Organic LETTERS

Letter

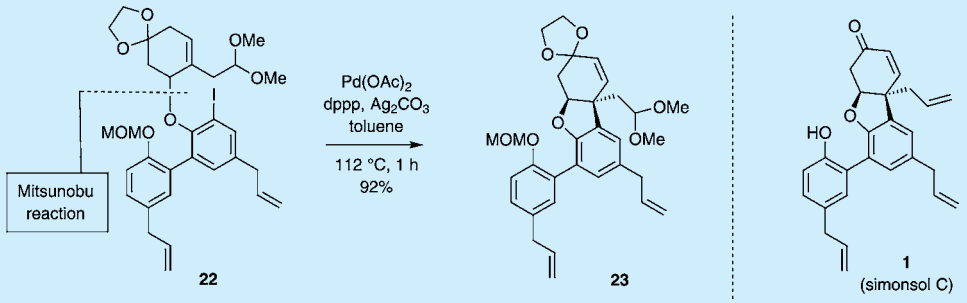
pubs.acs.org/OrgLett

Total Synthesis of the *Illicium*-Derived Sesquineolignan Simonsol C

Jeremy Nugent, Martin G. Banwell,* and Brett D. Schwartz

Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia

Supporting Information



ABSTRACT: The racemic form of the title natural product **1** has been synthesized by engaging, as a key step, the iodoarene-tethered cyclohexene **22** in an intramolecular Heck reaction to give compound **23**. This angularly substituted tetrahydrodibenzo[*b*,*d*]furan was elaborated over a further five steps into target (±)-**1**.

The *Illicium* genus of flowering plants is commonly encountered in various parts of Asia, and a range of secondary metabolites produced by them, including certain sesquineolignans,[1] display potentially useful neurological effects.[2−5] These include, *inter alia*, neurite-outgrowth-promoting and acetylcholine-esterase-inhibiting properties.[4−7] Recently, Wang and co-workers reported[5] the isolation of a series of such compounds, including simonsol C (**1**) (Figure 1),[8]

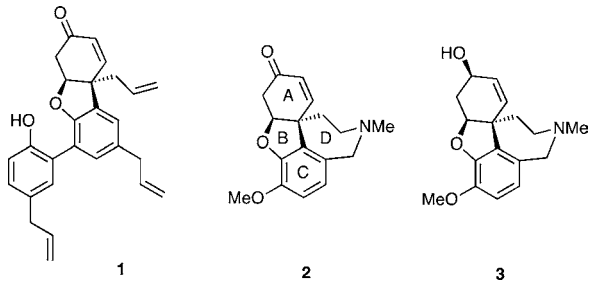


Figure 1. Structures of simsonsol C (**1**), narwedine (**2**), and galanthamine (**3**).

from the aerial parts of the toxic shrub *Illicium simonsii* collected in the Yunnan Province of southwest China. The tetrahydrodibenzo[*b*,*d*]furan substructure associated with compound **1**[9] bears a strong resemblance to the ABC-ring system of narwedine (**2**), an important precursor to the alkaloid galanthamine (**3**) that is now used clinically in the symptomatic treatment of Alzheimer's disease.[10]

Our continuing interest in the chemistry of galanthamine[11] and certain neurotrophically active metabolites derived from *Illicium* species[12] together with the absence of any reported synthetic approaches to the structurally distinct framework of simonsol C or its congeners prompted us to begin investigations in this area.[13,14] Herein we report the successful total synthesis of the racemic modification of compound **1** via a 12-step sequence that should permit access to other members of this interesting class of natural products.

The presence of three allyl residues, including an angular one, within the framework of the title compound presents various challenges including maintaining the positional integrity of the associated double bonds and achieving the required chemoselectivity in the reactions to be used. The retrosynthetic analysis employed in the present study is shown in Figure 2. It was envisaged that the central furan ring would be accessible through an intramolecular Heck reaction involving a substrate of the general form **4**, and this could itself be assembled using an intermolecular Mitsunobu reaction between the 2-allylcyclohex-2-en-1-ol **5** and a halogenated phenol of the general form **6**.

The synthetic sequence used to generate a seemingly suitable halogenated phenol is shown in Scheme 1 and involved initial monoprotection, under standard conditions, of commercially available magnolol (**7**) as the corresponding and previously unreported *tert*-butyldimethylsilyl (TBS) ether **8** (98%). Regioselective electrophilic bromination of the phenolate derived from compound **8** using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH)[15] then afforded compound **9** (89%), the spectral data for which were in complete accord with the assigned structure.

The synthesis of the A-ring precursor **5** started (Scheme 2) with the α-benzoyloxylation of commercially available cyclohexane-1,2-dione monoethylene ketal (**10**).[16] The resulting and previously reported[11b,16] oxidation product **11** (78%) was then

Received: June 20, 2016
Published: July 11, 2016

DOI: 10.1021/acs.orglett.6b01799
Org. Lett. 2016, 18, 3798−3801

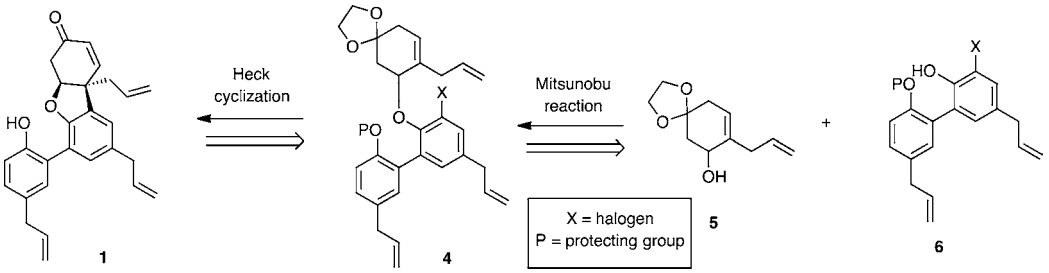
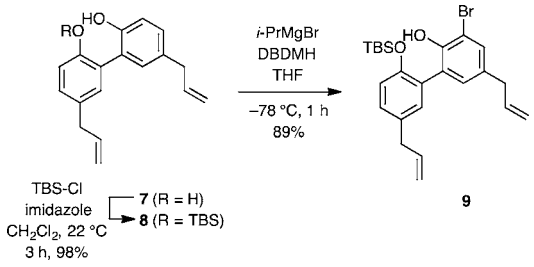
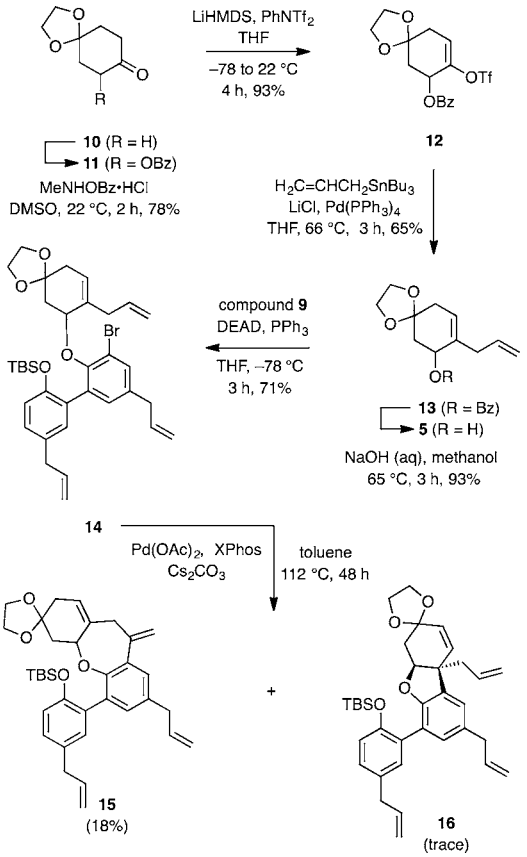


Figure 2. Retrosynthetic analysis of simonsol C used in the present study.

Scheme 1. Synthesis of Magnolol Derivative 9



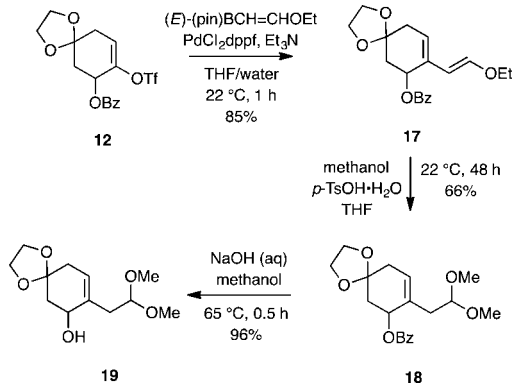
Scheme 2. Intervention of a 7-*exo*-trig Heck Cyclization Reaction



converted, by standard methods, into the corresponding enol triflate **12**[11b] (93%) that was itself engaged in a Stille cross-coupling reaction with allyltri-*n*-butylstannane in the presence of $Pd(PPh_3)_4$ and lithium chloride to give the nonconjugated diene **13** in 65% yield. Cleavage of the ester residue within this last compound was readily achieved using sodium hydroxide in methanol, and the resulting and targeted alcohol **5** (93%) participated, at −78 °C,[17] in a Mitsunobu reaction with the halogenated magnolol derivative **9** to give the desired coupling product **14** in 71% yield when diethyl azodicarboxylate (DEAD) and triphenylphosphine (PPh_3) were used as the activating agents. Disappointingly, when compound **14** was exposed to $Pd(OAc)_2$, XPhos, and cesium carbonate in refluxing toluene,[18] a reagent combination shown to be effective for promoting Heck-type cyclization reactions,[19] the oxepin derivative **15** (18%) proved to be the one isolable and fully characterizable product of reaction. Only trace amounts of the coproduced and desired isomer **16** were detected. Examination of various other reaction conditions led to essentially the same outcome. Compound **15** is clearly the product of a 7-*exo*-trig cyclization process involving the allyl residue appended to the cyclohexene ring of substrate **14**. On this basis, masking of the offending allyl group was undertaken in order to ensure that the desired 5-*exo*-trig Heck cyclization reaction would take place.

The reaction pathway leading to a congener of compound **5** that lacks an interfering allyl group is shown in Scheme 3. Thus,

Scheme 3. Synthesis of Acetal 19

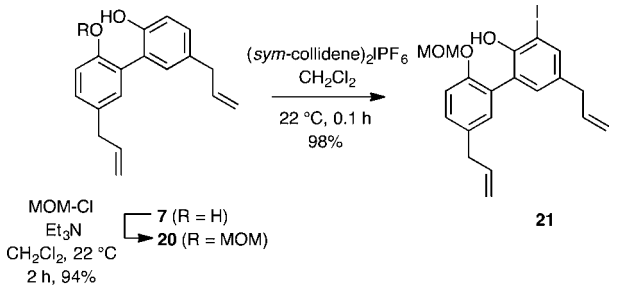


Suzuki−Miyaura cross-coupling of the enol triflate **12** described earlier with (*E*)-(pin)BCH=CHOEt[20] afforded the enol ether **17** (85%) that was itself treated with methanol and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) to produce acetal **18** (66%). The benzoate residue within this last compound was cleaved under standard conditions to give the targeted A-ring precursor **19** (96%).

Various aspects of the foregoing study resulted in the conclusion that the magnolol derivative of the general form **6** (see Figure 2) required for Mitsunobu coupling with compound **19** should incorporate a MOM protecting group[21] and iodine (rather than bromine). Accordingly, magnolol (**7**) was first treated (Scheme 4) with triethylamine and chloromethyl methyl ether (MOM-Cl, prepared under

DOI: 10.1021/acs.orglett.6b01799
Org. Lett. 2016, 18, 3798−3801

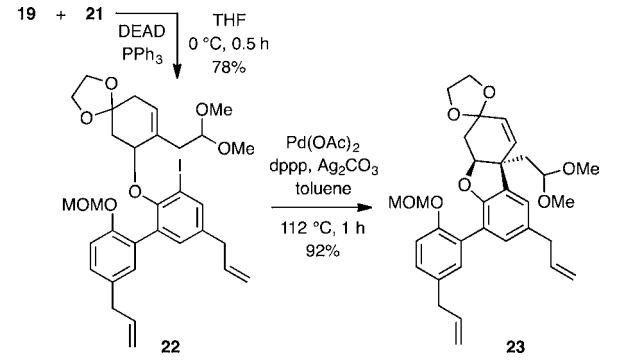
Scheme 4. Synthesis of Magnolol Derivative 21



conditions defined by Berliner and Belecki[22]), thus producing the targeted ether **20** (94%) that was immediately treated with bis(*sym*-collidine)iodine(I) hexafluorophosphate,[23,24] thereby effecting a regioselective iodination reaction to generate the desired compound **21** in 98% yield.

With compounds **19** and **21** to hand their coupling under standard Mitsunobu conditions was investigated (Scheme 5).

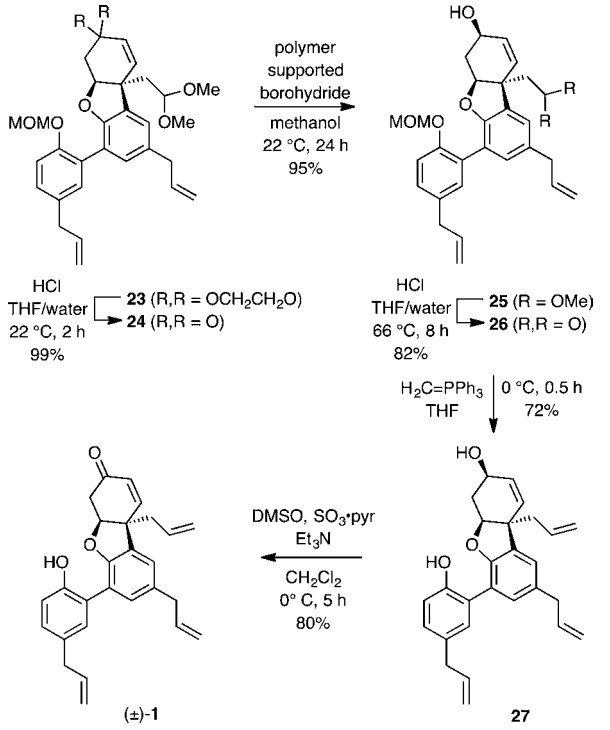
Scheme 5. Synthesis and Heck Cyclization of Compound 22



By such means the substrate, **22**, required for the pivotal Heck reaction was obtained in 78% yield. Treatment of aryl iodide **22** with $Pd(OAc)_2$, 1,3-bis(diphenylphosphino)propane (dppe), and silver carbonate in refluxing toluene[25] for 1 h allowed the desired 5-*exo*-trig Heck cyclization reaction to take place and so producing the tetrahydrodibenzofuran **23** in 92% yield. All the spectral data recorded on this material were in complete accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis (see below).

The elaboration of Heck cyclization product **23** to racemic simonsol C [(±)-**1**] followed the route shown in Scheme 6. This involved the initial and selective hydrolysis of the associated ethylene ketal moiety within the former compound using aqueous HCl in THF at 22 °C, affording enone **24** in 99% yield. Reduction of compound **24** with polymer-supported borohydride proceeded in a highly diasteroselective manner to give the allylic alcohol **25** in 95% yield,[26,27] and this was then treated, under reflux, with aqueous HCl in THF to provide aldehyde **26** (82%).[28] Wittig olefination of this last compound gave the triallyl-containing compound **27** (72%), the structure of which was confirmed by single-crystal X-ray analysis [see Supporting Information (SI) for details]. Finally, oxidation of allylic alcohol **27** under the Parikh–Doering conditions[29] afforded racemic simonsol C [(±)-**1**] in 80% yield. All the spectral data obtained on this material were in complete accord with the assigned structure and matched those reported for the natural product by Wang and co-workers (see the SI for relevant comparisons of the ^{13}C NMR spectral data).[5]

Scheme 6. Completion of the Synthesis of (±)-Simonsol C



The synthetic sequence reported here serves to further highlight the utility of the intramolecular Heck reaction as a means for effecting the assembly of heterocyclic ring systems embodying angular substituents[25,30] and the capacity of the Mitsunobu reaction to engage phenolic residues in C–O bond formation for the purposes of constructing tetrahydrodibenzo-[*b*,*d*]-furans.[31,32]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01799.

Experimental procedures, spectroscopic and analytical data, NMR spectra of new compounds, and X-ray data for compound **27** (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: Martin.Banwell@anu.edu.au.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the Australian Research Council for financial support. J.N. is the recipient of an Australian Government Postgraduate Award.

■ REFERENCES

(1) For a useful commentary on the nomenclature of lignans and neolignans, see: Moss, G. P. *Pure Appl. Chem.* **2000**, *72*, 1493.

(2) Kouno, I.; Morisaki, T.; Hara, Y.; Yang, C.-S. *Chem. Pharm. Bull.* **1991**, *39*, 2606.

DOI: 10.1021/acs.orglett.6b01799
Org. Lett. 2016, 18, 3798–3801

(3) Kouno, I.; Iwamoto, C.; Kameda, Y.; Tanaka, T.; Yang, C.-S. *Chem. Pharm. Bull.* **1994**, *42*, 112.
(4) Moriyama, M.; Huang, J.-M.; Yang, C.-S.; Hioki, H.; Kubo, M.; Harad, K.; Fukuyama, Y. *Tetrahedron* **2007**, *63*, 4243.
(5) Dong, C.; Liu, L.; Li, X.; Guan, Z.; Luo, H.; Wang, Y. *Planta Med.* **2013**, *79*, 338.
(6) For representative recent examples of biologically active sesquineolignans isolated from other sources, see: (a) Song, C.-W.; Wang, S.-M.; Zhou, L.-L.; Hou, F.-F.; Wang, K.-J.; Han, Q.-B.; Li, N.; Cheng, Y.-X. *J. Agric. Food Chem.* **2011**, *59*, 1199. (b) Cui, H.; Xu, B.; Wu, T.; Xu, J.; Yuan, Y.; Gu, Q. *J. Nat. Prod.* **2014**, *77*, 100. (c) Shi, Y.; Liu, Y.; Li, Y.; Li, L.; Qu, J.; Ma, S.; Yu, S. *Org. Lett.* **2014**, *16*, 5406. (d) Zhu, J.-Y.; Cheng, B.; Zheng, Y.-J.; Dong, Z.; Lin, S.-L.; Tang, G.-H.; Gu, Q.; Yin, S. *RSC Adv.* **2015**, *5*, 12202.
(7) For examples of other neolignans displaying neurite-outgrowth-promoting properties, see: Cheng, X.; Harzdorf, N. L.; Shaw, T.; Siegel, D. *Org. Lett.* **2010**, *12*, 1304 and references therein.
(8) Simonsol C is an optically active compound {$[\alpha]^{18}_{D}$ −10.5 (*c* 0.3, $CHCl_3$)}, but its absolute configuration has not yet been defined. We have chosen to represent it in the illustrated manner so as to emphasize its structural resemblance to the natural or (−)-enantiomeric form of galanthamine.
(9) For an example of a structurally related sesquilignan isolated from *Illicium dunnianum*, see: Sy, L.-K.; Brown, G. D. *Phytochemistry* **1996**, *43*, 1417.
(10) For useful points-of-entry into the literature on the history, chemistry, and pharmacology of galanthamine, see: (a) Henrich, M.; Teojh, H. L. *J. Ethnopharmacol.* **2004**, *92*, 147. (b) Marco-Contelles, J.; do Carmo-Carreiras, M.; Rodríguez, C.; Villarroya, M.; García, A. G. *Chem. Rev.* **2006**, *106*, 116. (c) Marco, L.; do Carmo Carreiras, M. *Recent Pat. CNS Drug Discovery* **2006**, *1*, 105. (d) Heinrich, M. *Alkaloids* **2010**, *68*, 157.
(11) (a) Banwell, M. G.; Buckler, J.; Jackson, C. J.; Lan, P.; Ma, X.; Matoušová, E.; Nugent, J. *Strategies and Tactics in Organic Synthesis* **2015**, *11*, 29. (b) Nugent, J.; Matoušová, E.; Banwell, M. G. *Eur. J. Org. Chem.* **2015**, *2015*, 3771.
(12) Sharma, M. K.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2015**, *80*, 2930.
(13) For a useful summary of the relatively limited efforts focused on the synthesis of sesquineolignans, see: Denton, R. M.; Scragg, J. T. *Org. Biomol. Chem.* **2012**, *10*, 5629.
(14) For representative recent examples of synthetic studies carried out on biologically active sesquilignans, see: (a) Xiao, Q.; Jackson, J. J.; Basak, A.; Bowler, J. M.; Miller, B. G.; Zakarian, A. *Nat. Chem.* **2013**, *5*, 410. (b) Harad, K.; Kubo, M.; Horiuchi, H.; Ishii, A.; Esumi, T.; Hioki, H.; Fukuyama, Y. *J. Org. Chem.* **2015**, *80*, 7076.
(15) Kwak, J.-H.; Cho, Y. A.; Jang, J.-Y.; Seo, S.-Y.; Lee, H.; Hong, J. T.; Han, S. B.; Lee, K.; Kwak, Y.-S.; Jung, J.-K. *Tetrahedron* **2011**, *67*, 9401.
(16) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729.
(17) This low reaction temperature was required in order to prevent migration of the TBS moiety to the other phenolic oxygen within compound **9**.
(18) Yagoubi, M.; Cruz, A. C. F.; Nichols, P. L.; Elliot, R. L.; Willis, M. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 7958.
(19) See, for example: Lan, P.; Jackson, C. J.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2014**, *79*, 6759.
(20) Whelligan, D. K.; Thomson, D. W.; Taylor, D.; Hoelder, S. *J. Org. Chem.* **2010**, *75*, 11.
(21) A MOM protecting group was chosen because of the observed migration of the TBS group from one phenolic residue to the other within compound **9**.
(22) Berliner, M. A.; Belecki, K. *J. Org. Chem.* **2005**, *70*, 9618.
(23) (a) Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1995**, *36*, 8217. (b) Homsi, F.; Robin, S.; Rousseau, G. *Org. Synth.* **2000**, *77*, 206.
(24) Attempts to effect this iodination reaction using *N*-iodosuccinimide resulted in competing reaction at one or both of the allyl groups within substrate **20**.
(25) These conditions are the ones used in the Trost synthesis of (−)-galanthamine: Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
(26) This reduction was necessary because on attempting to hydrolyze the acetal unit within compound **24** the resulting aldehyde hydrate engaged in a hetero-Michael addition reaction with the enone moiety to form a γ-lactol. For a related example of such a process, see: Magnus, P.; Sane, N.; Fauber, B. P.; Lynch, V. *J. Am. Chem. Soc.* **2009**, *131*, 16045.
(27) A small amount of the epimeric allylic alcohol was formed during this reduction.
(28) The ethylene acetal equivalent of compound **25** proved almost completely resistant to hydrolysis under the same conditions.
(29) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(30) See, for example: (a) Satcharoen, V.; McLean, N. J.; Kemp, S. C.; Camp, N. P.; Brown, R. C. D. *Org. Lett.* **2007**, *9*, 1867. (b) Chen, J.-Q.; Xie, J.-H.; Bao, D.-H.; Liu, S.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 2714. (c) Zang, Y.; Ojima, I. *J. Org. Chem.* **2013**, *78*, 4013. (d) Choi, J.; Kim, H.; Park, S.; Tae, J. *Synlett* **2013**, *24*, 379.
(31) For intramolecular variants of such processes, see: Lan, P.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2014**, *79*, 2829.
(32) For a related reaction sequence leading to (−)-morphine, see: Koizumi, H.; Yokoshima, S.; Fukuyama, T. *Chem. - Asian J.* **2010**, *5*, 2192.

DOI: 10.1021/acs.orglett.6b01799
Org. Lett. 2016, 18, 3798−3801