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Enantioselective Total Synthesis of a Natural Iridoid

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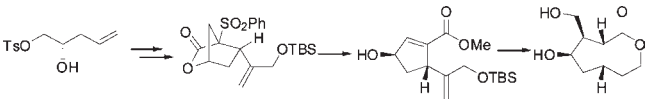
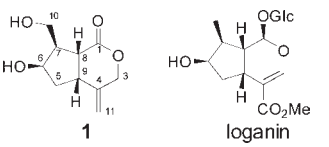
ABSTRACT



The first total synthesis of 6-hydroxy-7-(hydroxymethyl)-4-methylenehexahydrocyclopenta[*c*]pyran-1(3*H*)-one has been accomplished. A key feature of the synthesis includes facile construction of the bicyclic lactone intermediate via intramolecular Pd(0)-catalyzed allylic alkylation and the efficient transformation of this intermediate into the iridoid skeleton employing silicon tethered radical cyclization.

Iridoids are a large family of natural monoterpenoid products that are highly oxygenated and structurally characterized by a *cis*-fused cyclopenta[*c*]pyran ring system.[1] The various biological activities of iridoids have continuously attracted interests from both biologists and chemists.[2] The unique *cis*-fused cyclopenta[*c*]pyran ring system has presented a variety of challenges for chemical synthesis and in analysis of biological activities.[3] We have been interested in a recently reported iridoid lactone that is structurally related to loganin and consists of a C7-substituted C6-hydroxycyclopenta[*c*]lactone, as illustrated in Figure 1. Iridoid lactone **1** was isolated from the roots and rhizomes of *Nardostachys chinensis* Batalin (Valerianaceae).[4] This plant has been used as a Chinese folk medicine, and its roots and rhizomes exhibit a variety of biological activities, such as sedative, antimalarial, antinociceptive, cytotoxic, and enhancement of nerve growth factor activities.[5] However, the paucity of its key component **1** has hampered the systematic research of the iridoid, including structure–activity relationship (SAR) analysis and further pharmacological studies. Thus, we have worked on the development of an efficient synthetic route to the new iridoid lactone **1**. Herein we describe a concise and highly enantioselective synthesis of **1** that can be modulated to afford related iridoids.



1 loganin

Figure 1. Structures of iridoids.

Our retrosynthetic approach for iridoid lactone **1** is illustrated in Scheme 1. This process involves the efficient

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(1) (a) El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 649. (b) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173. (c) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2007**, *55*, 159.

(2) (a) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2007**, *55*, 689. (b) Tundis, R.; Loizzo, M. R.; Menichini, F.; Statti, G. A.; Menichini, F. *Mini-Rev. Med. Chem.* **2008**, *8*, 399. (c) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2009**, *57*, 765.

(3) For a review on iridoid synthesis, see: (a) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507. For recent selected highlights in synthesis, see: (b) Piccinini, P.; Vidari, G.; Zanoni, G. *J. Am. Chem. Soc.* **2004**, *126*, 5088. (c) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696. (d) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (e) D'Alfonson, A.; Pasi, M.; Porta, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2010**, *12*, 566. (f) Beckett, J. S.; Beckett, J. D.; Hofferberth, J. E. *Org. Lett.* **2010**, *12*, 1408. (g) Candish, L.; Lupton, D. W. *Org. Lett.* **2010**, *12*, 4836.

(4) Zhang, Y.; Lu, Y.; Zhang, L.; Zheng, Q.-T.; Xu, L.-Z.; Yang, S.-L. *J. Nat. Prod.* **2005**, *68*, 1131.

(5) Tanitsu, M.; Takaya, Y.; Akasaka, M.; Niwa, M.; Oshima, Y. *Phytochemistry* **2002**, *59*, 845 and references cited therein.

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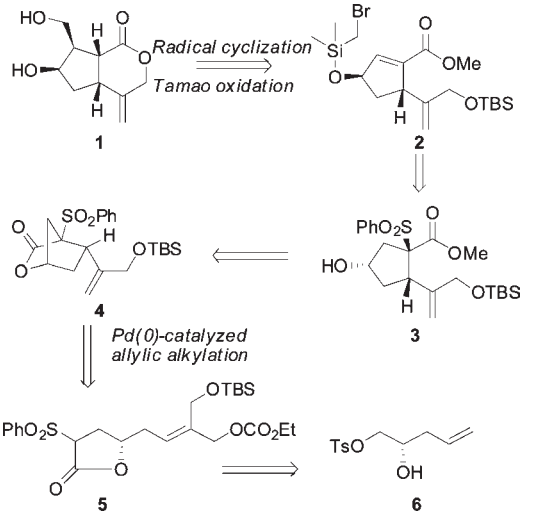
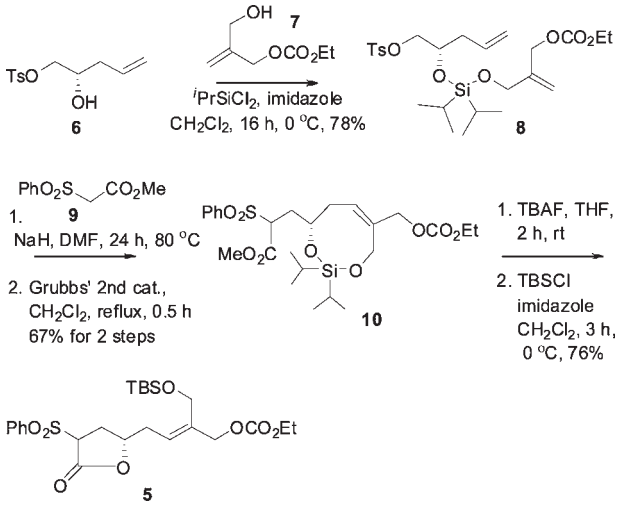
regio- and stereoselective elaboration of the C7-hydroxymethyl substituent through the silicon-tethered intramolecular radical cyclization[6] of cyclopentenol ether **2**, followed by Tamao–Fleming oxidation.[7] Its precursor cyclopentanol **3** is generated by functional group transformation from bicyclic lactone **4**, which can be efficiently constructed by the palladium-catalyzed cyclization of allylic carbonate **5** using the protocol developed by our group.[8] The allylic carbonate **5** was expected to be conveniently derived from the known hydroxy tosylate **6**.[9]

Scheme 1. Retrosynthetic Approach



The synthesis commenced with the preparation of the requisite γ-lactone **5** for Pd(0)-catalyzed allylic alkylation, as illustrated in Scheme 2. To address the trisubstituted alkene unit, we initially attempted olefin cross-metathesis of the allyl γ-lactone with the hydroxymethyl-substituted allyl carbonate to produce the Pd(0)-catalyzed cyclization precursor. However, the intermolecular cross-metathesis led to γ-lactone **5** with only 43% yield.[10] Thus, we turned our attention to silicon-tethered ring-closing metathesis (RCM),[11] which is considered superior in terms of entropic benefit and concomitant alcohol protection. Alkoxysilane **8** was prepared from the known hydroxy tosylate **6** with a 78% yield. Alkylation of tosylate **8** with the anion of benzenesulfonyl acetate **9** and subsequent RCM provided the cyclic bis-alkoxysilane **10**. Removal of the tethered silicon of bis-alkoxysilane **10** with TBAF and the spontaneous isomerization of the resulting hydroxy ester provided the γ-lactone intermediate, which was protected with TBSCl to afford allylic carbonate **5**.

Scheme 2. Synthesis of γ-Lactone **5**



We next conducted a survey of stereoselective Pd(0)-catalyzed cyclization of **5** under a variety of reaction conditions including ligands and solvents as summarized in Table 1. Stereoselective cyclization of **5** in the presence of $Pd(dppe)_2$ in THF afforded the desired product of **4** with a 91% yield along with a minor product **11** (entry 1). Cyclization of **5** in the presence of $Pd(PPh_3)_4$ resulted in low stereoselectivity regardless of the solvent (entries 3–5). Cyclization in the presence of $Pd(OAc)_2$ with dppp or dppb (entries 6 and 7) also showed good stereoselectivities, although the yield was slightly lower.

The excellent stereoselectivity is likely due to the presence of the silyloxymethyl substituent, given the lower stereoselectivity (10:1) for the disubstituted alkene **12** under the same conditions as shown in Scheme 3. This type of facial preference is well supported by our previous report.[12]

With the requisite building block **4** in hand, we focused our attention to the facile introduction of the hydroxymethyl

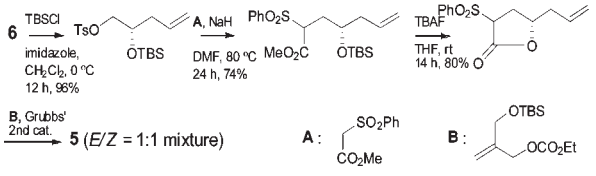
(6) For a review of silicon-tethered-radical cyclization, see: (a) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthisis* **1997**, *8*, 813. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253.

(7) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120.

(8) (a) Suh, Y.-G.; Jung, J.-K.; Kim, S.-A.; Shin, D.-Y.; Min, K.-H. *Tetrahedron Lett.* **1997**, *38*, 3911. (b) Suh, Y.-G.; Jung, J.-K.; Suh, B.-C.; Lee, Y.-C.; Kim, S.-A. *Tetrahedron Lett.* **1998**, *39*, 5377. (c) Suh, Y.-G.; Jung, J.-K.; Seo, S.-Y.; Min, K.-H.; Shin, D.-Y.; Lee, Y.-S.; Kim, S.-H.; Park, H.-J. *J. Org. Chem.* **2002**, *67*, 4127. (d) Seo, S.-Y.; Jung, J.-K.; Paek, S.-M.; Lee, Y.-S.; Kim, S.-H.; Lee, K.-O.; Suh, Y.-G. *Org. Lett.* **2004**, *6*, 429. (e) Paek, S.-M.; Seo, S.-Y.; Min, K.-H.; Shin, D.-M.; Chung, Y.-K.; Suh, Y.-G. *Heterocycles* **2007**, *71*, 1059.

(9) Klunder, J. M.; Onami, T.; Sharpless, K. B. *J. Org. Chem.* **1989**, *54*, 1295.

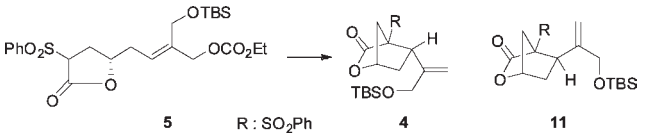
(10) When cross-metathesis was attempted using various solvents (CH_2Cl_2, toluene), catalysts (Grubbs' first- and second-generation catalysts, Grubbs–Hoveyda catalyst), and a microwave, disappointingly, the yield was no higher than 43% at any conditions.



(11) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702.

(12) Han, Y.-T.; Paek, S.-M.; Lee, S.; Jung, J.-W.; Jung, J.-K.; Seo, S.-Y.; Lee, J.; Suh, Y.-G. *Tetrahedron Lett.* **2010**, *51*, 2697.

Table 1. Pd(0)-Catalyzed Cyclization of **5**[a]

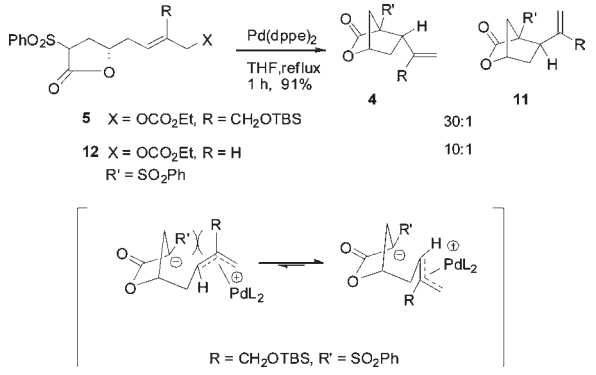


5 R : SO_2Ph **4** **11**

entry	catalyst	solvent	yield[b] (%)	ratio[c] (**4**:**11**)
1	$Pd(dppe)_2$	THF	91	30:1
2	$Pd(dppe)_2$	CH_2Cl_2	90	3.5:1
3	$Pd(PPh_3)_4$	THF	91	1:1
4	$Pd(PPh_3)_4$	CH_2Cl_2	90	2.5:1
5	$Pd(PPh_3)_4$	DMSO	78	1:1
6	$Pd(dppp)_2$[d]	THF	78	10:1
7	$Pd(dppb)_2$[d]	THF	89	25:1

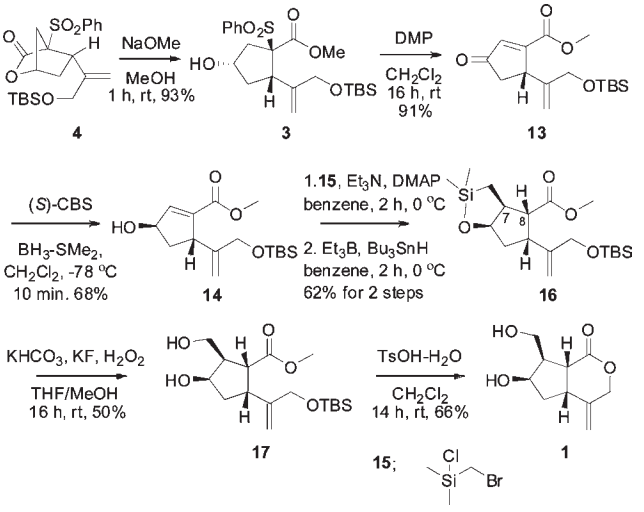
[a] All reactions were conducted under reflux conditions. [b] Isolated yields. [c] Determined by 300-MHz ^1H NMR spectra of the crude diastereomeric mixtures. [d] Premixed $Pd(OAc)_2$ and dppp/dppb in THF was added to a solution of **5**. dppe: bis(diphenylphosphino) ethane. dppp: bis(diphenylphosphino)propane. dppb: bis(diphenylphosphino)butane.

Scheme 3. Plausible Mechanism for High Stereoselectivity



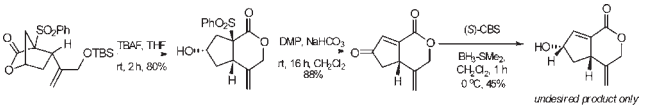
substituent at C7. Convenient methanolysis[13] of bicyclic lactone **4** afforded cyclopentanol **3**, which was subjected to Dess–Martin oxidation to produce enone **13** after concomitant β-elimination of sulfonate[14] (Scheme 4). At this stage, a direct α-hydroxymethylation with HCHO[15] or the introduction of a hydroxymethyl equivalent via α-methylenation with Eschenmoser's salt[16] as well as formylation with $HCO_2CH_2CF_3$[17] to the cyclopentanone did not provide satisfactory results. Stereoselective reduction of enone **13** with (*S*)-CBS[18] afforded cyclopentenol **14** with the correct stereochemistry.

Scheme 4. Completion of Synthesis of Iridoid **1**



Silylation of cyclopentenol **14** with (bromomethyl) chlorodimethyl silane **15** yielded the bromosilyl ether, which was directly subjected to the radical cyclization.[19] Intramolecular radical cyclization of the labile silyl ether intermediate with Et_3B[20] and Bu_3SnH afforded the desired *cis*-fused oxasilole **16** in good yield. The newly generated C8 stereogenic center could be established by an intramolecular hydrogen atom transfer from the proximal silylmethyl group to C8.[21] Subsequent Tamao–Fleming oxidation of oxasilole **16** gave diol **17**. Finally, lactone iridoid **1** was obtained in good yield by TBS deprotection with TsOH,[22] followed by a concomintant lactonization. The structure of **1** was confirmed by comparison of its spectral data with those of the authentic sample (optical rotation, ^1H NMR, ^{13}C NMR, IR, HRMS).

(13) Initially, deprotection of TBS with TBAF resulted in isomerization of the bicyclic lactone, and oxidation of cyclopentanol yielded elimination of cyclopentenone with an excellent yield. Disappointingly, stereoselective reduction of bicyclic cyclopentenone was unsuccessful as shown below.



(14) Swern oxidation/PCC oxidation/Ley oxidation followed by a diazabicycloundecene (DBU) workup to effect β-elimination of the resulting γ-sulfonyl ketone: (a) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346. (b) Cheng, W.-C.; Kurth, M. K. *J. Org. Chem.* **2002**, *67*, 4387. Acid-catalyzed β-elimination of sulfonate: (c) Yoshida, T.; Saito, S. *Chem. Lett.* **1982**, 165.

(15) Kokubo, M.; Ogawa, C.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6909 and references therein.

(16) Schreiber, J.; Maag, H.; Hashimoto, N.; Eschenmoser, A. *Angew. Chem., Int. Ed.* **1971**, *10*, 330.

(17) Zayia, G. H. *Org. Lett.* **1999**, *1*, 989.

(18) (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Robertson, J.; Meo, P.; Dallimore, J. W. P.; Doyle, B. M.; Hoarau, C. *Org. Lett.* **2004**, *6*, 3861. (c) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *J. Org. Chem.* **2003**, *68*, 5917.

(19) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. (c) Jenkins, P. R.; Wood, A. J. *Tetrahedron Lett.* **1997**, *38*, 1853. (d) Kessabi, F. M.; Winkler, T.; Luft, J. A. R.; Houk, K. N. *Org. Lett.* **2008**, *10*, 2255.

(20) Matsumoto, K.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1992**, *33*, 7031 and references therein.

(21) (a) Carroll, G. L.; Allan, A. K.; Schwaebe, M. K.; Little, R. D. *Org. Lett.* **2000**, *2*, 2531. (b) Devin, P.; Fensterbank, L.; Malacria, M. *J. Org. Chem.* **1998**, *63*, 6764.

(22) (a) Thomas, E. J.; Williams, A. C. *J. Chem. Soc., Chem. Commun.* **1987**, *13*, 992. (b) Jahn, U.; Hartmann, P.; Kaasalainen, E. *Org. Lett.* **2004**, *6*, 257.

In summary, the first total synthesis of (+)-6-hydroxy-7-(hydroxymethyl)-4-methylenehexahydrocyclopenta-[*c*]pyran-1(3*H*)-one **1** was accomplished in 13 steps. The key features of the synthesis involve the stereoselective and efficient preparation of the cyclopentanol intermediate via Pd(0)-catalyzed cyclization and then the silicon-tethered radical cyclization followed by Tamao−Fleming oxidation for the stereoselective introduction of the C7-hydroxymethyl substituent. This versatile synthetic approach is expected to be widely utilized for the syntheses of iridoids and iridoalkaloids.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.