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Synthetic Studies toward A-74528

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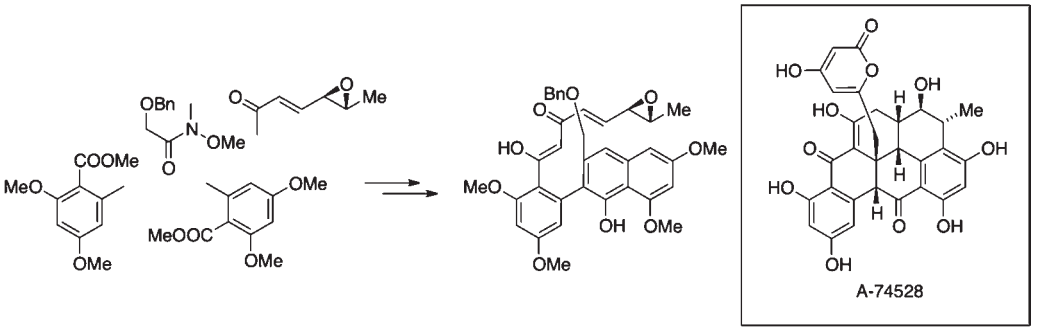
ABSTRACT



A potentially biomimetic approach toward the complex polyketide A-74528 is described. It is based on highly substituted biaryl compounds, synthesized using advanced cross-coupling and condensation methodologies.

A-74528 (**1**) is an unusual natural product that was recently isolated from *Streptomyces* sp. SANK 61196 by Ogita and co-workers (Figure 1). The compound was found to activate the interferon system *via* inhibition of 2′,5′-oligoadenylate phosphodiesterase (2′-PDE). Because an overabundance of 2′-PDE in tumor and viral cells prevents their apoptosis, this provides a potential therapy against cancer and viral infections.[1]

With its 30 carbons, A-74528 (**1**) is one of the most complex and largest aromatic polyketides known to date. Interestingly, the biosynthetic machinery responsible for its formation is very similar to the type II polyketide synthase that accounts for the formation of fredericamycin (**2**) in *Streptomyces griseus*.[2] This is surprising given the considerable structural diversity between the two natural products despite their identical carbon count.

Structurally, A-74528 consists of a hexacyclic core with an appended α-pyrone moiety. Its unprecedented carbon skeleton contains two acyl resorcinol motifs typical of type II polyketides, which are flanking a perhydropyrene core. This tetracyclic core features six contiguous stereocenters, one of which is quaternary. The secondary alcohol on ring A is in an unusual position for a polyketide, a fact that needs to be accounted for by any proposed biosynthetic pathway. Biosynthetically, A-74528 can be traced back to a C30 epoxy polyketide **7**, as shown in Scheme 1. This epoxide presumably undergoes a series of condensations, additions, and substitutions to assemble the molecular framework of the natural product.[2] The exact sequence of these ring formations, however, remains unknown. It is conceivable, for instance, that A-74528 (**1**) directly stems from a strained enone **3**, which engages in a transannular Michael addition and epoxide opening, as indicated. Compound **3**, in turn, could arise from a dearomatizing intramolecular Michael

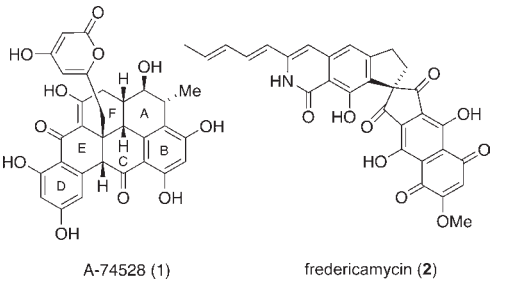


Figure 1. Two biosynthetically related C30-polyketides from *Streptomyces* sp.

(1) Fujita, Y.; Kasuya, A.; Matsushita, Y.; Suga, M.; Kizuka, M.; Iijima, Y.; Ogita, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4317–4321.

(2) Zaleta-Rivera, K.; Charkoudian, L. K.; Ridley, C. P.; Khosla., C. *J. Am. Chem. Soc.* **2010**, *132*, 9122–9128.

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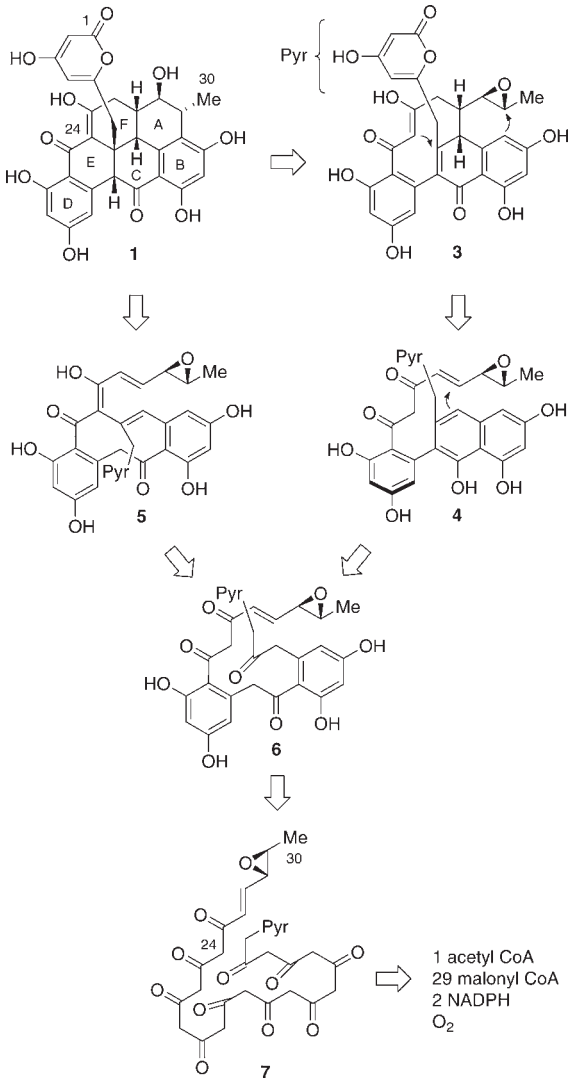
Scheme 1. A Biosynthetic and Retrosynthetic Analysis of A-74528

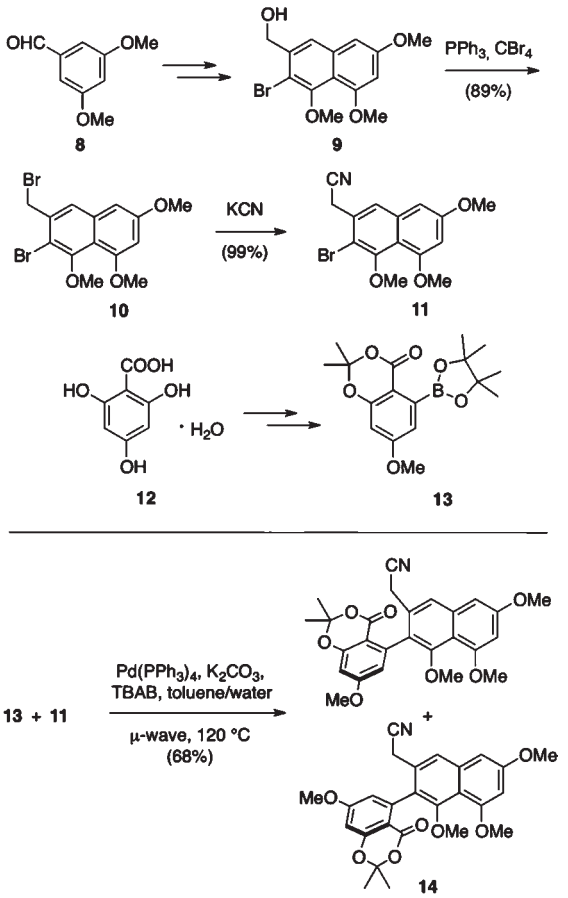


addition involving aryl naphthalene **4**.[3] Alternatively, A-74528 (**1**) could stem from a disrotatory 6π-electrocyclization of intermediate **5**, followed by tautomerization, conjugate addition, and attack on the epoxide. Both **4** and **5** could be formed by intramolecular condensation from the partially aromatized polyketide **6**, which we consider to be a key intermediate in the pathway. The question is whether this intermediate first forms a 6-, 10-, 12-, or 14-membered ring. Compound **6** itself presumably stems from epoxy polyketide **7**, which in turn is assembled by the polyketide synthase from acetyl and malonyl coenzyme A.

In Nature, it appears that these cyclizations are mediated by various enzymatic activities in the type II polyketide synthase, which determines their sequence and

(3) For tandem Michael−Michael addition, see: Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968–8969.

Scheme 2. Synthesis of a Key Biaryl **14** *via* Suzuki Coupling



stereoselectivity. We found it fascinating to test the limits of biomimetic synthesis and explore whether such a complex pathway could be emulated in the laboratory. We initially focused on aryl naphthalenes of type **4**, which seem to be more tractable than other polyketide intermediates postulated in Scheme 1. This required advanced biaryl chemistry, which is the subject of the present communication. We now report the synthesis of a complex aryl naphthalene that has most of the relevant features of the postulated biosynthetic intermediate **4** and discuss our first attempts toward its further cyclizations. These investigations initially focused on challenging transition-metal catalyzed cross-couplings and eventually led to a synthetic strategy based on potentially biomimetic condensation chemistry.

Our first approach started with the known naphthalene derivative **9**, which is accessible in a lengthy yet practical sequence from 3,5-dimethoxy benzaldehyde (**8**) (Scheme 2).[4] Conversion of the benzylic alcohol **9** into the corresponding bromide **10** followed by nucleophilic substitution with cyanide gave the naphthalene derivative **11** in good yield.[5] Its

(4) Piettre, A.; Chevenier, E.; Massardier, C.; Gimbert, Y.; Greene, A. E. *Org. Lett.* **2002**, *4*, 3139–3142.

(5) X-ray structures in cif format for compounds **11**, **13**, and **20** are available at the Cambridge Chrystallographic Data Centre (Registration numbers CCDC 795939, 795938, 795937).

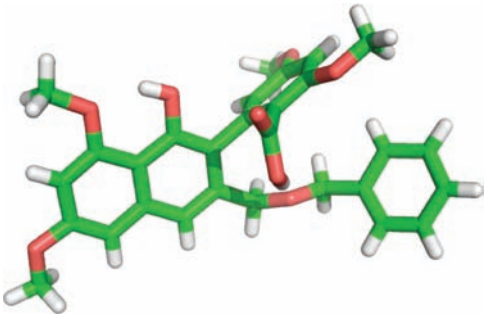
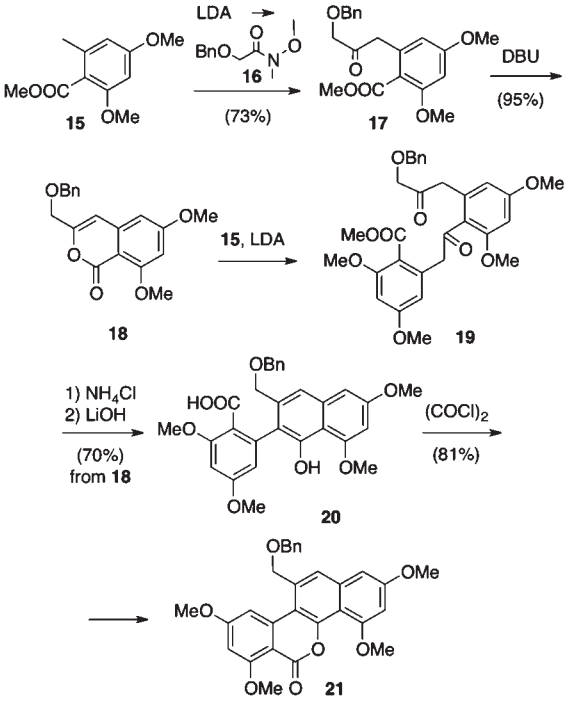


Figure 2. X-ray structure of biaryl acid **20**.

coupling partner, boronic ester **13**,[5] was obtained from trihydroxybenzoic acid **12** in four steps following a known protocol.[6] Linkage of these two components through Suzuki coupling required careful optimization. Eventually, we settled on a protocol that involved microwave irradiation and tetrakis(triphenylphosphine) palladium(0) as a catalyst. Under these conditions, **11** could be coupled with **13** to afford **14** as a racemic mixture of atropisomers (Scheme 2). This is one of the few examples where a 3-fold *o,o,o′*-substituted biaryl bond has been formed in acceptable yield through transition-metal mediated cross-coupling.[7]

Although we were able to find a satisfactory solution for the cross-coupling, we nevertheless felt that the pathway taken was too long to support a total synthesis of A-74528 (**1**). Therefore, we explored an alternative pathway that involves condensation chemistry and is also more biomimetic. It starts with the deprotonation of orsellinic acid derivative **15**, easily available on a large scale through trimerization of methyl acetoacetate.[8] Condensation of the corresponding organolithium compound with Weinreb amide **16**[9] gave ketone **17**. Upon treatment with DBU, this material underwent enolization and intramolecular condensation to afford isocoumarin **18**, which has the characteristics of an active ester. Indeed, **18** engaged in another Claisen-type condensation with the anion of **15** to afford aryl benzyl ketone **19**. This material underwent cyclization upon workup to yield a mixture of acid **20** and its corresponding methyl ester (not shown). Saponification of this mixture provided the carboxylic acid **20** in 70% overall yield. The X-ray structure of this compound is shown in Figure 2.[5] Treatment of **20** with oxalyl chloride in the presence of a base then gave phenolic δ-lactone **21** (Scheme 3).

Scheme 3. Biaryl Synthesis *via* Polyketide Condensation



Next, we explored the installation of a side chain corresponding to $C_{24}-C_{30}$ of the natural product. The solution we eventually found is remarkable for its simplicity. The achiral tetracyclic lactone **21**, which functions like an active ester, could be linked with the potassium enolate of methyl-1-propenyl ketone **22** to furnish the 1,3-diketone **23**, which mostly exists in its enolized form. It should be noted that, due to hindered rotation around the biaryl bond, this compound is chiral and is formed as a racemate. An analogous transformation could be carried out with the enolate of the enantiomerically enriched epoxy ketone **24**, whose synthesis is also shown in Scheme 4.[10] It involves the oxidation of the known sorbitol monoepoxide **26** to **27** followed by the addition of methyl lithium and another oxidation. Condensation of the potassium enolate of ketone **24** with **21** gave aryl naphthol **25** as an inseparable 1:1 mixture of diastereomers with respect to the biaryl axis (Scheme 4). Apparently, the stereogenic centers of the epoxide moiety are too far away to effect dynamic kinetic resolution and induce diastereoselectivity in the ring-opening reaction.[11]

With **23** and **25** in hand, we began to explore the projected key cyclizations toward the core of A-74528 (**1**) (Scheme 5). Thus far, our efforts have been met with limited success. Nevertheless, some interesting results have been obtained. For instance, treatment of the diketone

(6) (a) Danishefsky, S. J.; Dushin, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 655–659. (b) Takahashi, S.; Kamisuki, S.; Kobayashi, S.; Sugawara, F. *Tetrahedron* **2004**, *60*, 5695–5700. (c) Altenmöller, M.; Podlech, J.; Fenske, D. *Eur. J. Org. Chem.* **2006**, 1678–1684.

(7) For sterically hindered biaryl couplings, see: Tang, T.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Goa, J. J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senayake, C. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5879–5883 and references therein.

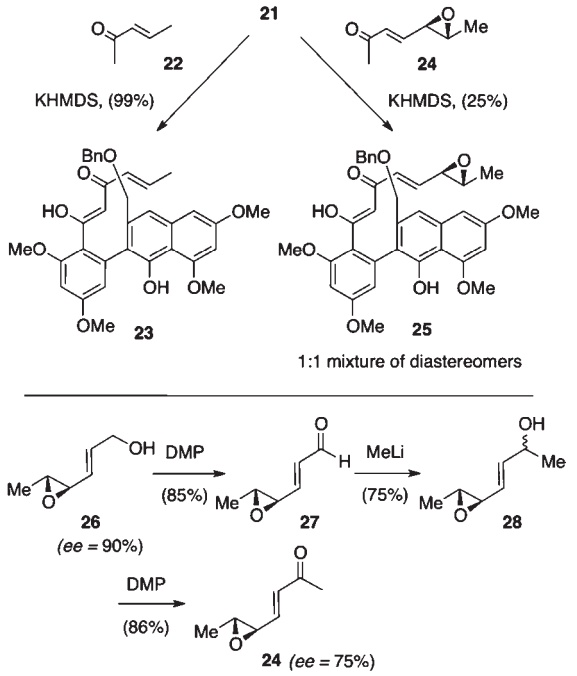
(8) (a) Chiarello, J.; Joullie, M. M. *Tetrahedron* **1988**, *44*, 41–48. (b) Pulgarin, C.; Gunzinger, J.; Tabacchi, R. *Helv. Chim. Acta* **1985**, *68*, 1948–1951.

(9) Williams, R. M.; Ehrlich, P. P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615–2617.

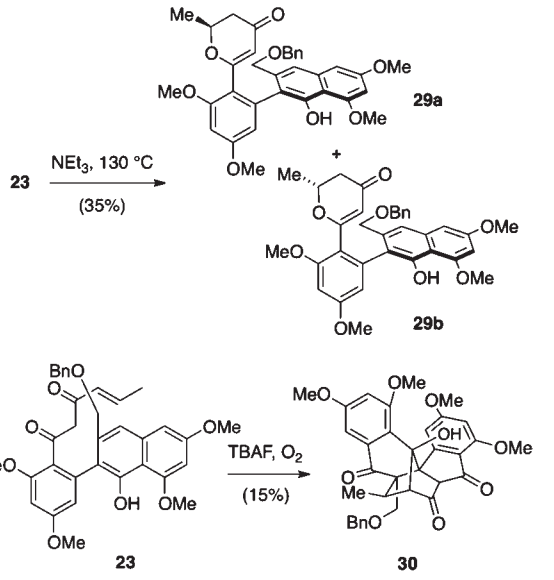
(10) Anson, C. E.; Dave, G.; Stephenson, G. R. *Tetrahedron* **2000**, *56*, 2273–2281.

(11) (a) Bringmann, G.; Vitt, D. *J. Org. Chem.* **1995**, *60*, 7674–7681. (b) Bringmann, G.; Price Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. *Angew. Chem.* **2005**, *117*, 5518–5563. *Angew. Chem., Int. Ed.* **2005**, *44*, 5384–5427.

Scheme 4. Synthesis of Epoxy Ketone **24** and Installment of the Enone



Scheme 5. Unexpected Cyclizations



23 with a weak base at high temperature provided the γ-pyrone **29** as a mixture of two separable diastereomers. These compounds are presumably formed *via* *O*-attack of the enolate of the β- diketone onto the Michael system of the side chain. Upon stirring of the diketone **23** in a DMF/THF mixture in the presence of TBAF and air, a complex structure was isolated, which was identified using 2D-spectroscopy data (COSY, NOESY, HMBC, HSQC) as **30**. This compound is presumably formed *via* an air oxidation of **23** to the corresponding naphthoquinone, followed by a Michael−Michael−aldol cascade (see Supporting Information).[3]

In summary, we have synthesized a range of highly substituted biaryl compounds that might serve as valuable intermediates in a total synthesis of A-74528. They were prepared using a challenging Suzuki coupling and biomimetic condensation chemistry, respectively. Efforts to convert these intermediates into our target molecule *via* biomimetic cyclization cascades are currently underway in our laboratories. Alternative cyclization modes shown in Scheme 1 are also being explored.

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Supporting Information Available. Experimental details, spectroscopic and analytical data for all new compounds (including X-ray data for **11**, **13**, and **20**). This material is available free of charge via the Internet at http://pubs.acs.org.