Organic LETTERS

Letter

pubs.acs.org/OrgLett

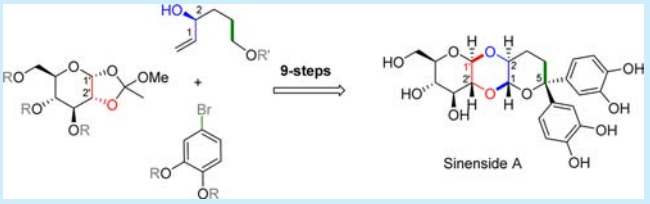
Total Synthesis of Sinenside A

Paresh M. Vadhadiya and Chepuri V. Ramana*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. HomiBhabha Road, Pune 411008, India

Supporting Information

ABSTRACT: The first total synthesis of norlignan glucoside sinenside A has been accomplished. An intramolecular acetalization reaction has been employed as the key skeletal construct to forge the central cyclic disaccharide core. The *trans*-1,2-diol configuration present in the cyclic disaccharide of this natural product is unique and has been addressed by setting this configuration at the beginning. A 1,2-orthoester group has been selected as a handle for both sp glycosidation and for differentiation of the C2′-OH (that participates in the key acetalization reaction) of the sugar unit.



In 2012, Ning Li and co-workers isolated two novel norlignan glucosides, namely sinensides A (**1**) and B (**2**) (Figure 1), along with six known norlignan glucosides from the ethanolic extract of the *Curculigo sinensis* plant.[1] Species belonging to the genus *Curculigo* (Hypoxidaceae) are widely encountered in the tropical and subtropical areas of Australia, Asia, South America, and Africa. In ancient China, various species of these plants were used in folk medicine to treat child pneumonia, rheumatism, and dysmenorrhea. In other instances, they have served as antiaging tonics. In a preliminary screening, the norlignan glucosides **1** and **2** showed strong 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity with IC_{50} values comparable to that of the positive control ascorbic acid (IC_{50} = 45.84 μM). The structural interpretations were performed by a variety of spectroscopic tools including 1D/2D NMR, HRESI-MS, and hydrolysis experiments. A close examination of the structures of these isolated norlignans indicates the involvement of novel rearrangements in their formation. Among them, sinenside A attracts considerable interest because of its novel structural architecture.[2]

The central skeleton of sinenside A (**1**) is characterized by a unique cyclic disaccharide (or saccharide dianhydride) in which two pyranose residues are fused with a challenging 1,2-*trans*-configuration.[3] The presence of a *gem*-diaryl (with free phenolic OH groups) unit on one of the tetrahydropyran moieties adds further complexity. Symmetric saccharide dianhydrides have been isolated as part of a complex mixture when the corresponding monomers were treated with acids[4] or anhydrous HF[5] or during the hydrolysis of polysaccharide,[6] or they have been synthesized selectively by employing cycloglycosidation.[7] There are three reports on cycloglycosidation leading to dianhydrides employing either trichloracetimidyl or thiomethyl glycosides.[8] Nonetheless, in all three cases, the products resulted in a *cis*-1,2-diol configuration in both of the pyranosyl residues (Figure 2). In contrast, in sinenside A (**1**), a *trans*-vicinal diol configuration is present on the sugar pyranose unit, which adds another challenge in its synthesis.

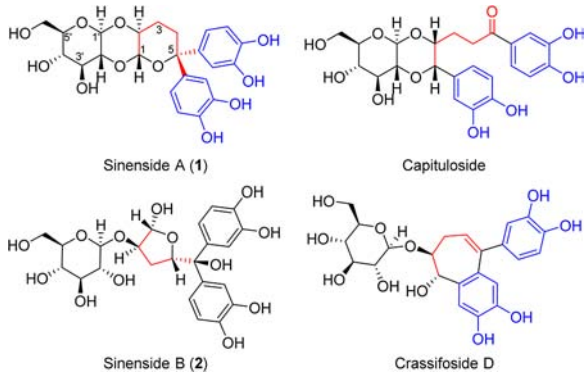


Figure 1. Structures of norlignan glycosides isolated from *Curculigo sinensis*.

In this context, an early installation of the β-glucoside link present in **1** was planned and the desired tricyclic core of sinenside A (**1**) would be constructed from the aldehyde via intramolecular acetalization, with an olefin unit serving as a surrogate for this aldehyde group (Figure 3). The orthoester **3** and tertiary alcohols **4** were selected as partners for the key glycosidation reaction, which was expected to give rise to exclusive β-anomeric selectivity.[9]

Our work in this direction commenced with an examination of the glycosidation of the known orthoester **3** with two different glycosyl acceptors **4a** (see the Supporting Information for the preparation) and **4b** (Scheme 1).[10] The acceptor **4a** brings with it the complete carbon framework, and a successful glycosidation with **4a** was expected to provide a product that could be directly converted into a analogue of **1** in two steps. However, the glycosidation of **4a** with orthoester **3** using $BF_3 \cdot Et_2O$ (0.15 equiv) in dichloromethane in the presence of 4 Å molecular sieves gave the β-glucoside **5** along with the cyclized ether **6**.[11] This undesired elimination and/or cyclization prior

Received: February 17, 2015
Published: March 12, 2015

DOI: 10.1021/acs.orglett.5b00505
Org. Lett. 2015, 17, 1724−1727

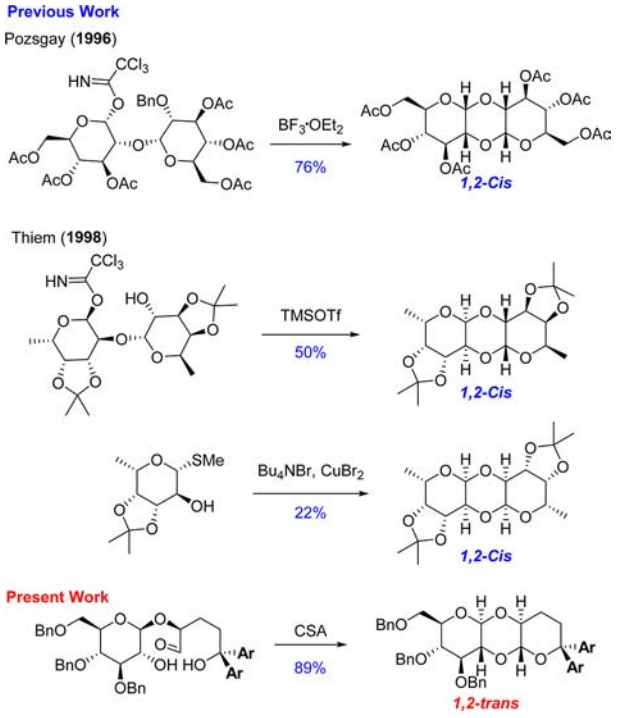


Figure 2. Intramolecular glycosylation strategies reported for the construction of the aldohexopyranose dianhydrides.

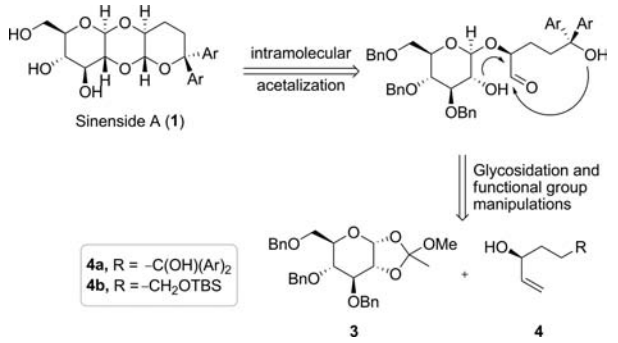
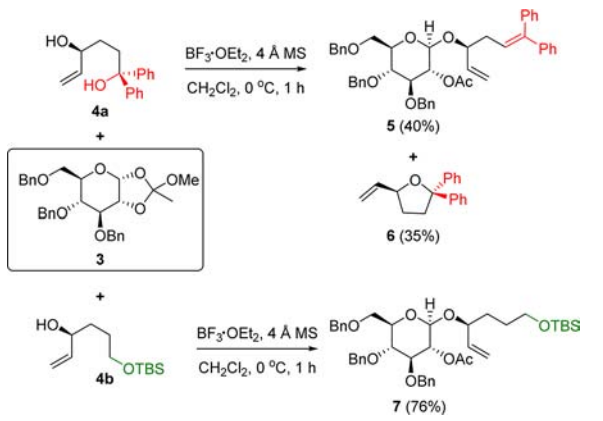


Figure 3. Our key retrosynthetic disconnections for sinenside A.

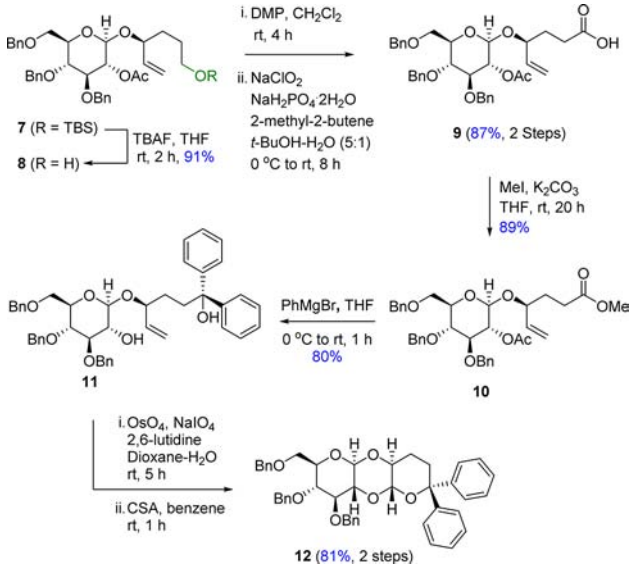
Scheme 1. Optimization of Glycosidation Reaction



to the glycosidation reaction prompted us to employ the simple allylic alcohol **4b** as an acceptor. The glycosidation of **4b** with **3** proceeded smoothly and provided exclusively the β-glucoside **7** in 76% yield.

The deprotection of the TBS group in compound **7** was carried out with TBAF to obtain the alcohol **8** in 91% yield (Scheme 2). Next, the alcohol **8** was subjected to a two-stage

Scheme 2. Construction of the Central Tricyclic Core of Sinenside A



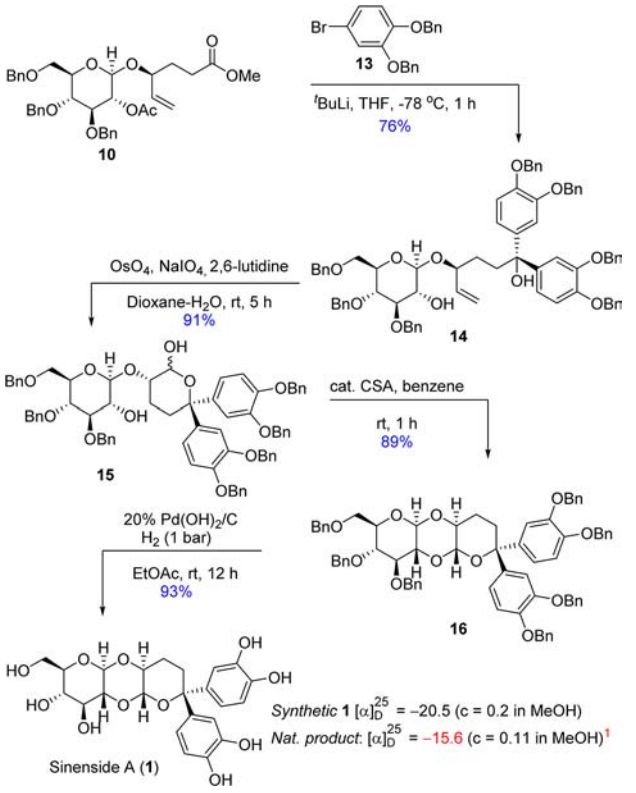
oxidation with Dess–Martin periodinane followed by further oxidation of the resulting intermediate aldehyde under Pinnick conditions to obtain the acid **9** in 87% yield over two steps.[12] Subsequent methylation of acid **9** with MeI in the presence of K_2CO_3 in dry THF gave the ester **10**.[13]

To quickly examine the proposed intramolecular acetalization, the key ester **10** was subjected to Grignard reaction with excess phenylmagnesium bromide. The reaction proceeded smoothly, providing the diol **11**. Oxidative cleavage of the olefin unit in diol **11** was carried out with $OsO_4/NaIO_4$ in the presence of 2,6-lutidine.[14] The intermediate aldehyde was immediately subjected to acetalization employing a catalytic amount of CSA in benzene to afford the tricyclic compound **12** in 81% yield over two steps.[15] Part of the ^{1}H NMR spectrum of **12** in $CDCl_3$ was comparable with that of the natural product. For example, the C(1)–H appeared as a singlet at 4.69 ppm [4.72 (s)] and the C(2)–H appeared at 4.23 ppm (J = 8.9 Hz) [3.77–3.79 (m)] as a triplet, which are comparable with the data reported for the natural product.[1]

After this success in building the complete core of sinenside A, we next proceeded toward the total synthesis of sinenside A (Scheme 3). The direct preparation of the Mg-based Grignard reagent using 3,4-bis(benzyloxy)bromobenzene **13** was found to be a problem.[16] Alternatively, by employing ^{t}BuLi for halogen–metal exchange, the diaryl addition to ester could be successfully conducted to obtain the diol **14** in 76% yield.[17] Subsequently, the resulting diol **14** was subjected to the oxidative olefin cleavage using $OsO_4/NaIO_4$/2,6-lutidine to afford an anomeric mixture of lactols **15**. An examination of the spectra of **15** revealed that the tertiary hydroxyl group had taken part in lactol formation. Next, the treatment of lactols **15** with a catalytic amount of CSA in benzene at rt directly gave the desired tricyclic compound **16** in 89% yield. Hydrogenolysis of the benzyl ethers in **16** required substantial experimentation. Under standard conditions (employing 10% Pd–C in methanol at 1 bar), the reaction was sluggish. Increasing either the H_2

DOI: 10.1021/acs.orglett.5b00505
Org. Lett. 2015, 17, 1724–1727

Scheme 3. Total Synthesis of Sinenside A (1)



pressure or prolonging the reaction for a longer period led to partial hydrogenolysis of the O−C(Ar)$_2$ bond as well. After varying the catalyst/solvents, it was observed that when we employed 20% Pd(OH)$_2$/C in EtOAc, exclusive hydrogenolysis of the benzyl ethers in **16** proceeded smoothly at 1 bar within 12 h, affording the natural product sinenside A (**1**) in quantitative yield. The spectral and analytical data of synthetic **1** were in full agreement (see the Supporting Information for comparison tables), and the specific rotation measured [−20.5 (c = 0.2 in MeOH)] was close to the values reported for the natural product [−15.6 (c = 0.11 in MeOH)].

In conclusion, the first total synthesis of the sinenside A has been completed in nine steps from readily accessible starting materials. The key step involves an intramolecular acetalization that directly affords the target parent tricyclic ring system. The approach adopted is divergent in nature and should be usable for the preparation of various analogues of sinenside A, along with the other norlignans of the same family.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data for all the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: vr.chepuri@ncl.res.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.V.R. and P.M.V. thank CSIR (India) for funding this project (12 FYP ORIGIN program, CSC0108) and for a fellowship to P.M.V.

■ REFERENCES

(1) Li, N.; Li, S.-P.; Wang, K.-J.; Yan, G.-Q.; Zhu, Y.-Y. *Carbohydr. Res.* **2012**, *351*, 64−67.
(2) (a) Lee, S. S.; Chang, W. L.; Chen, C. H. *Tetrahedron Lett.* **1996**, *37*, 4405−4408. (b) Di, L.; Wang, K.-J.; Zhu, C.-C.; Li, N. *Bull. Korean Chem. Soc.* **2010**, *31*, 2999−3002.
(3) (a) Gattuso, G.; Nepogodiev, S. A.; Stoddart, J. F. *Chem. Rev.* **1998**, *98*, 1919−1958. (b) Jung, K. H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423−4442.
(4) (a) Larsson, K.; Samuelso, O. *Acta Chem. Scand.* **1972**, *26*, 837−839. (b) Fujiwara, T.; Arai, K. *Carbohydr. Res.* **1979**, *69*, 107−115. (c) Kennedy, I. A.; Hemscheidt, T.; Britten, J. F.; Spenser, I. D. *Can. J. Chem.* **1995**, *73*, 1329−1337.
(5) (a) Bock, K.; Pedersen, C. *Acta Chem. Scand.* **1972**, *26*, 2360−2366. (b) Defaye, J.; Gadelle, A.; Pedersen, C. *Carbohydr. Res.* **1985**, *136*, 53−65. (c) Komalavilas, P.; Mort, A. J. *Carbohydr. Res.* **1989**, *189*, 261−272. (d) Bock, K.; Pedersen, C.; Defaye, J.; Gadelle, A. *Carbohydr. Res.* **1991**, *216*, 141−148. (e) Fernandez, J. M. G.; Defaye, J. *Tetrahedron Lett.* **1992**, *33*, 7861−7864. (f) Defaye, J.; Fernandez, J. M. G. *Carbohydr. Res.* **1992**, *237*, 223−247. (g) Defaye, J.; Fernandez, J. M. G. *Carbohydr. Res.* **1994**, *251*, 17−31.
(6) (a) Larsson, K. *Carbohydr. Res.* **1975**, *44*, 199−203. (b) Fujiwara, T.; Arai, K. *Carbohydr. Res.* **1979**, *69*, 97−105. (c) Capek, P.; Uhrin, D.; Rosik, J.; Kardosova, A.; Toman, R.; Mihalov, V. *Carbohydr. Res.* **1988**, *182*, 160−165. (d) Jansson, P. E.; Lindberg, B.; Ogunlesi, M.; Orebamjo, T. *Carbohydr. Res.* **1991**, *214*, 281−287.
(7) (a) Gagnaire, D.; Tran, V.; Vignon, M. *J. Chem. Soc., Chem. Commun.* **1976**, 6−7. (b) Thiem, J.; Klaffke, W. *J. Chem. Soc., Chem. Commun.* **1990**, 76−78. (c) Goddat, J.; Grey, A. A.; Hricovini, M.; Grushcow, J.; Carver, J. P.; Shah, R. N. *Carbohydr. Res.* **1994**, *252*, 159−170. (d) Dondoni, A.; Marra, A.; Scherrmann, M. C.; Bertolasi, V. *Chem.—Eur. J.* **2001**, *7*, 1371−1382.
(8) (a) Dubois, E. P.; Neszmelyi, A.; Lotter, H.; Pozsgay, V. *Tetrahedron Lett.* **1996**, *37*, 3627−3630. (b) Pozsgay, V.; Dubois, E. P.; Lotter, H.; Neszmelyi, A. *Carbohydr. Res.* **1997**, *303*, 165−173. (c) Ludewig, M.; Lazarevic, D.; Kopf, J.; Thiem, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1751−1752.
(9) For selected papers on the glycosidations with *ortho*-ester **3**, see: (a) Boren, H. B.; Ekborg, G.; Eklind, K.; Garegg, P. J.; Pilotti, A.; Swahn, C. G. *Acta Chem. Scand.* **1973**, *27*, 2639−2644. (b) Ogawa, T.; Nozaki, M.; Matsui, M. *Tetrahedron* **1980**, *36*, 2641−2648. (c) Ogawa, T.; Nakabayashi, S.; Shibata, S. *Agric. Biol. Chem.* **1983**, *47*, 1353−1356. (d) Skrydstrup, T.; Mazeas, D.; Elmouchir, M.; Doisneau, G.; Riche, C.; Chiaroni, A.; Beau, J. M. *Chem.—Eur. J.* **1997**, *3*, 1342−1356. (e) Draghetti, V.; Poletti, L.; Prosperi, D.; Lay, L. *J. Carbohydr. Chem.* **2001**, *20*, 813−819. (f) Torres-Sanchez, M. I.; Zaccaria, C.; Buzzi, B.; Miglio, G.; Lombardi, G.; Polito, L.; Russo, G.; Lay, L. *Chem.—Eur. J.* **2007**, *13*, 6623−6635. (g) Danieli, E.; Proietti, D.; Brogioni, G.; Romano, M. R.; Cappelletti, E.; Tontini, M.; Berti, F.; Lay, L.; Costantino, P.; Adamo, R. *Bioorg. Med. Chem.* **2012**, *20*, 6403−6415.
(10) (a) Enders, D.; Nguyen, D. *Synthesis* **2000**, 2092−2098. (b) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398−406.
(11) (a) Pandey, S. K.; Ramana, C. V. *J. Org. Chem.* **2011**, *76*, 2315−2318. (b) Rout, J. K.; Ramana, C. V. *J. Org. Chem.* **2012**, *77*, 1566−1571.
(12) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567−569. (c) Wakabayashi, T.; Mori, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1372−1375.
(13) Bigi, M. A.; Reed, S. A.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 9721−9726.

DOI: 10.1021/acs.orglett.5b00505
Org. Lett. 2015, 17, 1724−1727

(14) Yu, W. S.; Mei, Y.; Kang, Y.; Hua, Z. M.; Jin, Z. D. *Org. Lett.* **2004**, *6*, 3217−3219.
(15) (a) Hsu, D.-S.; Lin, S.-C. *J. Org. Chem.* **2012**, *77*, 6139−6146. (b) Hume, P. A.; Furkert, D. P.; Brimble, M. A. *Org. Lett.* **2013**, *15*, 4588−4591.
(16) Sharma, P. K.; He, M.; Romanczyk, L. J., Jr.; Schroeter, H. *J. Labelled Compd. Radiopharm.* **2010**, *53*, 605−612.
(17) Quideau, S.; Lebon, M.; Lamidey, A. M. *Org. Lett.* **2002**, *4*, 3975−3978.

DOI: 10.1021/acs.orglett.5b00505
Org. Lett. 2015, 17, 1724−1727