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Enantioselective Total Syntheses and Absolute Configuration of JBIR-02 and Mer-A2026B

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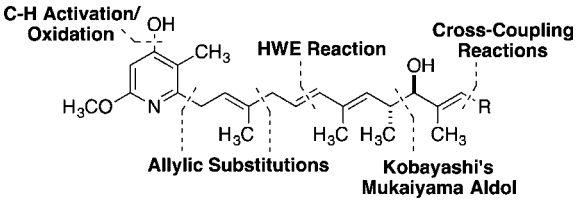
ABSTRACT



JBIR-02, R = $C(CH_3)CHCH_3$
Mer-A2026B, R = CH_3

The first total syntheses of the piericidin related natural products Mer-A2026B and JBIR-02 are reported. Key features of the synthetic approach involve an Ir-catalyzed one-pot C−H activation/oxidation procedure for the preparation of the hydroxypyridine, a vinylogous Mukaiyama aldol reaction, and a final Negishi cross-coupling of an advanced pyridine derivative with an allylic side chain precursor. In addition, the absolute configuration of Mer-A2026B (9*R*,10*R*) and JBIR-02 (9*R*,10*R*) was established.

The piericidin class of natural products has been known as potent inhibitors of the complex I electron transport for decades, and several studies have highlighted the structural similarity of these natural products to ubiquinone (coenzyme Q), a cofactor in NADH dehydrogenase mediated electron transport.[1] In particular, the dimethoxypyridone core has served as a central structural argument corroborating these observations.[2] Surprisingly, members of the piericidin family devoid of this dimethoxy motif have received much less attention. Compounds such as JBIR-02[3] and Mer-A2026B[4] lack the 4′-oxygenation of the piericidins but otherwise share many of their structural features regarding the pyridone core and the polyene side chain (Figure 1). Interestingly, JBIR-02 was reported as an inhibitor of nucleocytoplasmic transport,[3] which is appealing as these pyridones would constitute a new lead structure for inhibitors of this important biological process.[5f] We have investigated this phenomenon in the context of our studies on the anguinomycins, where we could identify structural features responsible for biological activity.[5a,b] In addition, JBIR-02 and Mer-A2026B share structural similarity to the neuritogenic pyridone polyenes such as militarinone D or torrubiellone C recently investigated in our group.[5c−e]

(1) Nelson, D. L.; Cox, M. M. *Lehninger Principles of Biochemistry*; Worth: New York, 2000; Chapter 19.

(2) Total synthesis of piericidin A1: (a) Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704–15705. (b) Schnermann, M. J.; Romero, F. A.; Hwang, I.; Nakamura-Ogiso, E.; Yagi, T.; Boger, D. L. *J. Am. Chem. Soc.* **2006**, *128*, 11799–11807. (c) Lipshutz, B. H.; Amorelli, B. *J. Am. Chem. Soc.* **2009**, *131*, 1396–1397. (d) Kikuchi, R.; Fujii, M.; Akita, H. *Tetrahedron: Asymmetry* **2009**, *20*, 1975–1983. (e) Total synthesis of 7-demethylpiericidin A1: Phillips, A. J.; Keaton, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 408–409.

(3) Ueda, J.; Togashi, T.; Matukura, S.; Nagai, A.; Nakashima, T.; Komaki, H.; Anzai, K.; Harayama, S.; Doi, T.; Takahashi, T.; Natsume, T.; Kisu, Y.; Goshima, N.; Nomura, N.; Takagi, M.; Shin-ya, K. *J. Antibiot.* **2007**, *60*, 459–462.

(4) (a) Kominato, K.; Watanabe, Y.; Hirano, S.-I.; Kioka, T.; Terasawa, T.; Yoshioka, T.; Okamura, K.; Tone, H. *J. Antibiot.* **1995**, *48*, 103–105. (b) Hirano, S.; Watanabe, Y.; Kaichiro, K.; Agata, N.; Hara, Y.; Shibamoto, N.; Yoshioka, T.; Kioka, T.; Iguchi, H.; Shirai, M.; Tone, H.; Okamoto, R. European Patent EP0491281A1, 1991.

(5) (a) Bonazzi, S.; Güttinger, S.; Zemp, I.; Kutay, U.; Gademann, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 8707–8710. (b) Bonazzi, S.; Eidam, O.; Güttinger, S.; Wach, J.-Y.; Zemp, I.; Kutay, U.; Gademann, K. *J. Am. Chem. Soc.* **2010**, *132*, 1432–1442. (c) Review: Jessen, H. J.; Gademann, K. *Nat. Prod. Rep.* **2010**, *27*, 1168–1185. (d) Jessen, H. J.; Schumacher, A.; Shaw, T.; Pfaltz, A.; Gademann, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 4222–4226. (e) Jessen, H. J.; Schumacher, A.; Schmid, F.; Pfaltz, A.; Gademann, K. *Org. Lett.* **2011**, *13*, 4368–4370. (f) Review: Gademann, K. *Curr. Drug Targets* **2011**, *12*, 1574–1580.

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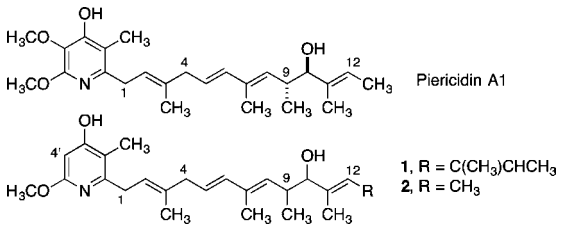
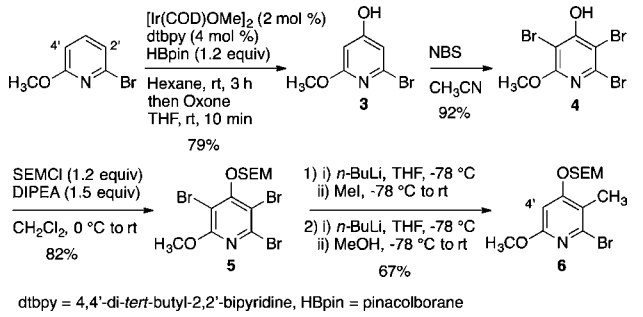


Figure 1. Structures of Piericidin A1, JBIR-02, **1** (R = C_4H_7), and Mer-A2026B, **2** (R = CH_3).

The combination of structural features with the reported mechanism of action for these compounds leads to the hypothesis that small variations on the pyridone core could result in a large variation of selectivity for biological targets.[5] As there are, to the best of our knowledge, no published reports on compounds lacking the 4′-methoxy group, we wanted to develop synthetic access to JBIR-02 and Mer-A2026B, which should also allow for the assignment of the unknown absolute and relative configuration of the two stereogenic centers of these compounds. In this communication, we report the total synthesis and absolute configuration of JBIR-02 and Mer-A2026B.

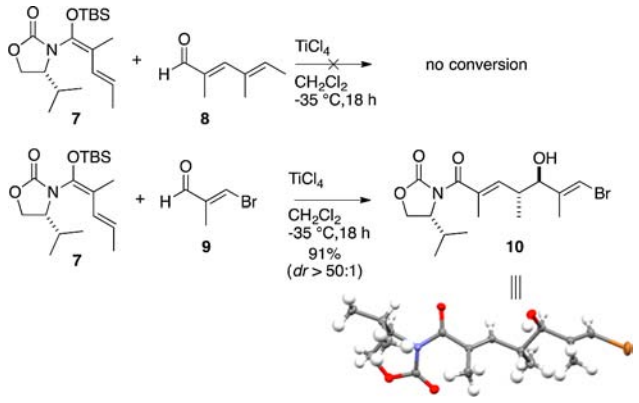
Scheme 1. Synthesis of the Heteroaromatic Intermediate **6** (Positions Labeled 2′ and 4′ Refer to the Piericidin Nomenclature)



The total synthesis started with the preparation of the protected bromopyridinol **6** in five steps, as shown in Scheme 1. Commercially available 2-bromo-6-methoxypyridine was converted to pyridinol **3** in 79% yield by a C−H activation reaction using 2 mol % of $[Ir(COD)OMe]_2$, 4 mol % of 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy), and pinacolborane (pinBH) in hexane at room temperature, followed by oxidation of the crude boronic acid intermediate with oxone in THF.[6] Subsequent treatment with *N*-bromosuccinimide (NBS) afforded tribromopyridinol **4** in 92% yield, as attempts to selectively monofunctionalize C2′ with different electrophilic bromination reagents were unsuccessful. Selective *O*-SEM protection to direct the aromatic functionalization in the next steps was accomplished using SEMCl. The correct substitution pattern at the heteroaromatic ring was installed by sequential two-fold Li halogen exchange using *n*-BuLi in THF at −78 °C: (1) trapping of the stabilized C2′-lithiated aryl species with MeI (for C2′ substitution) followed by (2) protonation with MeOH (for the C4′ position) completed the target fragment **6** with the correct substitution pattern in 67% yield over two steps. Apparently, the donor capacity of the neighboring bromine is higher than the stabilizing effect of the methoxy group. This strategy was found to be superior to ortho-metalation, in which even bulky non-nucleophilic bases such as LDA or LiTMP resulted in nucleophilic substitution of the bromo substituent and could not be suppressed by varying the reaction conditions.

The polyene side chain synthesis was addressed next. As the configuration of both target compounds was unknown, we assumed the same absolute configuration as established for piericidin A1. The preparation of the side chain started with a vinylogous Mukaiyama aldol reaction developed by Kobayashi and co-workers.[7] Treatment of *N*,*O*-silyl ketene acetal **7** and bromoacrylate **9**[8] provided the desired hydroxyl imide **10** via a $TiCl_4$ mediated C−C bond forming reaction with exclusive formation of one diastereomer (^{1}H NMR > 50:1) in 91% yield (12 mmol scale). The absolute configuration at C9 and C10 was established by the X-ray crystal structure analysis of the aldol product **10** (Scheme 2).

Scheme 2. Kobayashi's Vinylogous Mukaiyama Aldol Reaction[7a]



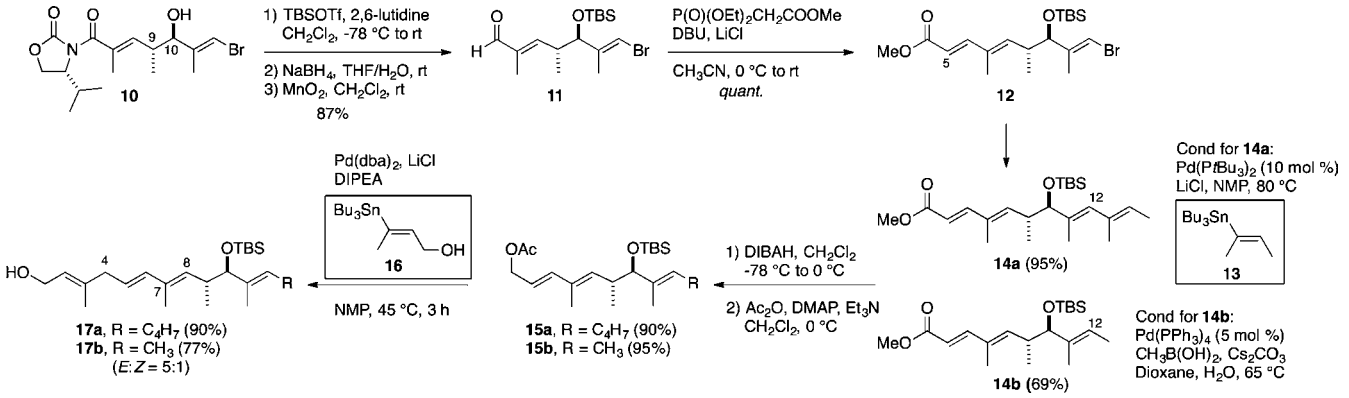
Silylation of hydroxyl imide **10** with TBSOTf in the presence of 2,6-lutidine in CH_2Cl_2 at −78 °C, followed by the removal of the chiral auxiliary in a two-step process via reduction with $NaBH_4$ and oxidation of the allylic alcohol with activated MnO_2, afforded aldehyde **11** in 87% over

(6) C−H activation: (a) Ishiyama, T.; Nobuta, Y.; Hartwig, J. F.; Miyaura, N. *Chem. Commun.* **2003**, 2924–2925. (b) Maleczka, R. E., Jr.; Shi, F.; Holmes, D.; Smith, M. R., III. *J. Am. Chem. Soc.* **2003**, *125*, 7792–7793.

(7) (a) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605. (b) Paterson, I.; Kan, S. B. J.; Gibson, L. J. *Org. Lett.* **2010**, *12*, 3724–3726.

(8) Murakami, Y.; Nakano, M.; Shimofusa, T.; Furuichi, N.; Katsumura, S. *Org. Biomol. Chem.* **2005**, *3*, 1372–1374.

Scheme 3. Synthesis of the Polyene Side Chain



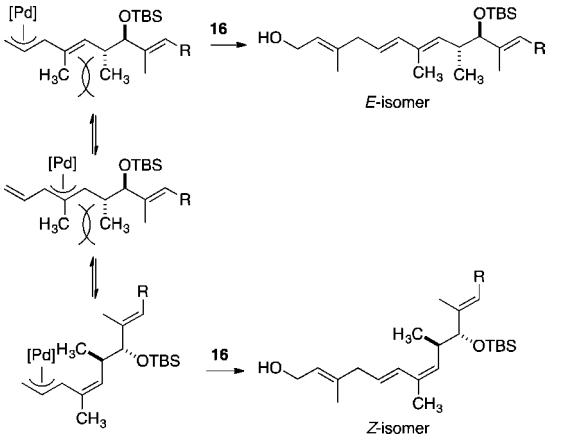
three steps. Elongation to the unsaturated ester **12** was achieved by a Horner–Wadsworth–Emmons (HWE) reaction applying a protocol developed by Masamune and Roush to avoid partial epimerization at C9.[9] When the scope of this strategy was expanded, this transformation allows, in principle, the introduction of different residues at C5—as for example CH_3 present in natural piericidins—by changing the phosphonate coupling partner.

Cross-coupling of vinyl bromide **12** under Stille conditions ($Pd(PtBu_3)_2$ (10 mol %), LiCl, NMP, 80 °C) with stannane **13**, derived from commercially available (*E*)-2-bromo-2-butene by lithiation and quenching with Bu_3SnCl, afforded tetraene **14a** in very good yield. Under these conditions, isomerization of the terminal methyl group could be avoided (see Supporting Information).

The vinylogous Mukaiyama aldol reaction with the more complex substrate (2*E*,4*E*)-2,4-dimethylhexa-2,4-dienal **8** (Scheme 2) as coupling partner targeting the identical side chain was found to be unsuccessful under the previously described conditions. This finding could be explained by the extended conjugation, transforming the dienal in a rather unreactive coupling partner toward nucleophilic attack.[10] Using the opportunity to transform **12** by transition metal catalysis into a number of natural piericidins (Scheme 3), the vinylbromide was elongated at C12 by Suzuki coupling ($Pd(PPh_3)_4$ (5 mol %), $CH_3B(OH)_2$, Cs_2CO_3, dioxane, H_2O, 65 °C) to triene **14b** in 69% yield.

DIBAH reduction of esters **14** followed by acetylation produced the allylic acetates **15** as precursors for the first allylic substitution (90% for **15a** and 95% for **15b**, over two steps). To remove traces of AcOH, which led to significantly reduced yields, Ac_2O was filtered through a small column of Al_2O_3 before use. Next, allylic substitution using $Pd(dba)_2$, LiCl, DIPEA, and hydroxystannane **16**[11] at 45 °C for 3 h delivered **17a** (90%) and **17b** (77%) in a ratio of 5:1 as its *E*- and *Z*-isomers. Both isomers could be separated for both **17a** and **17b** by preparative HPLC with hexane/*i*PrOH (99.5:0.5) as solvent.

Scheme 4. Possible Mechanism for the Isomerization during Allylic Substitution with Stannane **16**



Interestingly, the isomerization could be observed at the olefinic linkage between C7 and C8. A reasonable mechanism for the isomerization is shown in Scheme 4. Upon treatment with Pd catalyst and formation of the Pd-allyl complex, isomerization of this complex along the chain is likely to occur. Due to the allylic strain of the adjacent methyl groups, this complex could isomerize to the thermodynamically more stable *Z*-olefin and react further with stannane **16** to afford (7*Z*)-**17**. This ratio could not be improved by exploring different reaction parameters such as catalyst, reaction time, and temperature. Next, (7*E*)-allylic alcohols **17a/b** were transformed to their corresponding carbonates **18a/b** (CH_3OCOCl, Et_3N at 0 °C), thereby generating a suitable leaving group for the subsequent allylic substitution.

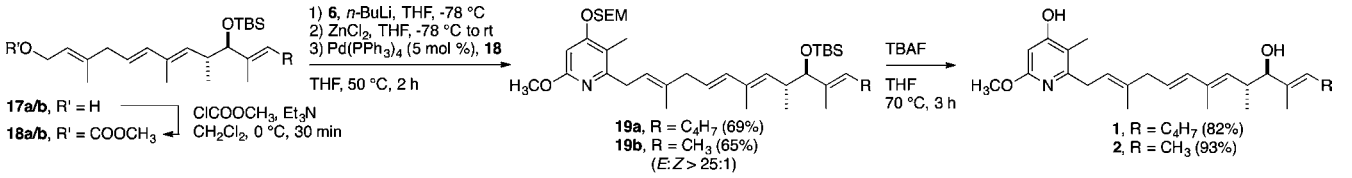
The crucial connection of both moieties, the 4-hydroxypyridine core and the fully elaborated polyene chain, was realized after extensive experimentation on the Negishi cross-coupling reaction and proved to be mild enough to

(9) Blanchette, M.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183–2186.

(10) (a) Bock, M.; Dehn, R.; Kirschning, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9134–9137. (b) Nakamura, Y.; Kiyota, H.; Baker, B. J.; Kuwahara, S. *Synlett* **2005**, 635–636.

(11) Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768–7780.

Scheme 5. Completion of the Synthesis of JBIR-02 and Mer-A2026B



avoid isomerization or decomposition.[12] The protected Br-pyridinol **6** was lithiated using *n*-BuLi in THF at −78 °C. After 10 min, $ZnCl_2$ was added and the resulting mixture was allowed to warm to room temperature over 1 h to form a relatively stable 2-pyridylzinc reagent[13] which was exposed to a freshly prepared mixture of carbonate **18** and 5 mol % of $Pd(PPh_3)_4$ and warmed to 50 °C for 3 h to provide **19a** (69% over two steps) and **19b** (65%) without detectable isomerization (Scheme 5). The Negishi conditions proved superior to Sn-based cross-coupling, in which significant isomerization was observed.[2e] Final deprotection was achieved by treatment with TBAF at elevated temperatures (70 °C, THF) to produce JBIR-02 (**1**, 82%) and Mer-A2026B (**2**, 93%) in good yield.

The comparison of spectra of natural and synthetic samples was carried out next, to confirm the reported structures and to assign the absolute configuration. The spectroscopic data of synthetic Mer-A2026B (**2**) were found to be identical in all respects (^1H, ^{13}C NMR, UV spectra, and optical rotation: $[\alpha]_D = -1.1$ ($c = 0.11$, MeOH) lit. $[\alpha]_D = -1.07$ ($c = 0.36$, MeOH)) to those reported in the literature for the natural product.[14] For JBIR-02, confirmation of the structure proved to be more complex. At first, several key signals of the aromatic core in the ^1H NMR spectra displayed different chemical shifts when compared to the reported data of the natural product. Therefore, a synthetic sample of JBIR-02 was compared to a natural one by NMR under the same conditions (solvent, NMR tube, and concentration), and the identity of spectra could be observed.[15] The final proof of identical constitution of synthetic and natural samples of JBIR-02 was established by co-injection of both samples and analysis by UHPLC.[14] Apparently, the amount of water and/or the amount of acid in the $CDCl_3$ solution can lead to the observation of tautomerism and, therefore, drastically different spectra. Interestingly, the pyridone form of these piericidin analogues has rarely been observed (see also the work of Boger and co-workers[2a,b]). The optical rotation ($[\alpha]_D = -11.1$ ($c = 0.21$, MeOH)) matched its literature value ($[\alpha]_D = -13.0$ ($c = 0.88$, MeOH)) and thereby established the absolute configuration of **1**.

In conclusion, the first total syntheses of piercidin derivatives Mer-A2026B and JBIR-02 (longest linear sequence 12 steps, overall yield 28% for **1** and 20% for **2**) were developed, and the absolute configuration could be established as (9*R*,10*R*). Salient features of this efficient and convergent synthetic route are (1) a highly diastereoselective Kobayashi−Mukaiyama aldol reaction, (2) a C−H activation reaction in combination with an oxidation protocol for the preparation of the highly functionalized pyridine moiety, and (3) a final Negishi cross-coupling reaction without isomerization of the labile side chain. Furthermore, this strategy opens up the stage for the synthesis of a number of piericidins by simply changing the coupling partner for the HWE reaction (C5 analogues) or the organometallic species for the cross-coupling reaction (C12 functionalization). Studies targeting these derivatives are underway in our laboratories.

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Supporting Information Available. Detailed experimental procedures, full characterization, and copies of all spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Negishi, E.; Liu, F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley: New York, 2002; pp 551−589.

(13) Selected 2-pyridylzinc reagents: (a) Luzung, M. R.; Patel, J. S.; Yin, J. *J. Org. Chem.* **2010**, *75*, 8330–8332. (b) Klosterman, J. K.; Linden, A.; Siegel, J. S. *Org. Biomol. Chem.* **2008**, *6*, 2755–2764. (c) Kiehne, U.; Bunzen, J.; Staats, H.; Lützen, A. *Synthesis* **2007**, 1061–1069. (d) Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385–2388. (e) Mongin, F.; Trécourt, F.; Mongin, O.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 309–314. (f) Savage, S. A.; Smith, A. P.; Fraser, C. L. *J. Org. Chem.* **1998**, *63*, 10048–10051.

(14) See Supporting Information for details.

(15) The identity of natural and synthetic JBIR-02 was confirmed by ^1H, ^{13}C NMR, and UHPLC measurements by Dr. Izumikawa in the laboratories of Prof. Dr. Shin-ya (National Institute of Advanced Industrial Science and Technology (AIST)) and later in our laboratories by ^1H and ^{13}C NMR spectroscopy.

The authors declare no competing financial interest.