ORGANIC LETTERS

2010
Vol. 12, No. 3
596−599

Synthesis and Assignment of Absolute Configuration of the Iridoid 9-Deoxygelsemide

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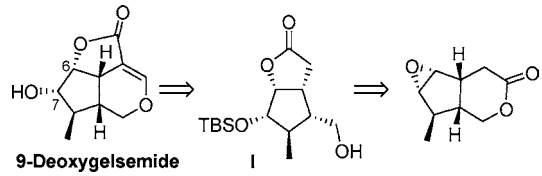
Received December 5, 2009

ABSTRACT



The first enantioselective synthesis of 9-deoxygelsemide, belonging to a rare group of iridoids isolated from *Gelsemium* plants, is described. The key synthetic steps are a variant of the Woodward−Prevost reaction to install the characteristic *cis*-α-1,2-dioxygenated system at C-6 and C-7 with complete diastereoselectivity. Construction of the dihydropyran ring was achieved via formylation of lactone I, followed by dehydration of the corresponding lactol. The synthesis allowed assignment of absolute configuration to 9-deoxygelsemide and related iridoids.

The iridoid 9-deoxygelsemide **1** was isolated in 1994 from the plant *Gelsemium elegans* Benth.,[1] which is the origin of "Yakatsu",[2] one of the ancient folkloric medicines stored in the Shosoin imperial repository in Japan.[3] Although the complete structure of **1** was unequivocally established by Takayama et al., the absolute configuration has not yet been determined. 9-Deoxygelsemide presents a variety of challenges for chemical synthesis, including the assembly of five continuous stereocenters on a cyclopentane ring and a *cis*-α-1,2-dioxygenated moiety at C-6 and C-7, which is quite unusual in iridoid structures, occurring only in the formulas of three other related iridoids **2**−**4**, occurring with **1** in the leaves of *G. elegans* (Figure 1).[4,5]

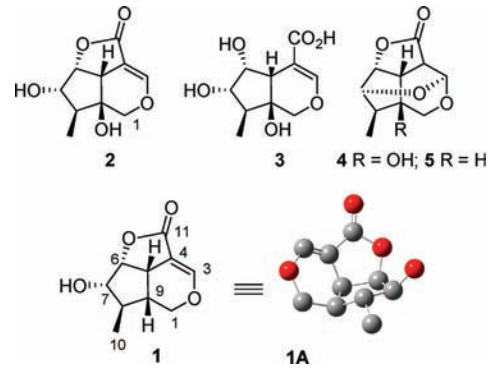


Figure 1. Structures of 9-deoxygelsemide (**1**), its PM3 model **1A** (H omitted), and plant iridoids (**2**−**5**) of the same group.

Of particular concern in our synthetic planning was the placement of the free 7-OH group, which resides inside the

(1) Takayama, H.; MoroHoshi, Y.; Kitajima, M.; Aimi, N.; Wongseripipatana, S.; Ponglux, D.; Sakai, S. *Nat. Prod. Lett.* **1994**, *5*, 15–20.

(2) Kitajima, M.; Aray, Y.; Takayma, H.; Aimi, N. *Proc. Jpn. Acad., Ser. B* **1998**, *74*, 159–163.

(3) This large warehouse contained about 8870 items, mainly used for daily life, such as books, furniture, costumes, handicrafts, musical instruments, food vessels, medicines, etc. They belonged to the Emperor Shomu, about 1200 years ago, and after his death, they were donated by the Empress Komyo to the Buddhist Todaiji temple in Nara (Japan).

(4) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2007**, *55*, 689–728, and references therein.

(5) Kogure, N.; Ishii, N.; Kobayashi, H.; Kitajima, M.; Wongseripipatana, S.; Takayama, H. *Chem. Pharm. Bull.* **2008**, *56*, 870–872.

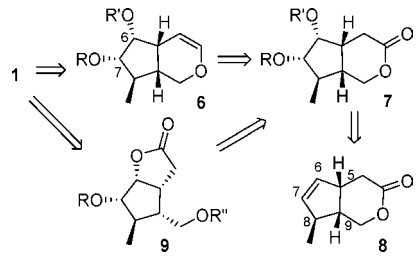
10.1021/ol902809v
Published on Web 12/28/2009

hindered concavity of the target tricyclic structure **1**, as the PM3 model **1A** clearly shows (Figure 1). To add another synthetic difficulty, a recent paper reporting the isolation of compound **4** reveals that the 7-OH group is particularly prone to add intramolecularly across the conjugated enol ether double bond to give the apparently more strained tetracyclic caged structure **5** (Figure 1).[5]

Several imaginative routes have been delineated for the stereoselective synthesis of iridoids,[6] many of which are enlightened by a challenging structural complexity and a wide spectrum of biological properties;[4] however, no total synthesis of compounds **1**−**4** has been published so far. Herein we describe a concise and highly convergent enantioselective approach to 9-deoxygelsemide **1** that, in principle, can be modulated to afford also the related iridoids **2**−**4**. In particular, this expeditious route features an innovative general approach to install the crucial *cis*-6α,7α-configured oxygenated pattern on the cyclopentane ring.

Our experience on iridoid synthesis indicated a suitable starting material in the readily available δ-lactone **8**,[6e] which contained all carbons of target compound **1**, except C-11. Retrosynthetically, we envisioned to add a *cis*-α-diol or an equivalent group to the double bond C-6/C-7 of lactone **8** to give **7**, before building the remaining γ-lactone ring of **1** on dihydropyran **6**. Alternatively, δ-lactone **7** might be isomerized to γ-lactone **9**, before completing the synthesis of **1** by installing the remaining dihydropyran ring (Scheme 1).

Scheme 1. Retrosynthetic Analysis of 9-Deoxygelsemide **1**



According to the more common absolute configuration of naturally occurring iridoids,[4] the enantioselective synthesis of **1** thus began from the (5*S*,8*S*,9*R*)-enantiomer **8**.[6e,7]

Oxidation of cyclopentene **8** was first attempted by standard methods; however, rather unexpectedly, the olefin was inert to Sharpless dihydroxylation conditions,[8] while, on exposure to *m*-CPBA, it returned a nearly 1:1, chromatographically inseparable, mixture of α- and β-epoxides **10** and **11**. The lack of diastereoselectivity in the epoxidation reaction was likely due to comparable effects exerted by the sterically hindered β-methyl group at C-8 and the folded shape of the *cis*-fused bicyclic structure **8** in directing the oxidant species on either faces of the double bond. In consideration of the presumably poor diastereocontrol exerted by substrate **8** on the addition of other external electrophiles to the double bond, we envisioned a stereospecific intramolecular reaction as a means to convert olefin **8** to a suitable precursor of compound **1**. According to this plan, compound **8** was converted to known iodo-lactone **12**;[6e] then protected **12a** was exposed to a couple of oxygen nucleophiles, with the aim to insert an α-configured oxygenated function at C-7 by iodine displacement under S_N2 conditions. However, treatment of **12a** either with AcOK in DMF at rt or with AgOTf in Me_2CO-H_2O, 9:1, at rt, mainly returned the E2 product **13a**, proving the difficult access of reagents to the concave side of the *cis*-fused diquinane structure **12a**.

To circumvent this stereochemical issue, we studied an indirect diastereoselective route to α-epoxide **10** and subsequent manipulation of the formed oxirane ring to afford an advanced precursor of the 6-α-acyl-7-α-hydroxyl moiety of iridoid **1**. According to this plan, DBU deprotonation of alcohol **12**[6e] in toluene at 50 °C initiated a cascade reaction leading to α-epoxide **10** via translactonisation of γ-lactone, followed by intramolecular S_N2 displacement of iodine. Chromatographically and diastereomerically pure (6*R*,7*S*)-epoxide **10** was obtained in 85% yield, accompanied by 8% elimination product **13**. Subsequently, oxirane ring-opening with 57% aq HI at −78 °C smoothly afforded a mixture of regioisomeric iodohydrins **14** and **15**, accompanied by lactone **12** [**15**:**14** ≥ 95:5; (**14**+**15**):**12**, about 6:1 (NMR)], in ≥95% combined yield. Clearly, lactone **12** was formed by acid catalyzed isomerization of **14**. After acetylation of the entire mixture, acetates **16** and **17** were readily separated by column chromatography from recovered lactone **12b**, which was recycled to starting epoxide **10** in a standard manner. The stereostructure of major iodolactone **17**, obtained in 77% overall yield from epoxide **10,** was established by NMR analysis. In fact, NOE experiments and the vicinal coupling constants $J_{5-6} = J_{6-7} = J_{7-8} = 10.1$ Hz, nicely agreed with the stereochemistry at the four consecutive stereocenters C(5)−C(8), as shown in **17** (Figure 2).[1,5,9]

Subsequently, we examined the feasibility of converting both regioisomeric acetates **16** and **17** to the same α-con-

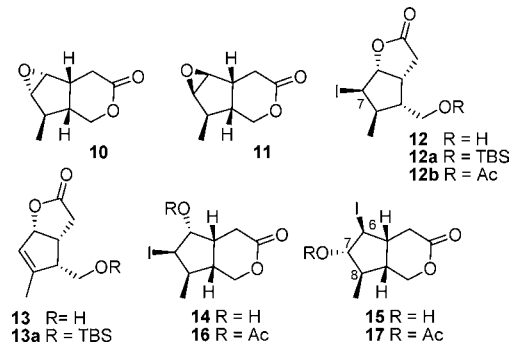
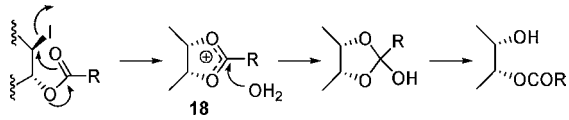


Figure 2. Structures of compounds **10**−**17**.

(6) For selected iridoid syntheses see: (a) Callant, P.; Storme, P.; Van der Eycken, E.; Vanderwalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797–5800. (b) Trost, B. M.; Balkovec, J. M.; Mao, M. K. T. *J. Am. Chem. Soc.* **1986**, *108*, 4974–4983. (c) Tietze, L. F.; Fischer, R.; Remberg, G. *Liebigs Ann. Chem.* **1987**, 971–975. (d) Santangelo, E. M.; Roticci, D.; Liblikas, I.; Norin, T.; Unelius, C. R. *J. Org. Chem.* **2001**, *66*, 5384–5387. (e) Piccinini, P.; Vidari, G.; Zanoni, G. *J. Am. Chem. Soc.* **2004**, *126*, 5088–5089. (f) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696–3697.

figured *cis*-monoacyl-diol moiety at C-6 and C-7. To this goal, anchimeric assistance of the secondary acetate group in **16** and **17** could conveniently be exploited for displacing the vicinal *trans*-iodine in accordance to a Woodward−Prévost-like S_N2 mechanism, which would then proceed through the same 2-alkyl-1,3-dioxolan-3-ylium ion **18** (Scheme 2).[10] In this context, a poorly known protocol developed

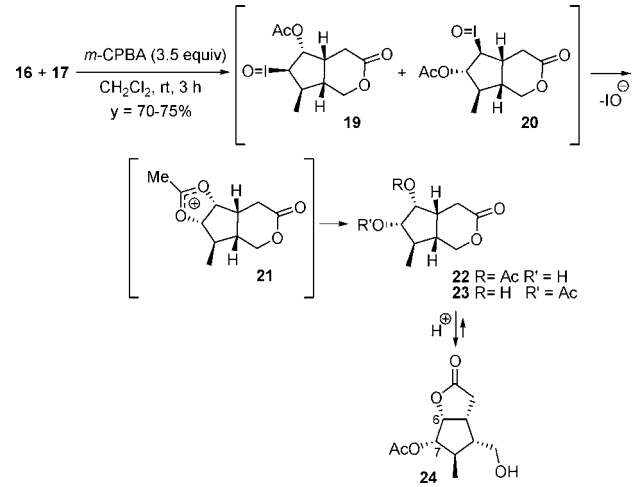
Scheme 2. Last Steps of the Woodward−Prevost Reaction



years ago by Woodgate et al. for displacing iodine from *trans*-1-acyloxy-2-iodocyclohexanes to give *cis*-cyclohexanediol derivatives, drew our attention.[11] The authors noticed inversion of configuration with iodocyclohexyl acetate and trifluoroacetate when exposed to *m*-CPBA to give *cis*-*vic*-hydroxy-esters.[11] A mechanism similar to that depicted in Scheme 2 was proposed, in which a iodoso-compound, formed by peracid oxidation of iodine, provided a better leaving group than univalent halogen.[11] To our knowledge, this reaction has been reported so far only for the simple iodocyclohexyl esters and it has never been employed in the synthesis of natural products. Extension of the method to more rigid substrates, like the bicyclic iodocyclopentanes **16** and **17**, seemed, however, to be feasible, in spite of the higher steric strain required to attain a **18**-like planar ion in the step of iodine removal. In the event, exposure of iodoacetates **16** and **17** to excess *m*-CPBA slowly afforded, in reproducible 70−75% yields, an inseparable mixture of isomeric lactones **22, 23**, and **24** (2:1:5 by NMR). Presumably, acetates **16** and **17** at first gave iodoso intermediates **19** and **20**, respectively, which converged to lactones **22** and **23** through the same oxonium cation **21** (Scheme 3); subsequently, δ-lactone **23** mainly converted to γ-lactone **24** by equilibration under acidic reaction conditions.

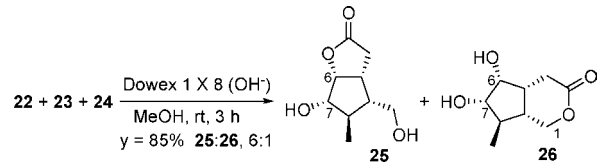
The higher stabilty of five-membered γ-lactone **24**, compared with δ-lactone **23**, suggested to us a convenient procedure to readily convert the three lactones **22**−**24** to a common **9**-like advanced intermediate of 9-deoxygelsemide synthesis. As anticipated, upon exposure of the crude mixture **22**−**24** to Dowex 1 × 8 (OH^- form) in MeOH at rt, smooth hydrolysis of the acetate groups occurred, followed by hydroxy-lactone interconversion to deliver a thermodynamic mixture of isomeric lactones **25** and **26** in 85% yield (Scheme

Scheme 3. Diastereoconvergent Conversion of Iodoacetates 16 and 17 to 6α,7α-Diol Derivatives **22**−**24**



4).[12] The two compounds were identified and quantified (**25**:**26**, 6:1) by diagnostic, well separated, ^{1}H NMR signals; for

Scheme 4. Convergent Transformation of Isomers **22**−**24** Mainly to Lactone **25**



example, the proton 6-H of γ-lactone **25** resonated at δ 4.87 (1H, dd, J = 6.4 and 4.8 Hz), while the signal for 1-H of δ-lactone **26** occurred at 4.30 (1H, dd, J = 11.4 and 4.3 Hz).

Having secured an efficient and completely diastereoselective route to install all the five stereocenters of the target compound **1**, we then focused our efforts on the construction of the remaining dihydropyran ring of iridoid **1**. To this goal, at first dehydration of hemiacetal **28** was envisioned to provide the straightest access to the enol ether moiety of compound **1**.

Claisen formylation of lactone **25**, followed by an acidic workup, afforded directly the expected hemiacetal in 62% yield (Scheme 5).[12] Its ^{1}H NMR spectrum showed the presence of ≥90% tricyclic β-anomer **28**, accompanied by an undentified minor compound. The stereochemistry at C-3 and C-4 of lactol **28** was assigned on the basis of the vicinal coupling constant between 3-H and 4-H ($J_{3,4} \leq 0.5$ Hz),

(7) Iridoid numbering was used for all reported compounds.

(8) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768–2771.

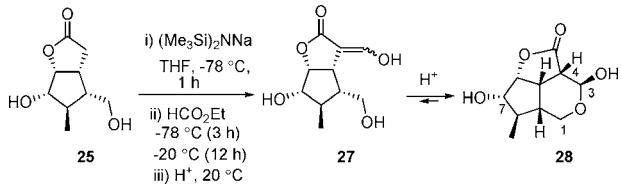
(9) Boros, C. A.; Stermitz, F. R. *J. Nat Prod* **1990**, *53*, 1055–1147, and references cited therein.

(10) Woodward, R. B.; Brutcher, F. V., Jr. *J. Am. Chem. Soc.* **1958**, *80*, 209–211.

(11) Cambie, R. C.; Chambers, D.; Lindsay, B. G.; Rutledge, P. S.; Woodgate, P. D. *J. Chem. Soc., Perkin Trans. I* **1980**, 822–827.

(12) The inseparable mixture of lactones **25** and **26** was used in the following steps, as products formed from γ-lactone **25** were readily separated by flash column chromatography from those originated from **26**. Subsequent reported yields are, therefore, referred to the estimated amount of **25** in the mixture with **26**.

Scheme 5. Formylation of Lactone **25** to Give Hemiacetal **28**



which indicated a dihedral angle of 90°, as reported for iridoids showing the same stereostructure.[5]

The *cis*-relationship between the 3-OH and 4-H suggested to us that elimination of H_2O from **28** to give **1** would require E1 conditions. Compound **28** was, therefore, exposed to glacial AcOH at reflux, to induce formation of a **29**-like oxonium ion with the expectation that it would easily lose the enolic proton to afford **1**. In the event, the reaction proceeded readily; however, no signal attributable to the expected unsaturated γ-lactone **1** was observed in the ^{1}H NMR spectrum of the crude reaction mixture; instead, tetracyclic acetal **5** was subsequently isolated in 35% yield. Compound **5** likely originated from addition of 7-OH onto oxonium ion **29**, which derived either directly from **28** or by reprotonation of first formed enol ether **1**. An identical product was obtained by exposing **28** either to ethereal BF_3 or *p*-TsOH in CH_2Cl_2. These results clearly indicated the need to protect the 7-OH of diol **28** prior to the elimination of the hemiacetalic 3-OH; moreover, subsequent unmasking of the secondary protected alcohol at C-7 had to be realized under mild, nearly neutral conditions. According to this synthetic plan, diol **25**[12] was converted to the bis-silyl ether **30** which, upon exposure to PPTS in *i*-PrOH−CH_2Cl_2 (1:1)[13] and clean chromatographic separation of products, afforded monosilyl ether **31** and free diol **25**, in unoptimized 50% and 35% yield, respectively. Recovered **25** was resubmitted to another cycle of protection−deprotection steps to raise overall yield of **31** to 60% from **25**. The remaining three steps from lactone **31** to 9-deoxygelsemide **1** were accomplished uneventfully in 33% overall yield. As anticipated, formylation of **31** under our standard conditions gave directly hemiacetal **32** (≥90% β-isomer), which was smoothly dehydrated to enol ether **33** upon exposure to MsCl and Et_3N in CH_2Cl_2. Final unmasking of the 7-OH in **33** to give **1** was obtained with Bu_4NF in moist THF to controll the basicity of fluoride anion (Figure 3).[14]

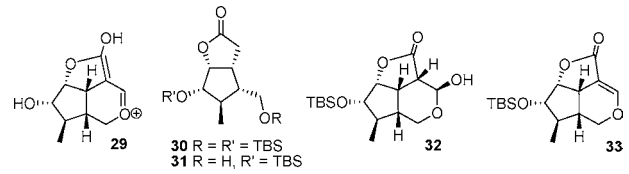


Figure 3. Structures of compounds **29**−**33**.

The ^{1}H and ^{13}C NMR spectra of synthetic **1** were identical to those described for 9-deoxygelsemide.[1] In addition, the CD spectrum of **1** [$\Delta\epsilon$ (MeOH) −10.0 (247 nm)] was in excellent agreement with the data of the natural iridoid [$\Delta\epsilon$ (MeOH) −7.9 (247 nm)].[1] Thus, the sterecontrolled synthesis of **1** from (5*S*,8*S*,9*R*)-lactone **8**[6e] proved the absolute configuration 5*S*,6*R*,7*S*,8*R*,9*R* of 9-deoxygelsemide unequivocally. We assume that also the related iridoids **2**−**4** belong to the same enantiomeric family for biosynthetic reasons.[5]

In summary, this first total synthesis of 9-deoxygelsemide **1** was achieved in 11 steps[15] and 6.6% overall yield from the enantiomerically pure lactone **8**,[6e] which confirmed to be a versatile building block for iridoid synthesis. En route, we also accomplished the synthesis of the tetracyclic caged backbone of the naturally occurring iridoid GEIR-1 (**4**).[5]

Synthetic **1** showed an $EC_{50} = 22.6 \pm 0.9$ μM against A549 lung tumor cells.

Acknowledgment. Financial support of the MIUR (funds PRIN) and bioactivity tests done by Dr. Mayra Paolillo, Università di Pavia, are greatly acknowledged.

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

OL902809V

(13) Acharya, H. P.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 3329–3343.

(14) Clark, J. H. *Chem. Rev* **1980**, *80*, 429–452, and references cited therein.

(15) In summary, the entire synthetic sequence is: **8**→**12**→**10**→**14**+**15**→**16**+**17**→**22**−**24**→**26**+**25**→**30**→**31**→**32**→**33**→**1**.