Natural Products

DOI: 10.1002/ange.201402335

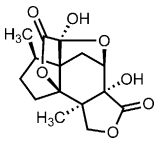
An Enantiospecific Synthesis of Jiadifenolide**

*David A. Siler, Jeffrey D. Mighion, and Erik J. Sorensen**

In memory of Donald C. Dittmer and Harry H. Wasserman

Abstract: *A Robinson annulation, van Leusen homologation, and a desymmetrizing C–H oxidation enabled an enantiospecific synthesis of the neurotrophic natural product jiadifenolide. From a pulegone-derived building block, a key propellane intermediate was constructed through the use of simple reagents in a highly diastereoselective fashion. A short series of oxidations of this tricylic framework allowed progression to the natural product.*

The investigations of the chemical constituents of the flowering plant *Illicium jiadifengpi* by Fukuyama and co-workers led to the isolation of a new metabolite which was given the name jiadifenolide.[1] High-resolution mass spectrometric and infrared spectroscopic analyses revealed the molecular formula ($C_{15}H_{18}O_7$) and functional-group content of jiadifenolide, respectively, while interpretations of the spectroscopic data suggested a structural analogy to the known sesquiterpene jiadifenin.[2] A single-crystal X-ray crystallographic analysis confirmed this structural analogy and revealed that jiadifenolide is a *seco*-prezizaane-type sesquiterpene with the novel cagelike architecture shown in Figure 1. Thirteen of the fifteen carbon atoms and three oxygen atoms of jiadifenolide (**1**) define an intricate ring system comprising two γ-lactones, a five-membered ring hemiketal, and seven contiguous stereocenters.



1: Jiadifenolide

Figure 1. The molecular structure of jiadifenolide (**1**).

Jiadifenolide was also found to significantly potentiate neurite outgrowth in primary cultured rat cortical neurons at a concentration of 10 nM.[1] This compound belongs to a growing class of natural products which offers new entities with promising neurotrophic properties, as well as compelling objectives for undertakings in chemical synthesis.[3] In 2011, Theodorakis and co-workers described their impressive, pioneering synthesis of jiadifenolide.[4] Herein, we describe the ideas and reactions which permitted our laboratory to achieve a concise, enantiospecific synthesis of this pentacyclic natural product.

There is a correspondence between the highlighted domain of jiadifenolide (**1**) and the seven highlighted carbon atoms of the β-ketoester **2** (Figure 2). This insight, enabled by an exercise in pattern recognition,[5] identified the pulegone-derived chiral building block **2**[6] as the foundation for the synthesis. This functionalized compound, which possesses the needed cyclopentane frame and the C1 secondary methyl group, would allow a rapid advance to late-stage intermediates in a left-to-right ring annulation strategy. The reliable chemistry associated with 1,3-dicarbonyl compounds would thus be leveraged in a synthesis of an intermediate of the type shown as **4**, wherein the unspecified directing group (DG) would serve the synthesis by guiding a pivotal oxidation of one of the C–H bonds in the highlighted methyl group.[7] This concept was, in fact, the heart of our design for synthesis, and we were mindful that the powerful catalytic method, reported by Sanford and co-workers, for achieving directed site-selective acetoxylations of unactivated C–H bonds[8] might be ideally suited for enabling the desired oxidation of **4** to a compound of the type **5**. A successful Sanford oxidation in the structural context of **4** (in which the unspecified DG would be a trigonal oxime functional group) would simplify the strategy because it would allow us to carry simple geminal

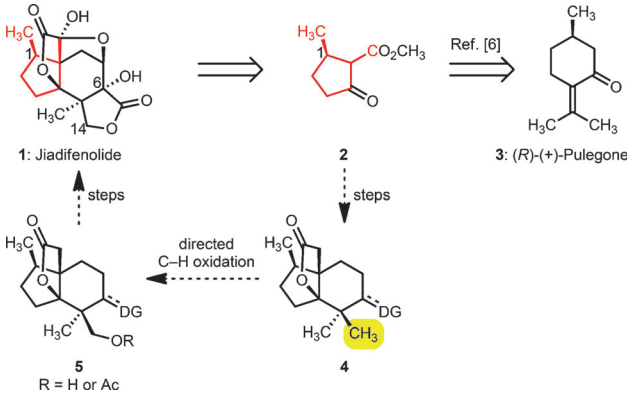
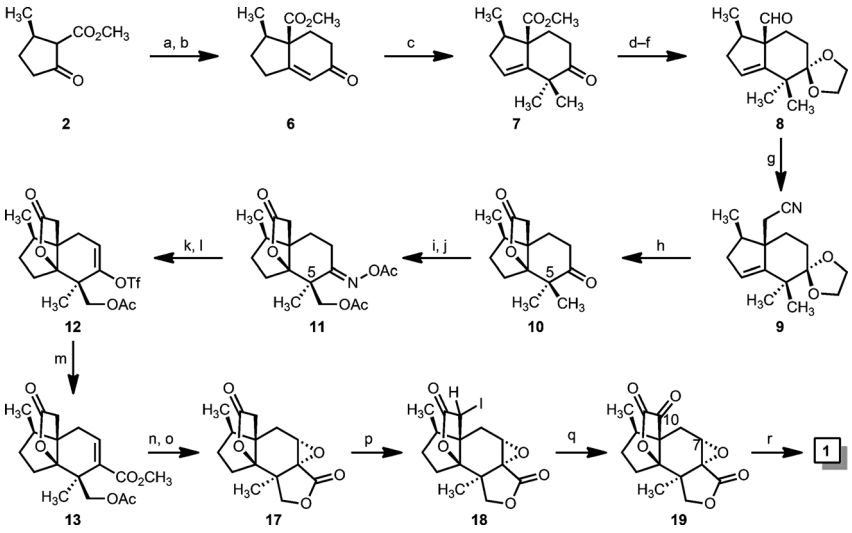


Figure 2. Toward a strategy for synthesizing jiadifenolide (**1**): the pulegone connection and a concept for differentiating geminal methyl groups by a directed catalytic C–H oxidation.

[*] D. A. Siler, J. D. Mighion, Prof. E. J. Sorensen
Frick Chemistry Laboratory, Department of Chemistry
Princeton University
Washington Road, Princeton, NJ 08544 (USA)
E-mail: ejs@princeton.edu
Homepage: http://www.princeton.edu/~ejsgroup/

[**] This work was supported by the National Institute of General Medical Sciences (GM065483) and Princeton University. We also acknowledge helpful discussions with Prof. Huw Davies and the CCI Center for Selective C–H Functionalization supported by the National Science Foundation (CHE-1205646). We thank Dr. István Pelczer, Ken Conover, and Dr. John Eng of Princeton University for assistance with NMR spectroscopic analyses, the collection of NMR data, and the collection of HRMS data, respectively.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201402335.



Scheme 1. Synthesis of jiadifenolide: a) methyl vinyl ketone (1.2 equiv), DBU (0.25 equiv), EtOH, RT, 97%; b) *p*-TsOH (0.8 equiv), benzene, reflux, 85%; c) CH_3I (6 equiv), KO*t*Bu (3.1 equiv), *t*BuOH, RT, 91%; d) ethylene glycol (6 equiv), *p*-TsOH (0.1 equiv), benzene, reflux; e) DIBAL-H (3.1 equiv), CH_2Cl_2, −78 °C→0 °C, 77% (over two steps); f) $(COCl)_2$ (1.5 equiv), DMSO (3 equiv); then Et_3N (5 equiv), CH_2Cl_2, −78 °C→RT, 90%; g) TosMIC (1.7 equiv), KO*t*Bu (2.6 equiv), THF, −50 °C, then CH_3OH, 65 °C, 90%; h) H_2SO_4, CH_3OH, 100 °C, 73%; i) $NH_2OH{\cdot}HCl$ (1.5 equiv), pyridine, 80 °C, 91%; j) $Pd(OAc)_2$ (0.05 equiv), $PhI(OAc)_2$ (1.5 equiv), 1:1 Ac_2O/AcOH, 100 °C, 12 h, 22% of **11**; (k) Fe (10 equiv), AcOH (cat.), Me_3SiCl (cat.), THF, RT, 89%; l) $KN(SiMe_3)_2$ (1.1 equiv), Comins's reagent (1.2 equiv), THF, −78 °C; m) $Pd(OAc)_2$ (0.1 equiv), Ph_3P (0.2 equiv), Et_3N (2 equiv), CO (1 atm), CH_3OH, DMF, 40 °C, 49% (over two steps); n) K_2CO_3 (2 equiv), CH_3OH, RT; o) 3 M NaOH (3 equiv), H_2O_2 (10 equiv), CH_3OH, 0 °C→RT, 61% (over two steps); p) Me_3SiCl (2.5 equiv), $LiN(SiMe_3)_2$ (2.1 equiv), THF, −78 °C, then NIS (1.1 equiv); q) DMDO (0.05 M in acetone, 6 equiv), CH_2Cl_2, RT; r) LiOH (2 equiv), THF, RT, 40% (over three steps). DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, DMDO = dimethyldioxirane, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide, NIS = *N*-iodosuccinimide, THF = tetrahydrofuran, TosMIC = *para*-toluenesulfonylmethyl isocyanide, *p*-TsOH = *para*-toluene sulfonic acid.

methyl groups through the early and middle phases of our synthesis. The key directed oxidation would differentiate those methyl groups and introduce the oxygen atom that is attached to C14 in jiadifenolide (**1**). The manner in which these ideas were brought to fruition is outlined in Scheme 1 and described below.

To achieve the desired Robinson annulation[9,10] of the central six-membered ring of jiadifenolide, we modified a known two-step method for merging the pulegone-derived β-ketoester **2** with methyl vinyl ketone.[11] This process, in which the Michael addition and ring-forming aldol condensation steps are performed in sequence, afforded the bicyclic enone **6** which was subsequently advanced to **7** by a base-mediated deconjugative dimethylation.[12] After a protection of the keto group in the form of a dioxolane ketal, the carbomethoxyl group was reduced with diisobutylaluminum hydride and the resulting primary alcohol was oxidized to the aldehyde **8** by using the Swern method.[13] This synthesis of **8** from **2** proceeded with an overall yield of 52% and could be conducted on large scale.

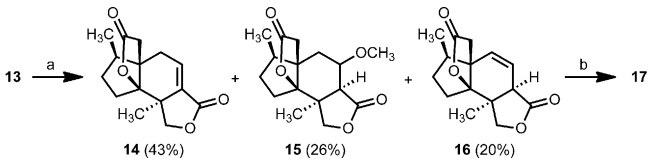
Despite its sterically crowded nature, the aldehyde function of **8** reacted at −50 °C with the conjugate base of tosylmethyl isocyanide (TosMIC) and gave rise to the homologated nitrile **9** in 90% yield after methanolysis of the putative *N*-formyl iminoketene.[14] This method, which was among the few that enabled the needed one-carbon homologation of **8**,[15] afforded a nitrile which could be hydrolyzed in acid with a concomitant lactone ring formation. In fact, the simple exposure of **9** to concentrated sulfuric acid in wet methanol brought about three desired changes en route to **10**: the hydrolysis of the nitrile function, the desired heterocyclization of the γ,δ-unsaturated acid,[16] and the hydrolysis of the dioxolane ketal. The manner in which this simple procedure served the synthesis was pleasing.

With an effective synthesis of the the [4.3.3] propellane **10**, we approached the pivotal CH_3 oxidation step with cautious optimism. Molecular models revealed the unique Y-shaped architectures of **10**[17] and its derived oxime, and that it would be difficult to make a confident prediction about site selectivity in a directed C–H oxidation event. We considered these compounds to be unique contexts for Sanford's catalytic C–H oxidation method, and our plan for using this method was at least bolstered by prior examples of oxime-directed oxidations of unactivated methyl groups.[8] Thus, with the aim of differentiating the C5 geminal methyl groups in the course of a directed C–H oxidation reaction,[8] we heated a mixture of the oxime derived from **10** (not shown), (diacetoxyiodo)benzene, and a catalytic amount of $Pd(OAc)_2$ in Ac_2O/AcOH to 100 °C for 12 hours. This reaction accomplished the desired methyl oxidation, although it afforded a 1:1 mixture of the desired oxime acetate **11** and a diastereoisomeric oxime acetate, epimeric at C5, in addition to a small amount of a compound having two acetoxymethyl groups attached to C5. In other structural contexts, this method actually yielded greater amounts of the undesired C5 epimer of **11**.[18]

We observed the desired reactivity, although the lack of diastereoselectivity was a concern. We hypothesized that the high temperature requirement for this reaction and the conformational flexibility of the six-membered ring in our [4.3.3] propellane system led to an equal sampling of the methyl groups by the palladium catalyst. This supposition was realized by performing the reaction under conditions developed previously by the group of Baldwin,[19] and thus allowed a stoichiometric palladium-mediated activation of the C–H bond at room temperature. In this experiment, a preference for one diastereoisomer was observed. However, it was the undesired C5 epimer that was the major component.[20] While the yield of the desired oxime acetate **11** was only 22%, Sanford's catalytic oxidation method permitted the needed methyl group oxidation, and it was straightforward to resolve the mixture of C–H oxidation products by silica gel chroma-

tography. In one experiment, we obtained 1.4 grams of **11** from 4.46 grams of the oxime derived from **10**.

With access to significant quantities of **11**, we could address the annulation of the second γ-lactone ring and the final three oxidations required for completion of the synthesis. After a reductive cleavage of the oxime acetate group in **11** by the method of Weinreb,[21] the resulting C6 ketone was advanced to the vinyl triflate **12** by a reaction of the derived enolate ion with Comins's reagent.[22] A palladium-catalyzed carbomethoxylation[23] of **12** afforded **13** and was followed by a base-induced methanolysis of the acetate ester with concomitant lactone ring formation. Interestingly, this method for lactonizing **13** afforded a mixture of the compounds **14**, **15**, and **16** (Scheme 2). However, this three-



Scheme 2. a) K_2CO_3 (2 equiv), CH_3OH, RT; b) 3 M NaOH (3 equiv), H_2O_2 (10 equiv), CH_3OH, 0 °C→RT, 61 % (over two steps).

component mixture was transformed into a single epoxy bis(lactone), **17**, upon treatment with hydrogen peroxide and sodium hydroxide. We assume that **15** and **16** are converted into **14** under the basic conditions of this reaction and that the nucleophilic epoxidation of **14** selectively forms the *cis*-fused epoxy lactone shown as **17** (Scheme 1).

From the epoxy lactone **17**, the ascent to jiadifenolide was achieved in three transformations (Scheme 1). As we contemplated potential end-game sequences, we were drawn to the teachings of Danishefsky and Cox[24] who had demonstrated that the active methylene of a structurally complex γ-lactone could be oxidized to the corresponding ketone under mild reaction conditions by way of an ostensible iodoso-Pummerer rearrangement.[25] In the case at hand, an iodination of the silyl ketene acetal derived from **17** furnished the α-iodo lactone **18** in a diastereoselective fashion, although the configuration of the newly formed, iodine-bearing stereocenter was not assigned. This stereochemical matter was, however, inconsequential because a subsequent exposure of **18** to dimethyldioxirane in methylene chloride at room temperature resulted in the formation of the desired α-keto lactone **19**. In the final transformation, the electrophilic carbon atoms at positions 7 and 10 were bridged through an oxygen atom by a simple reaction of **19** with lithium hydroxide. A neutralization of this reaction with aqueous acid furnished jiadifenolide (**1**).[26] The spectroscopic data that we accumulated for this substance matched the data reported previously by Fukuyama and co-workers.[1]

From a (*R*)-(+)-pulegone-derived building block that incorporates the C1 secondary methyl group, this synthesis of the highly oxygenated, cagelike structure of jiadifenolide (**1**) is reliant on the time-honored Robinson annulation and rather simple reagents for inducing three heterocyclizations. This synthesis also offers what we believe to be the first application of Sanford's powerful catalytic method, for achieving directed C–H oxidations, to a problem in natural product synthesis. While the yield for this application is only moderate, this method for oxidizing a methyl group afforded significant amounts of an advanced intermediate en route to jiadifenolide (**1**). This method also yielded a stereoisomeric intermediate which could serve syntheses of new, structurally unique relatives of the natural product. Our effort to achieve that aim and expand the class of jiadifenolide-related neurotrophic agents is underway.

Received: February 13, 2014
Published online: April 24, 2014

Keywords: C–H activation · chiral pool · natural products · terpenoids · total synthesis

[1] M. Kubo, C. Okada, J.-M. Huang, K. Harada, H. Hioki, Y. Fukuyama, *Org. Lett.* **2009**, *11*, 5190 – 5193.
[2] R. Yokoyama, J.-M. Huang, C.-S. Yang, Y. Fukuyama, *J. Nat. Prod.* **2002**, *65*, 527 – 531.
[3] For a recent review, see: J. Xu, M. H. Lacoske, E. A. Theodorakis, *Angew. Chem.* **2014**, *126*, 972 – 1004; *Angew. Chem. Int. Ed.* **2014**, *53*, 956 – 987.
[4] a) J. Xu, L. Trzoss, W. K. Chang, E. A. Theodorakis, *Angew. Chem.* **2011**, *123*, 3756 – 3760; *Angew. Chem. Int. Ed.* **2011**, *50*, 3672 – 3676; b) L. Trzoss, J. Xu, M. H. Lacoske, W. C. Mobley, E. A. Theodorakis, *Chem. Eur. J.* **2013**, *19*, 6398 – 6408.
[5] R. M. Wilson, S. J. Danishefsky, *J. Org. Chem.* **2007**, *72*, 4293 – 4305.
[6] a) J. N. Marx, L. R. Norman, *J. Org. Chem.* **1975**, *40*, 1602 – 1606; b) H. Niwa, K. Kunitani, T. Nagoya, K. Yamada, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3094 – 3099.
[7] For discussions about strategies and methods for achieving site-selective C–H functionalization reactions, see: a) K. Godula, D. Sames, *Science* **2006**, *312*, 67 – 72; b) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417 – 424; c) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147 – 1169.
[8] a) L. V. Desai, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2004**, *126*, 9542 – 9543; b) S. R. Neufeldt, M. S. Sanford, *Org. Lett.* **2010**, *12*, 532 – 535; c) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.* **2012**, *45*, 936 – 946.
[9] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285 – 1288.
[10] For reviews of the Robinson annulation and related reactions, see: a) R. E. Gawley, *Synthesis* **1976**, 777 – 794; b) M. E. Jung, *Tetrahedron* **1976**, *32*, 3 – 31.
[11] P. R. Vettel, R. M. Coates, *J. Org. Chem.* **1980**, *45*, 5430 – 5432.
[12] a) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, R. B. Kelly, *J. Am. Chem. Soc.* **1954**, *76*, 2852 – 2853; b) H. J. Ringold, G. Rosenkranz, *J. Org. Chem.* **1957**, *22*, 602 – 605; c) H. J. Ringold, S. K. Malhotra, *J. Am. Chem. Soc.* **1962**, *84*, 3402 – 3403.
[13] A. Mancuso, D. Brownfain, D. Swern, *J. Org. Chem.* **1979**, *44*, 4148 – 4150.
[14] a) O. H. Oldenziel, D. van Leusen, A. M. van Leusen, *J. Org. Chem.* **1977**, *42*, 3114 – 3118; b) A. M. van Leusen, P. G. Oomkes, *Synth. Commun.* **1980**, *10*, 399 – 403; c) D. van Leusen, A. M. van Leusen, *Org. React.* **2001**, *57*, 417 – 666; d) T. Hampel, R. Brückner, *Org. Lett.* **2009**, *11*, 4842 – 4845.
[15] A Peterson olefination of the aldehyde **8** with (methoxymethyl)-trimethylsilane was also successful. However, hydrolysis of the resulting enol ether was problematic and resulted in a longer sequence leading to **10**.

[16] Multiple mechanistic possibilities exist for this transformation, including attack by the oxygen atom of a protonated imino carboxylic acid onto a tertiary carbocation and subsequent hydrolysis of the resulting cyclic imidate. An acid-induced Markovnikov addition of water to the trisubstituted alkene and subsequent Pinner cyclization could also lead to the same cyclic imidate.
[17] For a review of propellanes, see: J. Altman, E. Babad, J. Itzchaki, D. Ginsburg, *Tetrahedron* **1966**, *Suppl. 8* (part I), 279 – 304.
[18] The structure of the C5 epimer of **11**, including full characterization data, are provided in the Supporting Information.
[19] J. E. Baldwin, C. Nájera, M. Yus, *J. Chem. Soc. Chem. Commun.* **1985**, 126 – 127.
[20] See the Supporting Information.
[21] M. M. Majireck, J. A. Witek, S. M. Weinreb, *Tetrahedron Lett.* **2010**, *51*, 3555 – 3557.
[22] D. L. Comins, A. Dehghani, *Tetrahedron Lett.* **1992**, *33*, 6299 – 6302.
[23] a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.* **1974**, *39*, 3318 – 3326; b) M. Hidai, T. Hikita, Y. Wada, Y. Fujikura, Y. Uchida, *Bull. Chem. Soc. Jpn.* **1975**, *48*, 2075 – 2077; c) J. K. Stille, P. K. Wong, *J. Org. Chem.* **1975**, *40*, 532 – 534.
[24] C. Cox, S. J. Danishefsky, *Org. Lett.* **2000**, *2*, 3493 – 3496.
[25] H. J. Reich, S. L. Peake, *J. Am. Chem. Soc.* **1978**, *100*, 4888 – 4889.
[26] This enantiospecific synthesis required 18 steps from the β-ketoester **2** and 21 steps from (*R*)-(+)-pulegone (**3**).

