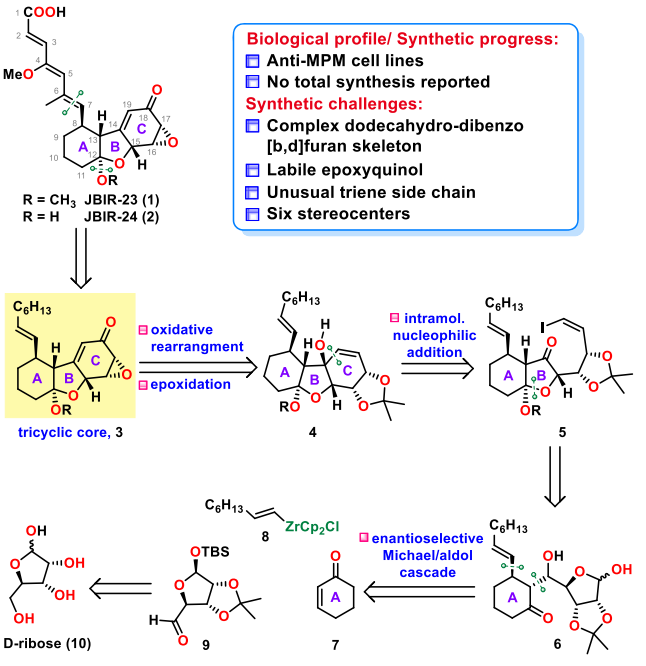


ABSTRACT: The synthetic study toward highly enantio- and diastereoselective synthesis of the tricyclic framework of 12-*epi*-JBIR-23/24, a natural product analogue showing inhibitory activity against four malignant pleural mesothelioma cell lines, is presented herein. In this synthesis, a rhodium-catalyzed asymmetric three-component Michael/aldol reaction introduces three consecutive tertiary carbon centers, while the unique epoxyquinol core motif is successfully forged via [3,3]-sigmatropic rearrangement of an allylic xanthate, vinylogous Pummerer rearrangement, and a selective mesylation/epoxidation cascade of a triol.

JBIR-23 and -24 were isolated from *Streptomyces* sp. AK-AB27 by Shin-ya and co-workers in 2009.[1a] Structurally, they contain a novel dodecahydrodibenzo[b,d]furan skeleton bearing six stereogenic centers, three of which are located on the compactly and highly oxygenated cyclohexane platform, and a trienyl acid side chain (Scheme 1). Notably, both of them display inhibitory activity against four malignant pleural mesothelioma (MPM) cell lines. JBIR-23 not only shows stronger antitumoral efficacy (10−50 μM) than JBIR-24 but also prevents tumor growth in tumor-bearing nude mice for in vivo studies.[1b] In spite of their intriguing structural motifs and promising pharmacological properties, no total synthesis or synthetic study toward JBIR-23 and -24 has yet been reported. Herein, we present our endeavors on the synthesis of the tricyclic core structure of 12-*epi*-JBIR-23 and -24.

Construction of the epoxyquinol motif of JBIR-23 and -24 is challenging[2] because its aromatization is feasible under both basic and acidic conditions. Accordingly, to minimize the side reactions, we consider introducing the brittle epoxyquinol core at the late stage of synthesis, by devising an A−AB−ABC synthetic strategy. As depicted in Scheme 1, we envision that JBIR-23 and -24 could be advanced from compound **3** through sequential ozonolysis and Wittig olefination or Horner−Wadsworth−Emmon reaction as in our previous synthesis of cuevaene A.[3] We conceived that compound **3** could be produced from **4** via oxidative rearrangement of a tertiary allylic alcohol and selective epoxidation. Furthermore, ring C of compound **4** could be installed through an intramolecular nucleophilic addition of vinyl to ketone in **5**. We consider that **5** could arise from **6** via necessary functional group

Scheme 1. Retrosynthetic Analysis of JBIR-23/-24



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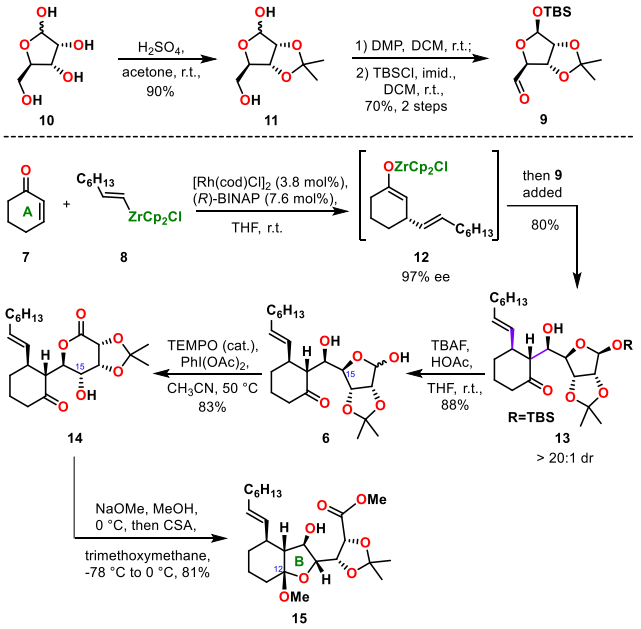
manipulations involving ketalization and Wittig reaction. A Rh-catalyzed enantioselective Michael addition between cyclohexanone **7** and alkenyl zirconium **8**,[4] followed by aldol reaction with aldehyde **9** in one pot, might generate **6**. Finally, **9** could be derived from commercially available D-ribose **10**.

Our synthesis commenced with D-ribose **10**, which was transformed to aldehyde **9** through a three-step sequence involving acetonide protection,[5] selective oxidation of the primary alcohol, and silyl protection of the secondary alcohol (Scheme 2). Taking inspiration from asymmetric Michael reaction,[4] we initially treated the enone **7** with **8** in the presence of $[Rh(COD)Cl]_2$ (3.8 mol %) and (*R*)-BINAP (7.6 mol %) by following Oi's methodology[4a] and generated a Michael adduct with excellent 97% ee. We were then encouraged to conduct a cascade Michael/aldol reaction, in which the resulting alkenylzirconium **12** was treated with the aldehyde **9**. Pleasingly, compound **13** was achieved in 80% overall yield with excellent diastereoselectivity (>20:1 dr).

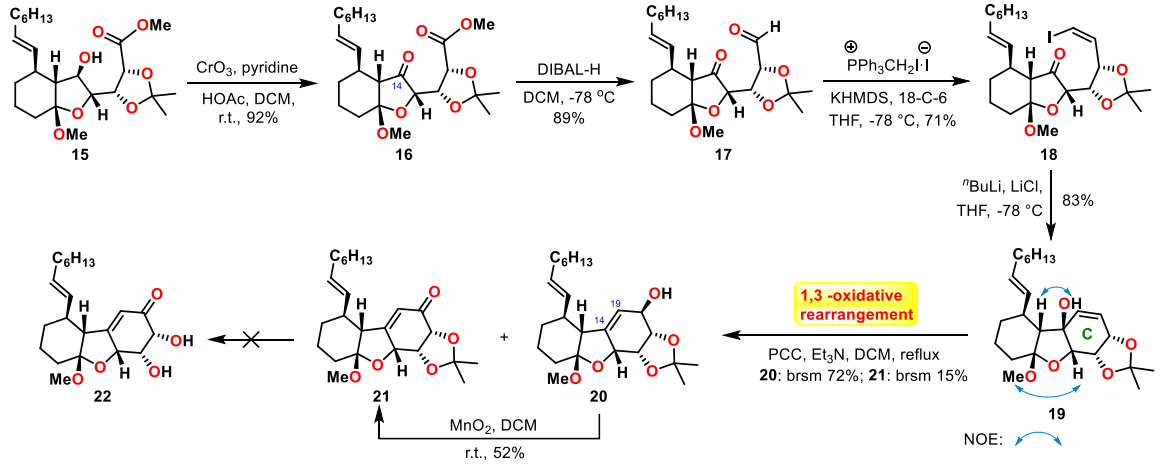
Scheme 2. Synthesis of 15



With **13** in hand, we embarked on the construction of ring B of the tricyclic core. Accordingly, desilylation of **13** in the presence of TBAF and HOAc afforded **6**. Treatment of **6** with TEMPO/$PhI(OAc)_2$ at 50 °C resulted in selective oxidation of the semiacetal and then ester migration, providing **14** in 83% yield together with a five-membered lactone in 15% yield (see the Supporting Information for details). After numerous trials, we fortunately identified that treating **14** with CH_3ONa, followed by a CSA-mediated cyclization, could generate compound **15** in 81% yield.[6] Although **15** embraced a *cis*-fused 6/5 bicyclic skeleton, not in accordance with that of either JBIR-23 or JBIR-24, we envisioned the desired *trans*-fused 6/5 bicycle could be achieved through equilibration at the final stage of synthesis.

The stage was now set for establishment of ring C with the epoxyquinol substructure. Initially, an alkene was devised to be installed at C_{14} to facilitate RCM reaction, leading to ring C. Thus, oxidation of **15** secured the corresponding ketone **16** (Scheme 3). However, the ketone at C_{14} was inert to various olefination reagents involving Tebbe reagent, Peterson reagent, and phosphorus ylide. Then we resorted to an oxidative rearrangement of tertiary allylic alcohol to construct the enone motif in ring C, instead of the RCM strategy. In practice, in the presence of the ketone at C_{14}, treating **16** with DIBAL-H enabled chemoselective reduction of the ester into an aldehyde to give **17**. Such abnormal selectivity indicated steric hindrance surrounding the ketone at C_{14}, accounting for the inert reactivity of its olefination. Compound **17** was further advanced to the vinyl iodide **18** via Wittig reaction. Then, we extensively screened classical NHK reaction conditions, but no productive reactivity could be identified.[7] Satisfactorily, exposure of vinyl iodide **18** into ^{n}BuLi/LiCl at −78 °C induced expedient lithium/halide exchange, and the resulting vinyl lithium attacked the ketone (C_{14}) to deliver **19** as a single stereoisomer in 83% yield.[8] The relative configuration of tricyclic compound **19** was confirmed by NOE analysis. Next, we started to investigate installation of the enone via 1,3-oxidative rearrangement of allylic alcohol.[9] Preliminary experimentations under typical conditions, such as PCC, PDC, and Dess−Martin periodinane, led to either decomposition of **19** or a complex mixture, plausibly due to the instability of **19** under acidic conditions. Thus, different bases were tested to suppress acidity in the oxidative rearrangement process, and the combination of PCC and Et_3N generated

Scheme 3. Synthesis of 21 and Attempt to Synthesize α,β-Unsaturated Ketone 22 through a Cleavage of Acetonide



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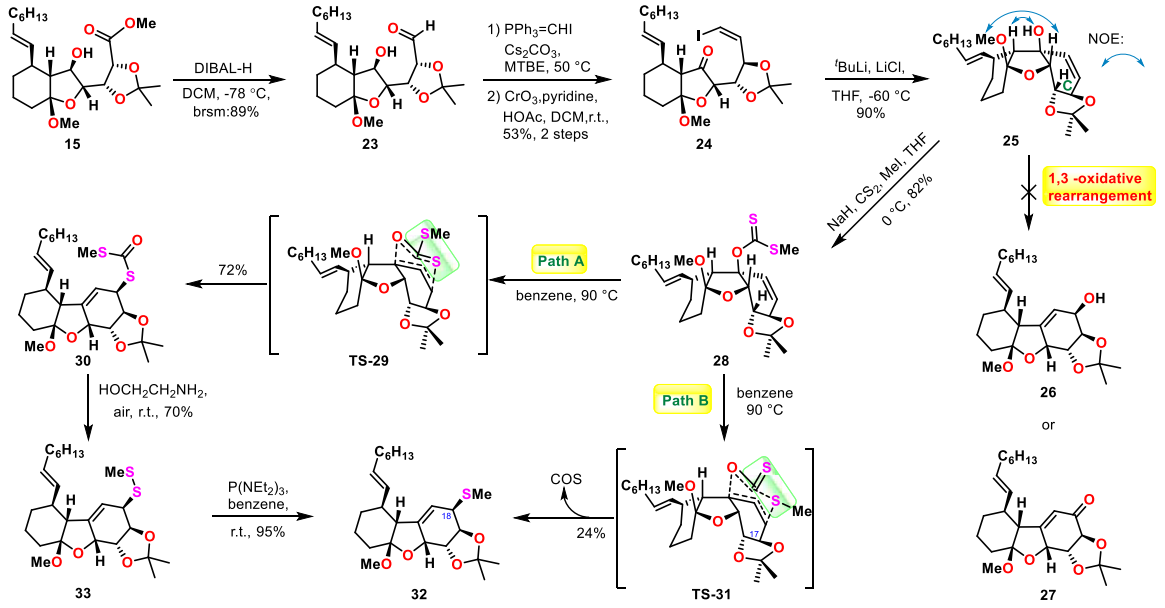
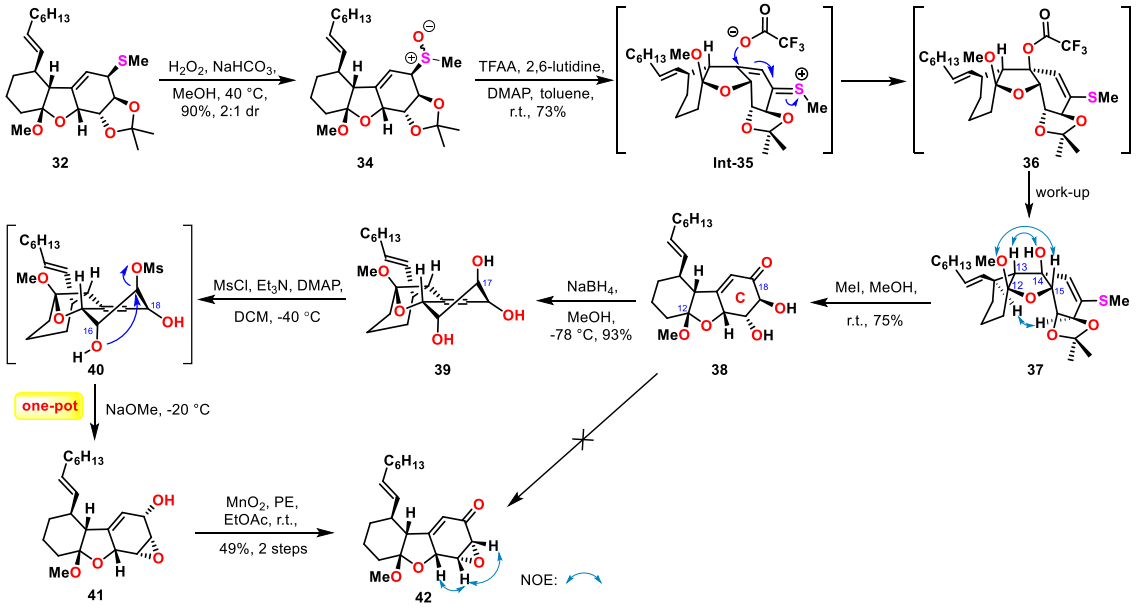
Scheme 4. Synthesis of Compound 32



Scheme 5. Synthesis of the Tricycle 42



compounds **20** and **21** in 72% and 15% yield, respectively, based on the recovery of starting material (see the Supporting Information for details). Allylic oxidation with MnO_2 could transform **20** into **21**, albeit in moderate yield. To our dismay, although considerable protonic acids and Lewis acids were investigated, we failed to remove the acetonide-protecting groups in either **20** or **21** (see the Supporting Information for details).

Learning from the above failure, we perceived that the *cis*-fused 6/5 ring junction between ring C and the acetonide moiety was stable to weak acidity, while the BC bicycle was prone to aromatization under typical acidic conditions. To comprise the stability of the BC bicycle and requirement of deprotection of acetonide, we planned to achieve a compound with *trans*-diol on ring C instead of compound **19** with a *cis*-diol moiety.

Reduction of the ester **15** with DIBAL-H furnished **23** in 89% yield (Scheme 4). Exposure of **23** to Cs_2CO_3 in MTBE triggered epimerization to a thermodynamically favorable *trans*-fused acetonide, which was *in situ* advanced to the vinyl iodide **24** after sequential Wittig reaction and oxidation of the secondary alcohol. Subsequent treatment of **24** with ^{t}BuLi provided **25** as a single diastereomer in 90% yield. The stereochemistry of **25** was assigned by NOE analysis. Unlike its epimer **19**, compound **25** underwent various oxidative rearrangement conditions without delivering the desired **26** or **27**, disappointingly (see the Supporting Information for details). Such a failure could be attributed to the twisty boat-like conformation of ring C in **25**, which prompted us to resort to [3,3]-rearrangement. However, although an array of attempts involving Eschenmoser−Claisen rearrangement,[10] Johnson−Claisen rearrangement,[11] Overman rearrangement,[12]

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and aliphatic Claisen rearrangement[13] were surveyed, either recovery of **25** or the formation of undesired aromatized compounds was discovered. Alternatively, we prepared the xanthate **28** from **25**, as a precursor of [3,3]-sigmatropic rearrangement. Heating **28** in benzene at 90 °C afforded the dithiolcarbonate **30** predominantly in 72% yield via TS-**29** (path A),[14] while the unexpected retro-Ene-type fragmentation occurred simultaneously to produce 2-alkenyl methyl sulfide **32** in 24% yield via TS-**31** (path B).[15] Exposing **30** to ethanolamine under air achieved the disulfide **33**,[16] which was treated by $P(NEt_2)_3$ to smoothly furnish **32**, with the stereochemistry at C_{18} maintained.[17] The relative configurations of **30**, **32**, and **33** were established by extensive spectroscopic analysis including NOE analysis (see the Supporting Information for details).

After considerable experiments, we discovered a strategy involving vinylogous Pummerer rearrangement to establish the enone moiety in ring C.[18] In practice, oxidation of **32** with H_2O_2 gave the sulfoxide **34** in 90% yield as a 2:1 separable mixture of diastereomers (Scheme 5). Treatment of **34** with TFAA in the presence of 2,6-lutidine resulted in the vinylogous Pummerer rearrangement,[19] affording **37** after hydrolysis. For **37**, NOE interactions between H13/14-OH, H15/12-OMe, and H8/H17 were shown in Scheme 5. These results indicate that **37** is a unique cage-like compound. Treating **37** with MeI[20] produced the cyclohexanone **38** in 75% yield, showing a result of simultaneous desulfurization, elimination to form enone, and deprotection of acetonide. Direct conversion of the *trans*-diol **38** into an epoxide failed after numerous attempts, while the aromatization byproduct was observed instead.

By following a circuitous strategy to bypass the facility of aromatization, the ketone in **38** was reduced to give the triol **39**, in which the rigid tricycle scaffold made ring C exist with a stable half-chair conformation. Thus, selective mesylation of the C_{17} hydroxyl in **39** was achieved in the presence of the other two hydroxyls at C_{16} and C_{18}, and basic treatment of the intermediate in one pot realized formation of the epoxide **41**. Due to its lability, compound **41** was immediately subjected to allylic oxidation to afford **42**, an epimer of core **3**, in 49% overall yield from **39**. Notably, compound **42** is difficult to prepare in large quantities due to the instability of **40** and **41**. Actually, an array of acidic conditions aiming at achievement of equilibration between **42** and **3** were examined but unfortunately unsuccessful (see the Supporting Information for details). Thus, we conceive of constructing the *trans*-fused 6/5/6 tricycle, i.e., **3**, from the *cis*-fused 6/5/6 tricycle, i.e., **42**, through a precisely tailored chiral catalyst under neutral conditions.[21] The related studies are currently ongoing in our laboratory, and further results will be described in the future.

In summary, we have completed synthesis of the tricyclic core of 12-*epi*-JBIR-23 and -24 through a A−AB−ABC ring construction sequence. Key features include a tandem asymmetric Michael/aldol reaction to establish three consecutive tertiary carbon centers and [3,3]-sigmatropic rearrangement of an allylic xanthate, followed by vinylogous Pummerer rearrangement and a selective mesylation/epoxidation cascade of a triol, to access the brittle epoxyquinol motif. Inspired by this achievement, further endeavors toward total synthesis of JBIR-23 and -24 are currently in progress in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00853.

Experimental procedures, Tables 1−5, and nmr spectra of new compounds (PDF)

Original HRMS spectra for compounds **9**, **24**, **S2**, **15**−**18**, **21**, **23**, **24**, **25**, **28**, **30**, **32**, **34a**, **34b**, and **38** (PDF)

FAIR data, including the primary NMR FID files, for compounds **6**, **9**, **12**−**21**, **23**−**25**, **28**, **30**, **32**−**34**, **37**−**39**, and **42** (ZIP)

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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