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Total Synthesis of Jerangolid A

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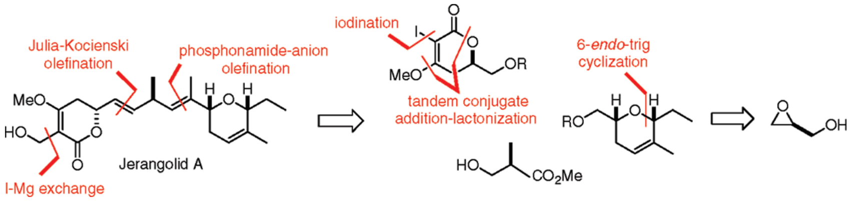
ABSTRACT



The first total synthesis of the antifungal polyketide jerangolid A has been accomplished. Starting with the readily available (*R*)-Roche ester and (*S*)-glycidol as chirons, the synthesis involved a highly *syn*-selective Lewis acid catalyzed 6-*endo-trig* cyclization for the construction of the dihydropyran subunit. The lactone segment was built through a tandem NaOMe conjugate addition-lactonization reaction, and further functionalized through a sequence consisting of iodination, I−Mg exchange, and hydroxymethylation. Other key steps in the synthesis featured a novel application of a phosphonamide-anion based olefination and a Julia−Kocienski reaction.

The antifungal polyketide jerangolid A (**1a**) belongs to a family of at least five naturally occurring members (A, B, D, E, and H), which were isolated in 1992 from myxobacterium *Sorangium cellulosum* So ce307 (Figure 1). Jerangolid A shows potent antifungal activity against a range of pathogens, including *Hansenula anomala* and *Mucor hiemalis* (MIC 0.07 μg/mL), *Debaryomyces hansenii* and *Trisporo terrestre* (0.1 − 0.4 μg/mL), and *Candida albicans* (4.2 μg/mL).[1]

The jerangolids share a common segment with the ambruticins, another group of naturally occurring, potent antifungal polyketides, isolated from closely related myxobacterium *Polyangium cellulosum*[2b] or *Sorangium cellulosum* So ce10, respectively.[2a,3] Due to their close resemblance in terms of structural features and biochemical profiles, as well as their common biosynthesis,[4] the jerangolids may be considered as truncated analogues of the ambruticins.

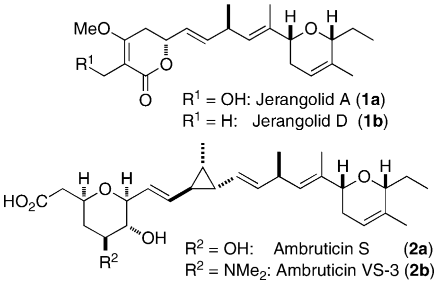


Figure 1. Selected members of the jerangolid and ambruticin families, isolated from *Sorangium cellulosum*.

It is suggested that ambruticins induce the high osmolarity glycerol (HOG) signaling pathway by targeting hik1, a histidine kinase.[5]

Despite the intriguing biological activity of jerangolid A (**1a**), no total synthesis has been reported yet.[6] The synthesis

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(1) (a) Reichenbach, H.; Höfle, G.; Gerth, K.; Washausen, P. *PCT Int. Appl.* WO97/31912, 1997. (b) Gerth, K.; Washausen, P.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996**, *49*, 71.

(2) (a) Höfle, G.; Steinmetz, H.; Gerth, K.; Reichenbach, H. *Liebigs Ann. Chem.* **1991**, 941. (b) Connor, D. T.; Greenough, R. C.; von Strandtmann, M. *J. Org. Chem.* **1977**, *42*, 3664.

(3) Review on ambruticins: Michelet, V.; Genêt, J.-P. *Curr. Org. Chem.* **2005**, *9*, 405.

(4) (a) Wenzel, S. C.; Müller, R. *Nat. Prod. Rep.* **2007**, *24*, 1211. (b) Julien, B.; Tian, Z.-Q.; Reid, R.; Reeves, C. D. *Chem. Biol.* **2006**, *13*, 1277.

(5) (a) Dongo, A.; Bataillé-Simoneau, N.; Campion, C.; Guillemette, T.; Hamon, B.; Iacomi-Vasilescu, B.; Katz, L.; Simoneau, P. *Appl. Environ. Microbiol.* **2009**, *75*, 127. (b) Vetcher, L.; Menzella, H. G.; Kudo, T.; Motoyama, T.; Katz, L. *Antimicrob. Agents Chemother.* **2007**, *51*, 3734. (c) Knauth, P.; Reichenbach, H. *J. Antibiot.* **2000**, *53*, 1182.

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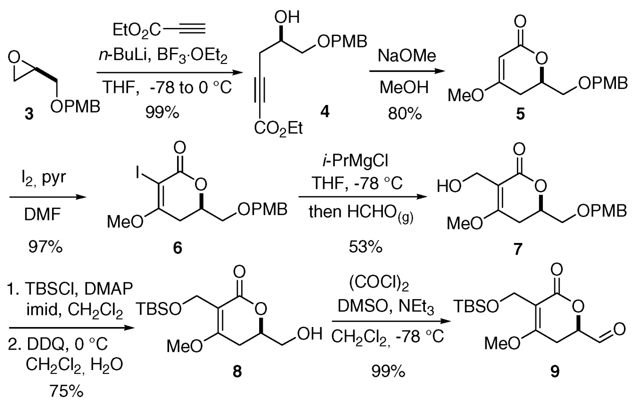
of jerangolid D (**1b**), in which the hydroxymethyl group is replaced by a methyl, was achieved by Pospíšil and Markó in 2007.[7] Herein, we report our efforts leading to the first total synthesis of jerangolid A (**1a**), reportedly, the most active member in the series.[1,8]

Scheme 1. Synthesis of the Lactone Subunit of Jerangolid A

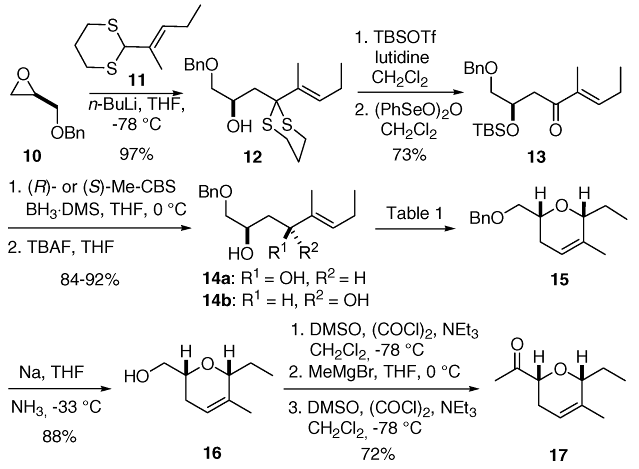


In our synthetic strategy, we envisaged a convergent, late-stage assembly of two advanced ring segments through our phosphonamide anion based olefination methodology[9] and a Julia−Kocienski reaction, respectively. It was thought that the lactone ring would arise from addition of ethyl propiolate to an ether derivative of (*S*)-glycidol, followed by conjugate addition of methanol and lactonization. The construction of the *syn*-dihydropyran ring would employ a highly diastereoselective 6-*endo-trig* cyclization of an allylic 1,3-diol, also starting from (*S*)-glycidol. In spite of this relatively straightforward assembly strategy, we were cognizant of the sensitive nature of the unsaturated lactone toward a number of planned transformations.

As shown in Scheme 1, our initial approach to build the lactone subunit started from (*R*)-glycidol PMB ether (**3**) and took advantage of an efficient, tandem conjugate addition−lactonization sequence. Thus, opening of epoxide **3** with the anion generated from ethyl propiolate in the presence of $BF_3 \cdot OEt_2$ delivered quantitatively known alkyne **4**.[10] Treatment of the latter with NaOMe in MeOH led to a conjugate addition followed by attack of the free hydroxyl group on the ester to furnish lactone **5** in 80% yield.[11]

Introduction of the hydroxymethyl group was done employing a two-step sequence. Thus, iodination of lactone **5** in the presence of pyridine in DMF furnished the iodo lactone **6** in 97% yield. Treatment of the latter with *i*-PrMgCl led to a smooth I−Mg exchange at −78 °C.[12] Reaction of the generated organomagnesiate with a solution of freshly cracked formaldehyde[13] furnished hydroxymethyl lactone **7** in 53% yield. Conversion into its TBS-ether and removal of the PMB-protecting group proceeded uneventfully, delivering alcohol **8** in 75% yield. Oxidation under Swern conditions gave unstable aldehyde **9**, which was prone to form hydrates.[14,15] Workup at low temperature proved to be essential for obtaining aldehyde **9** in sufficient purity for subsequent conversion. Other methods for oxidation such as Dess−Martin periodinane, PCC, TEMPO, and TPAP either yielded impure aldehyde or resulted in overoxidation products.

Scheme 2. Synthesis of the Dihydropyran Ring of Jerangolid A



Our synthetic plan toward the construction of the dihydropyran ring was aimed at using a transition-metal-catalyzed methodology for the formation of pyran units developed by Uenishi and others.[16] Allylic diols are known to undergo stereoselective 6-*exo*- or 6-*endo-trig* cyclization upon treatment with catalytic amounts of $Pd(CH_3CN)_2Cl_2$ forming tetrahydro- or dihydropyrans, respectively, with the selectivity being controlled by the relative configuration of the diol.

To this end, the allylic diols were synthesized via opening of (*R*)-glycidol benzyl ether (**10**) with dithiane **11**, followed

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(6) For other syntheses of the right hand segment, cf. ref 3.

(7) (a) Pospíšil, J.; Markó, I. E. *Tetrahedron Lett.* **2008**, *49*, 1523. (b) Pospíšil, J.; Markó, I. E. *J. Am. Chem. Soc.* **2007**, *129*, 3516.

(8) To the best of our knowledge, no biological activity for jerangolids B, D, E, and H has been reported; cf. ref 1.

(9) (a) Hanessian, S.; Bennani, Y. L.; Leblanc, Y. *Heterocycles* **1993**, *35*, 1411. Asymmetric olefination with cyclic phosphonamides: (b) Hanessian, S.; Beaudoin, S. *Tetrahedron Lett.* **1992**, *33*, 7655–7659. (d) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754. (e) See also: Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161.

(10) Ahmed, A.; Hoegenauer, E. K.; Enev, V. S.; Hanbauer, M.; Kaehlig, H.; Öhler, E.; Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026.

(11) For selected, related examples, see: (a) Taniguchi, T.; Tanabe, G.; Muraoka, O.; Ishibashi, H. *Org. Lett.* **2008**, *10*, 197. (b) Donner, C. D. *Tetrahedron Lett.* **2007**, *48*, 8888. (c) Friesen, R. W.; Vanderwal, C. *J. Org. Chem.* **1996**, *61*, 9103.

(12) Selected references: (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Thibonnet, J.; Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron* **2002**, *58*, 4787. (c) Vu, V. A.; Bérillon, L.; Knochel, P. *Tetrahedron Lett.* **2001**, *42*, 6847.

(13) Schlosser, M.; Jenny, T.; Guggisberg, Y. *Synlett* **1990**, 704.

(14) See also Casar, Z.; Kosmrlj, J. *Synlett* **2009**, 1144.

(15) See the Supporting Information for details.

(16) Pd catalysis: (a) Kawai, N.; Hande, S. M.; Uenishi, J. *Tetrahedron* **2007**, *63*, 9049. (b) Kawai, N.; Lagrange, J.-M.; Ohmi, M.; Uenishi, J. *J. Org. Chem.* **2006**, *71*, 4530. (c) Uenishi, J.; Ohmi, M.; Ueda, A. *Tetrahedron: Asymmetry* **2005**, *16*, 1299. (d) Uenishi, J.; Ohmi, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2756. (e) Miyazawa, M.; Hirose, Y.; Narantsetseg, M.; Yokoyama, H.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **2004**, *45*, 2883. Au catalysis: Aponick, A.; Li, C.-Y.; Biannic, B. *Org. Lett.* **2008**, *10*, 669.

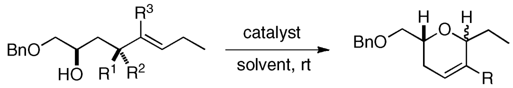
by unmasking of the enone system and stereoselective reduction (Scheme 2). The required dithiane **11** was obtained as a 9:1 mixture of *E*/*Z* isomers from treatment of 2-methyl-2-pentenal with 1,3-propanedithiol and $BF_3{\cdot}OEt_2$.[15,17] Interestingly, only the anion derived from the *E*-isomer by deprotonation with *n*-BuLi reacted with epoxide **10** furnishing adduct **12** in 97% yield. Protection of the hydroxyl group in **12** proved to be necessary in order to unmask the α,*β*-unsaturated system. Thus, exposure of adduct **12** to TBSOTf in the presence of 2,6-lutidine provided the corresponding TBS-ether in 93% yield. After some optimization, we found that the dithiane moiety could be removed conveniently from the latter compound by treatment with benzeneseleninic anhydride[18] giving the relatively sensitive enone **13** in 73% yield.

Reduction of enone **13** with either (*R*)-Me-CBS or (*S*)-Me-CBS followed by treatment with TBAF furnished the diastereomerically pure diols **14a** and **14b**, respectively. Using a similar sequence of steps, the analogs **14c** and **14d** were prepared from the corresponding enone, lacking the vinylic methyl group (Table 1).[15]

While cyclization of the latter compounds under Uenishi's conditions ($Pd(CH_3CN)_2Cl_2$, THF) proceeded as expected yielding the *anti*- or *syn*-pyran **18** selectively from **14c** or **14d**, respectively (Table 1, entries 1 and 2), we were surprised to find that the introduction of a methyl substituent was detrimental for selectivity. Thus, treatment of diols **14a** and **14b** with $Pd(CH_3CN)_2Cl_2$ in THF both led to a 1.4:1 *syn*/*anti* mixture of dihydropyran **15** (Table 1, entries 3 and 4). The selectivity could be enhanced to 6:1 by employing CH_2Cl_2 as solvent (Table 1, entry 5). Inspired by Gouverneur's study on the formation of pyranones from enones,[19] we decided to use the cationic complex $Pd(CH_3CN)_4(BF_4)_2$ as a catalyst in the reaction.

Remarkably, the diastereomeric diols **14a** and **14b** both yielded the same *syn*-pyran in excellent selectivity (>25:1) upon treatment with $Pd(CH_3CN)_4(BF_4)_2$ (Table 1, entries 6 and 7). Thus, the stereochemistry of the allylic alcohol was of no importance in the cyclization reaction, strongly suggesting a cationic mechanism. Consequently, for preparative purposes we later applied Luche conditions ($NaBH_4$ and $CeCl_3$) for the reduction of enone **13**. Subsequent treatment with TBAF gave a 3.6:1 diastereomeric mixture of diols in 80% yield favoring **14a**.[15] Using this mixture, the same *syn*-selectivity was obtained in the cyclization (Table 1, entry 8). Excited by the possibility that the Lewis acidity of the cationic Pd complex might induce the cyclization, we therefore tested the applicability of $BF_3{\cdot}OEt_2$ and the Brønsted acid TfOH in the reaction.[20] Indeed, the desired *syn*-dihydropyran **15** was obtained in both cases in excellent yield, albeit with slightly lower selectivity (Table 1, entries 9 and 10).[21]

Table 1. Formation of Dihydropyrans from Allylic 1,3-Diols via a Pd-Catalyzed 6-*Endo-Trig* Cyclization



14a: R^1 = OH, R^2 = H, R^3 = Me
14b: R^1 = H, R^2 = OH, R^3 = Me
14c: R^1 = OH, R^2 = H, R^3 = H
14d: R^1 = H, R^2 = OH, R^3 = H

15: R = Me

18: R = H

entry	diol	catalyst (equiv)	solvent	yield (%)	syn/anti
1	**14c**	$Pd(CH_3CN)_2Cl_2$ (1.0)	THF	54	1:5
2	**14d**	$Pd(CH_3CN)_2Cl_2$ (1.0)	THF	54	99:1
3	**14a**	$Pd(CH_3CN)_2Cl_2$ (1.0)	THF	53	1.5:1
4	**14b**	$Pd(CH_3CN)_2Cl_2$ (1.0)	THF	53	1.4:1
5	**14b**	$Pd(CH_3CN)_2Cl_2$ (1.0)	CH_2Cl_2	56	6:1
6	**14b**	$Pd(CH_3CN)_2(BF_4)_2$ (0.1)	CH_2Cl_2	73	25:1
7	**14a**	$Pd(CH_3CN)_2(BF_4)_2$ (0.1)	CH_2Cl_2	72	25:1
8	**14a**[a]	$Pd(CH_3CN)_2(BF_4)_2$ (0.05)	CH_2Cl_2	72	25:1
9	**14a**[a]	$BF_3{\cdot}OEt_2$ (0.1)	CH_2Cl_2	82	20:1
10	**14a**[a]	TfOH (0.1)	CH_2Cl_2	81	16:1

[a] Obtained from Luche reduction of **13**, dr = 3.6:1.

The benzyl group of **15** was removed under Birch conditions, giving rise to **16** in 88% yield. Swern oxidation, and reaction of the resulting aldehyde with MeMgBr, followed by a second Swern oxidation provided the desired ketone **17** in 72% yield (three steps).[22]

The final steps of the synthesis of jerangolid A (**1a**) are depicted in Scheme 3. The connection of the two ring systems was considered using two subsequent olefination reactions, commencing with methyl ketone **17**. The latter was subjected to an olefination reaction with cyclic phosphonamides **21a**−**c**, which are obtained from alkylation of 1,3-dialkyl-2-oxo-1,3,2-diazaphospholidines **20a**−**c** with iodide **19**,[23] derived from (*R*)-Roche ester. The deprotonation of phosphonamides **21a**−**c** at low temperature using *n*-BuLi followed by addition of ketone **17** and quenching with AcOH at −78 °C furnished separable mixtures of *E*/*Z* isomers of TBS-ether **24a**, with the desired compound as the major product (Table 2).

Condensation of dimethyl phosphonamide **21a** with **17** gave **24a** with a 3:1 *E*/*Z* ratio, albeit in modest yield with recovery of starting materials (Table 2, entry 1). The *E*/*Z* ratio improved to 6:1 when the reaction mixture was allowed to equilibrate at room temperature before addition of AcOH (Table 2, entry 2). Increasing the steric demand of the phosphonamide substituents also helped to enhance the *E*/*Z*

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(17) For the preparation of an analogous dithiane, see: Ziegler, F. E.; Fang, J.-M.; Tam, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 7174.

(18) Cussans, N. J.; Ley, S. V.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1654.

(19) Reiter, M.; Turner, H.; Gouverneur, V. *Chem.—Eur. J.* **2006**, *27*, 7190.

(20) For a recent Lewis acid mediated synthesis of 2,6-disubstituted pyrans, see: Guérinot, A.; Serra-Muns, A.; Gnamm, C.; Bensoussan, C.; Reymond, S.; Cossy, J. *Org. Lett.* **2010**, *12*, 1808.

(21) The *syn*- and *anti*-pyrans **15** are stable under the reaction conditions and do not epimerize when treated with $BF_3{\cdot}OEt_2$.

(22) For previous syntheses of **17**, see: (a) Kirkland, T. A.; Colucci, J.; Geraci, L. S.; Marx, M. A.; Schneider, M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 12432. (b) Lukesh, J. M.; Donaldson, W. A. *Tetrahedron Lett.* **2005**, *46*, 5529. See also ref 7b.

(23) For alkylation of phosphorus acid diamides, see: Koeller, K. J.; Spilling, C. D. *Tetrahedron Lett.* **1991**, *32*, 6297.

Scheme 3. Completion of the Synthesis of Jerangolid A (**1a**)

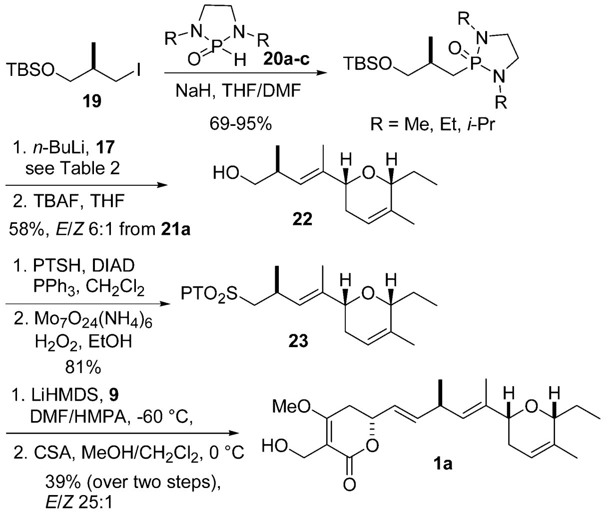
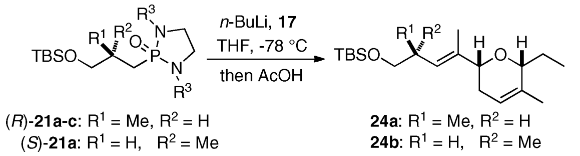


Table 2. Olefination of Ketone **17** Employing Cyclic Phosphonamides **21**[a]



entry	phosphonamide	product	yield[b] (%)	*E*/*Z*
1	(*R*)-**21a**:R^3 = Me	**24a**	57	3:1
2	(*R*)-**21a**: R^3 = Me	**24a**	62	6:1[c]
3	(*R*)-**21b**: R^3 = Et	**24a**	38	5:1
4	(*R*)-**21c**: R^3 = *i*-Pr	**24a**	20	13:1
5	(*S*)-**21a**: R^3 = Me	**24b**	63	19:1

[a] Reaction conditions: **21** (1.5−2.0 equiv), *n*-BuLi (1.4−1.8 equiv), THF, −78 °C, 1 h; **17** (1.0 equiv), −78 °C, 1 h; then AcOH (excess), −78 °C to rt. [b] Recovery of ketone **17**: 20−60%. [c] Addition of AcOH at rt.

selectivity. Thus, changing the substituents from methyl to isopropyl increased the selectivity from 3:1 to 13:1, concominant with a decline in yield from 57% to 20% and increased recovery of starting materials (Table 2, entries 1 and 4). A corresponding Julia−Kocienski olefination[24a,b] employing a phenyltetrazole sulfone (PT-sulfone) and LiHMDS in CH_2Cl_2 gave, at best, a 3:1 *E*/*Z* ratio of olefin **24a**, while employing the classical Julia−Lythgoe conditions[24c,d] reportedly gave an *E*/*Z* ratio of 95:1.[7] Intriguingly, employing the (*S*)-enantiomer of dimethyl phosphonamide **21a** in the olefination of **17** resulted in an excellent 19:1 *E*/*Z* selectivity, forming diastereomer **24b** (Table 2, entry 5).

Removal of the TBS group from **24a** with TBAF afforded alcohol **22** in 90% yield. Transformation into known PT-sulfone **23**[7,25] was achieved in 81% yield by treatment of **22** with 1-phenyltetrazole-5-thiol (PTSH) under Mitsunobu conditions and subsequent oxidation. The fully elaborated PT-sulfone **23** was eventually used for coupling with aldehyde **9** to access the corresponding olefination product in moderate yield. After some optimization, we found that by using LiHMDS in the solvent system DMF/HMPA,[26] we obtained almost exclusively the desired *E*-olefin (46%, *E*/*Z* > 25:1), with recovered **23** (ca. 30%). Finally, removal of the TBS group under mild acidic conditions led to jerangolid A (**1a**). The spectroscopic data of the synthetic compound matched those reported for the natural product.[1,15]

In summary, we have reported the first total synthesis of jerangolid A (**1a**) in 16 linear steps and 6% yield starting from glycidol **10**. Relevant reactions involved a highly diastereoselective $BF_3{\cdot}OEt_2$ or Pd-catalyzed formation of dihydropyran **17** and elaboration of the lactone **9**, both starting from a common chiron. Stereoselective olefinations were achieved using phosphonamide anion and Julia−Kocienski couplings.

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Supporting Information Available: Experimental procedures and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772.