Organic LETTERS

Letter

pubs.acs.org/OrgLett

A Pot-Economical Approach to the Total Synthesis of Sch-725674

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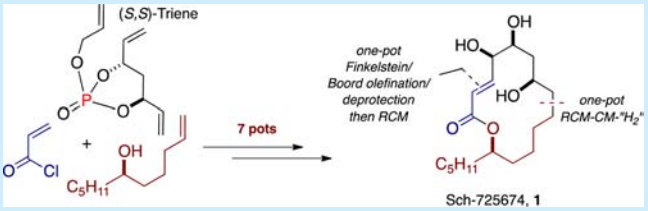
Supporting Information

ABSTRACT: A pot-economical total synthesis of antifungal Sch-725674, **1**, is reported. The approach takes advantage of a number of one-pot, sequential transformations, including a phosphate tether-mediated one-pot, sequential RCM/CM/chemoselective hydrogenation protocol, a one-pot tosylation/acrylation sequence, and a one-pot, sequential Finkelstein reaction/Boord olefination/acetonide deprotection procedure to streamline the synthesis route by reducing isolation and purification procedures, thus saving time. Overall, an asymmetric route has been developed that is efficiently accomplished in seven pots from phosphate (*S*,*S*)-triene and with minimal purification.



Sch-725674, **1**, is an antifungal macrolide that was isolated and structurally elucidated in 2005 by Yang and co-workers from the culture of *Aspergillus sp.*[1] This natural product exhibits activity against *Saccharomyces cerevisiae* and *Candida albicans* with MIC values of 8 and 32 μg/mL, respectively. Key structural features of **1** include a 14-membered ring, an *E*-configured α,β-unsaturated ester, a lipophilic *n*-pentyl side chain and a 1,3-*anti*-diol moiety embedded within a four-carbon subunit containing three stereogenic carbinol centers (Figure 1). An intriguing feature of **1** is the absence of commonly found methyl groups on the backbone of macrolides (i.e., erythromycin and derivatives). The closest structural relatives of Sch-725674 are the self-germination inhibitor gloeosporone, **2**,[2] and the recently isolated gliomasolides A to E, **3**–**7**[3] (Figure 1), thus making **1** an attractive biological and synthetic target.

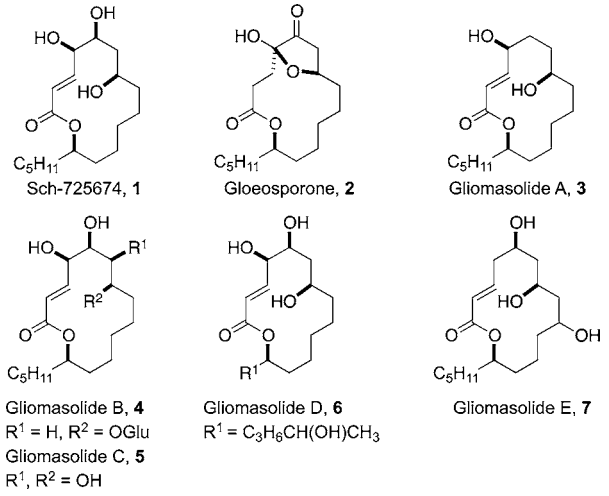


Figure 1. Natural product macrolactones Sch-725674 (**1**), gloeosporone (**2**), and gliomasolides A–E (**3**–**7**).

The Curran group reported the first total synthesis of Sch-725674 and a complete library of stereoisomers by using fluorous tagging technology developed in their laboratory, which also established the absolute stereochemistry of **1**.[4] In 2014, Prasad and co-workers reported an enantioselective synthesis of the macrolactone core,[5] followed by the second reported total synthesis featuring a Ley dithiaketalization and ring-closing metathesis (RCM).[6] Kaliappan and co-workers later accomplished the total synthesis of **1** employing dithiane alkylation, cross-metathesis (CM), and Yamaguchi macrolactonization as strategic transformations.[7] Most recent, a Wacker-type oxidation was showcased in a formal total synthesis of **1** by Reddy and co-workers, along with the first total synthesis of structural relative gliomasolide C, **5**.[8]

Given that 14-membered macrolactones lacking methyl group substitutions are rare in nature and underexplored in biological studies, we wish to provide a streamlined and library amenable synthetic method to access **1**. In this regard, pot-economical[9] processes have emerged as valuable tools for the synthesis of natural products as they enable the formation of several bonds and stereocenters while using minimal synthesis steps.[10] Pot economy is achieved via one-pot reactions, which combine multiple transformations into a single reaction flask without the need for workup and chromatography operations between sequential reactions. The application of one-pot protocols in natural products and medicinal drugs has recently been reviewed,[10b] and among several elegant examples contained in this review, seminal efforts by Hayashi[11] are highly notable in that they demonstrate use of multiple one-pot transformations to streamline the synthesis of complex molecules.

Taken together, a pot-economic route attains a streamlined process that saves operational time and minimizes waste by carrying out successive reactions in one pot. Herein, we report

Received: December 14, 2015
Published: January 13, 2016

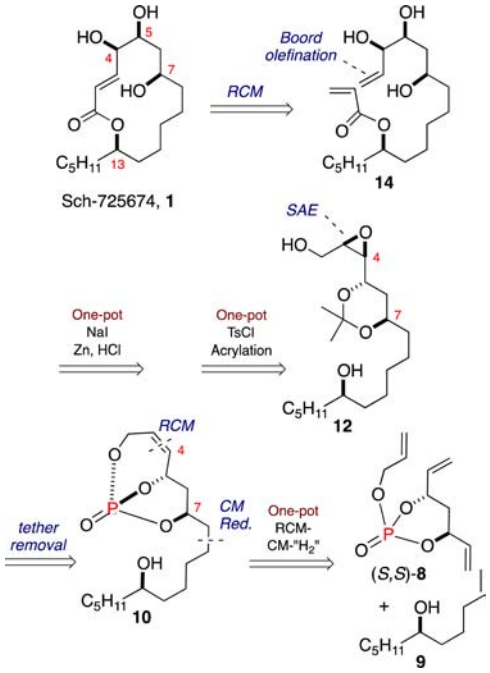
DOI: 10.1021/acs.orglett.5b03547
Org. Lett. 2016, 18, 516–519

a pot-economical total synthesis of Sch-725674 by incorporating technically simple and effective one-pot, sequential protocols to the route, reducing postreaction workup and overall purification events.

Previous reports in our group have emphasized the utilization of phosphate tethers to mediate reactions in a chemo- and diastereoselective fashion, with recent work incorporating one-pot, sequential protocols to the synthesis of 1,3-*anti*-diol containing natural products[12] and complex polyols.[13] To continue our efforts toward the development of modular and pot-economical approaches for the synthesis of complex molecules, we planned an asymmetric synthesis of Sch-725674 by carrying out a series of one-pot, sequential protocols in an overall minimal number of pots.

From a retrosynthetic viewpoint, macrocyclization to **1** can be accomplished via RCM of linear diene **14** (Scheme 1).

Scheme 1. Synthesis Plan Toward Sch-725674, 1



Derivation of triol **14** was planned using two consecutive one-pot, sequential protocols from epoxide **12**, namely, a Finkelstein substitution/Boord olefination/acetonide deprotection procedure and a two-reaction sequence involving tosylation and acrylation. Epoxide **12** can be synthesized from bicyclic phosphate **10** following reductive tether removal and employing a Sharpless asymmetric epoxidation (SAE) on *cis*-olefin at C4−C3. The phosphate tethered-triol **10** can be accessed from triene phosphate (*S*,*S*)-**8** following a one-pot RCM/CM/chemoselective hydrogenation ["H_2"] sequence utilizing **9** as the CM partner, simultaneously installing the requisite C13 *n*-pentyl side chain and the C5−C7 1,3-*anti*-diol subunit.[14] A salient feature of this approach is the modular installation of the C13−C9 fragment via CM, as well as introduction of the acrylate at a later stage, opening opportunities for future analogue generation.

Following optimized conditions for one-pot, sequential RCM/CM/["H_2"],[15] triene (*S*,*S*)-**8** was subjected to an RCM reaction using the second-generation Hoveyda−Grubbs catalyst[16] (**HG-II**) (2 mol %) in refluxing CH_2Cl_2 (Scheme 2). After RCM completion (30 min), the solvent was changed[17] to 1,2-dichloroethane (DCE) and the *n*-pentyl-substituted CM partner **9** was introduced to the same pot, followed by a second addition of **HG-II** (4 mol %). The CM event proceeded for 5 h under reflux, and subsequent chemoselective diimide reduction at the external olefin was achieved by addition of *o*-nitrobenzenesulfonylhydrazine (*o*-NBSH)[18] into the reaction mixture. This one-pot, three-reaction, sequential operation provided bicyclic phosphate **10** in 59% yield over one-pot, representing an average yield of 84% per reaction (84% av/rxn).

Next, the phosphate tether in **10** was removed under reductive conditions using $LiAlH_4$ (THF, 0 °C) (Scheme 2). The corresponding tetrol was obtained in high purity following the Fieser workup,[19] and without chromatography purification the crude 1,3-*anti*-diol was subsequently subjected to a selective acetonide protection. The crude triol was treated with 2,2-dimethoxypropane (2,2-DMP) and catalytic amounts of camphorsulfonic acid (CSA) as outlined in Scheme 2, providing 1,3-acetonide **11** in 71% yield after two reactions in two pots. The strategy proceeded with a SAE[20] event [(−)-diethyl tartrate (DET), $Ti(O^iPr)_4$, cumene hydroperoxide][21] on sterically hindered *cis*-allyl alcohol **11** to give the corresponding diastereomeric products in 72% yield (80% brsm) with **12** as the desired major diastereomer (*ds* = 88%) (Scheme 2).[22]

Following the successful assembly of epoxide **12** in scalable quantities, a second one-pot, sequential protocol consisting of tosylation and acrylation was applied. To this end, the primary alcohol in **12** was chemoselectively transformed to tosylate (TsCl, Et_3N, DMAP) in the presence of the C13 carbinol following overnight reaction. Next, acryloyl chloride was simply added to the same pot at 0 °C to afford acrylate **13** in 86% yield over two reactions in one-pot (93% av/rxn) (Scheme 2).

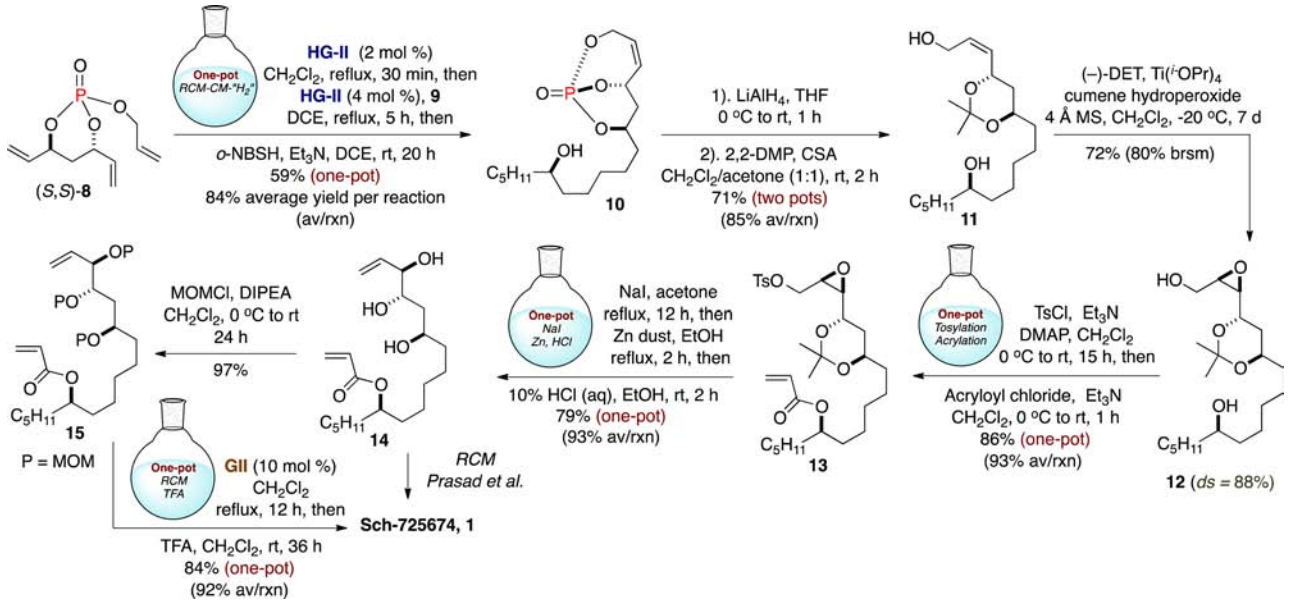
A subsequent, consecutive one-pot, sequential protocol was established by treating **13** to a Finkelstein substitution, Boord olefination (Zn, EtOH), and acetonide deprotection sequence to assemble triol **14**. This three-reaction, one-pot process commenced by exposing the tosyl group in **13** to Finkelstein conditions (NaI, acetone, reflux), followed by a solvent change from acetone to ethanol and addition of activated zinc powder to promote Boord elimination over a 2 h period under reflux. Final addition of HCl at room temperature released the 1,3-*anti*-diol to deliver triol **14** in 79% yield over three reactions in a single pot operation (93% av/rxn).[23]

With **14** in hand, Sch-725674, **1**, was accessed via a final RCM as reported by Prasad and co-workers, and characterization data was in good accord with that reported by the authors.[6] Overall, the total synthesis of **1** was accomplished in seven pots from triene (*S*,*S*)-**8** and olefin **9**. Chromatography isolations were also reduced to six procedures, which saved time and minimized chemical waste generation. While we were unable to match the reported RCM yield (36%),[24] we found that simple protection of the alcohols significantly increased the efficiency of this final macrocyclization event. In this regard, we developed a two-reaction, one-pot sequential method that consists of RCM and methoxymethyl (MOM) deprotection to further streamline the synthesis toward **1**.

To this end, the carbinols in **14** were protected as MOM ethers, in which the triprotected diene **15** was obtained in 97% yield after treating with MOMCl in basic conditions (Scheme 2). Next, the one-pot protocol began by treating metathesis precursor **15** with the second-generation Grubbs catalyst[25] (**GII**) (10 mol %) in refluxing CH_2Cl_2. Following metathesis

DOI: 10.1021/acs.orglett.5b03547
Org. Lett. 2016, 18, 516−519

Scheme 2. Total Synthesis of Sch-725674, 1



completion (12 h), the solvent volume was reduced and MOM deprotection proceeded after adding trifluoroacetic acid [TFA (60 v/v%)] to the same pot, delivering natural product **1** in 84% yield over two-reactions in one pot (92% av/rxn). This alternative approach considerably improved the yield of the RCM event, providing Sch-725674 in 14.6% total yield from triene (*S*,*S*)-**8** and olefin **9** following eight pots and seven chromatography purifications.

In summary, we have disclosed a pot-economical synthesis route to the antifungal natural product Sch-725674. Overall, a seven-pot route was developed from readily prepared phosphate triene (*S*,*S*)-**8** and olefin fragment **9**, including seven isolations and six chromatography purifications. Key to the strategy is the application of a phosphate tether-mediated one-pot, sequential RCM/CM/hydrogenation process, a one-pot tosylation/acrylation sequence, and a one-pot, sequential Finkelstein reaction/Boord olefination/acetonide deprotection protocol. An alternative approach was introduced at the final stage of the synthesis involving a one-pot, sequential RCM/MOM-deprotection protocol to overcome efficiency challenges during the macrocyclization event. Taken together, the use of sequential reactions in the same pot provided a streamlined synthesis of Sch-725674 in minimal production time by allowing multiple bond transformations in a single flask without the need for purification of several intermediates, thus also reducing waste generation.

We anticipate that the outlined pot-efficient approach can be exploited for the synthesis of related macrocycles, such as 1,3-*anti*-diol containing gliomasolides (Figure 1) and derivatives in a rapid, efficient, and pot-economical manner, thus augmenting opportunities to explore this class of understudied structures in biological settings. Efforts from our laboratory in this regard will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03547.

Experimental details and spectroscopic data of new compounds (PDF)

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Author Contributions

†These authors contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript./

Notes

The authors declare the following competing financial interest(s): P.R.H. is on the Scientific Advisory Board of Materia, Inc.

■ ACKNOWLEDGMENTS

This investigation was generously supported by funds provided by the National Institute of General Medical Sciences (NIH R01GM077309). J.T. acknowledges support from the NIGMS Diversity Program. The authors thank Justin Douglas and Sarah Neuenswander in the University of Kansas NMR Laboratory and Todd Williams for HRMS analysis. Support for the NMR instrumentation was provided by NSF Grant #9512331, #9977422, and #0320648 and NIH Center Grant #P20 GM103418, #S10RR024664, and #S10 OD016360. The authors also thank Materia, Inc. for supplying metathesis catalyst.

■ REFERENCES

(1) Yang, S. W.; Chan, T. M.; Terracciano, J.; Loebenberg, D.; Patel, M.; Chu, M. *J. Antibiot.* **2005**, *58*, 535−538.

(2) (a) Meyer, W. L.; Schweizer, W. B.; Beck, A. K.; Scheifele, W.; Seebach, D.; Schreiber, S. L.; Kelly, S. E. *Helv. Chim. Acta* **1987**, *70*, 281−291. (b) Carling, R. W.; Holmes, A. B. *Tetrahedron Lett.* **1986**, *27*, 6133−6136.

(3) Zhang, J.; Lin, X.-P.; Li, L.-C.; Zhong, B.-L.; Liao, X.-J.; Liu, Y.-H.; Xu, S.-H. *RSC Adv.* **2015**, *5*, 54645−54648.

DOI: 10.1021/acs.orglett.5b03547
Org. Lett. 2016, 18, 516−519

(4) Moretti, J. D.; Wang, X.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 7963−7970.
(5) Sunnam, S. K.; Prasad, K. R. *Tetrahedron* **2014**, *70*, 2096−2101.
(6) Bali, A. K.; Sunnam, S. K.; Prasad, K. R. *Org. Lett.* **2014**, *16*, 4001−4008.
(7) Ramakrishna, K.; Kaliappan, K. P. *Org. Biomol. Chem.* **2015**, *13*, 234−240.
(8) Seetharamsingh, B.; Khairnar, P. V.; Reddy, D. S. *J. Org. Chem.* **2016**, *81*, 290.
(9) (a) Clarke, P. A.; Santos, S.; Martin, W. H. C. *Green Chem.* **2007**, *9*, 438−440. (b) Clarke, P. A.; Zaytzav, A. V.; Whitwood, A. C. *Tetrahedron Lett.* **2007**, *48*, 5209−5212. (c) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304−1307.
(10) For reviews on pot economy, see: (a) Vaxelaire, C.; Winter, P.; Christmann, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 3605−3607. (b) Hong, B.-C.; Raja, A.; Sheth, V. M. *Synthesis* **2015**, *47*, 3257−3285. (c) Kashinath, K.; Reddy, D. S. *Org. Biomol. Chem.* **2015**, *13*, 970−973. For reviews on step economy, see: (d) Wender, P. A.; Verma, V. A.; Paxton, T. J.; Pillow, T. H. *Acc. Chem. Res.* **2008**, *41*, 40−49. (e) Wender, P. A. *Nat. Prod. Rep.* **2014**, *31*, 433−440. For reviews on atom economy, see: (f) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (g) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. For a review on redox economy, see: (h) Burns, N. Z.; Baran, P. S.; Hoffmann, R. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 2854−2867.
(11) (a) Ishikawa, H.; Honma, M.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 2824−2827. (b) Umemiya, S.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 3450−3452. (c) Hayashi, Y.; Sakamoto, D.; Okamura, D. *Org. Lett.* **2016**, *18*, 4.
(12) (a) Venukadasula, P. K. M.; Chegondi, R.; Maitra, S.; Hanson, P. R. *Org. Lett.* **2010**, *12*, 1556−1559. (b) Hanson, P. R.; Chegondi, R.; Nguyen, J.; Thomas, C. D.; Waetzig, J.; Whitehead, A. J. *J. Org. Chem.* **2011**, *76*, 4358−4370. (c) Chegondi, R.; Tan, M. M. L.; Hanson, P. R. *J. Org. Chem.* **2011**, *76*, 3909−3916. (d) Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. *Org. Lett.* **2014**, *16*, 122−125. (e) Chegondi, R.; Hanson, P. R. *Tetrahedron Lett.* **2015**, *56*, 3330−3333. For a review, see: (f) Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Markley, J. L. *Top. Curr. Chem.* **2014**, *361*, 253−271.
(13) (a) Whitehead, A.; McReynolds, M. D.; Moore, J. D.; Hanson, P. R. *Org. Lett.* **2005**, *7*, 3375−3378. (b) Thomas, C. D.; McParland, J. M.; Hanson, P. R. *Eur. J. Org. Chem.* **2009**, *2009*, 5487−5500. (c) Chegondi, R.; Maitra, S.; Markley, J. L.; Hanson, P. R. *Chem. - Eur. J.* **2013**, *19*, 8088−8093. (d) Hanson, P. R.; Jayasinghe, S.; Maitra, S.; Ndi, C. N.; Chegondi, R. *Beilstein J. Org. Chem.* **2014**, *10*, 2332−2337.
(14) Triene (*S,S*)-**8** is readily prepared via a two-step coupling of the corresponding C_2-symmetric 1,3-antidiene diol and allyl alcohol with $POCl_3$ (see refs 13a and 13b), or in one step by employing phosphoramidite chemistry (see ref 12a). The C_2-symmetric 1,3-antidiene diol can be prepared in two steps from *bis*(1,5-dichloro-2,4-pentanedione)copper(II) complex (a) Matsui, K.; Motoi, M.; Nojiri, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 562−565. (b) Rychnovsky, S. D.; Griesgraber, G.; Powers, J. P. *Org. Synth.* **2000**, *77*, 1−11. (c) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161−5169. We have routinely prepared the starting copper(II) salt in >100 g batches and have found that, if it is washed appropriately with diethyl ether, it can be stored for long-term (>2 years) at room temperature on the benchtop. The CM partner **9** can be generated from (*S*)-epichlorohydrin in two steps, see: Kubizna, P.; Špánik, I.; Kožíšek, J.; Szolcsányi, P. *Tetrahedron* **2010**, *66*, 2351−2355.
(15) Venukadasula, P. K. M.; Chegondi, R.; Suryn, G. M.; Hanson, P. R. *Org. Lett.* **2012**, *14*, 2634−2637.
(16) (a) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791−799. (b) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179. (c) Gessler, S.; Randl, S.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 9973−9976.
(17) Switching from CH_2Cl_2 (40 °C) to DCE (70 °C) is necessary in order to reduce homodimerization of the CM partner **9** (type I olefin), see ref 15.
(18) (a) Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507−7507. (b) O'Doherty, G. A.; Haukaas, M. H. *Org. Lett.* **2002**, *4*, 1771−1774. (c) Buszek, K. R.; Brown, N. J. *J. Org. Chem.* **2007**, *72*, 3125−3128.
(19) (a) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. *1*, pp 581−595. (b) Mićović, V. M.; Mihailović, M. L. *J. Org. Chem.* **1953**, *18*, 1190−1200. (c) See Supporting Information.
(20) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974−5976.
(21) Krishna, P. R.; Reddy, V. V. R.; Sharma, G. V. M *Synthesis* **2004**, *2004* (13), 2107−2114.
(22) The minor diastereomer was isolated in 8.6%, see Supporting Information.
(23) The spectroscopic data of diene **14** matched in all aspects with literature data, see ref 6.
(24) Despite several trials of conditions attempted, in our hands the RCM yields from **14** to **1** were no more than 20%. For the reported procedure, see ref 6.
(25) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

DOI: 10.1021/acs.orglett.5b03547
Org. Lett. 2016, 18, 516−519