Organic LETTERS

Letter

pubs.acs.org/OrgLett

Enantioselective Synthesis, Stereochemical Correction, and Biological Investigation of the Rodgersinine Family of 1,4-Benzodioxane Neolignans

Lisa I. Pilkington,[†] Jessica Wagoner,[‡] Stephen J. Polyak,[‡,§] and David Barker*[,†]

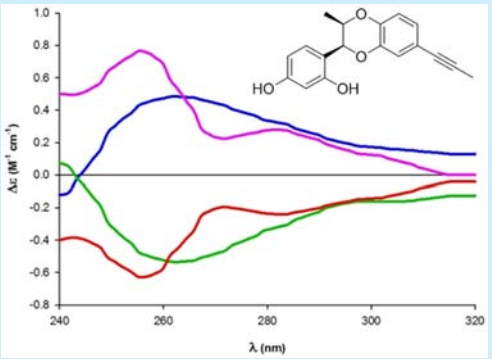
[†]School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand

[‡]Department of Laboratory Medicine, University of Washington, Seattle, Washington 98195, United States

[§]Department of Global Health, University of Washington, Seattle, Washington 98195, United States

Supporting Information

ABSTRACT: The enantioselective synthesis and chiroptic analysis of all members of the rodgersinine family of 1,4-benzodioxane neolignans has been achieved. ECD spectra and optical rotation analysis determined that the previously published stereochemistry of *trans*-rodgersinines A and B was incorrect. The *cis*-rodgersinines A and B did not follow the model ECD study commonly used to assign the absolute stereochemistry of 1,4-benzodioxane natural products. This finding has implications on the absolute stereochemistry of other natural products of this type. Additionally, the rodgersinines were found to have anti-HCV activities.



A significant subgroup within the lignan class, 1,4-benzodioxane neolignans (BNLs), have demonstrated hepaprotective, antioxidant, cytotoxic, and antimicrobial activities in addition to properties that indicate therapeutic applications in areas such as antidepressant, antihyperglycemic, and other treatments.[1−5] Interest in this class of compounds has been further instigated by their structural similarities to bioactive 1,4-benzodioxane flavonolignans such as silybin A.[6]

Several families of BNLs, including the largest—the eusiderin family—are found to be chiral in nature due to a stereoselective, presumably enzymatic, coupling of two phenylpropane units. Most BNL natural products have a *trans* configuration between the substituents at C-7 and C-8, although some *cis* natural products have been isolated, an observation that is consistent with the thermodynamic control of the ring forming step.[7]

Four structurally related BNLs were isolated by Chin et al. in 2004 from rhizomes of *Rodgersia podophylla*, entities that have been used to treat enteritis and bacillary dysentery in China and Korea, and are also recognized to exhibit antipyretic, hepaprotective, and analgesic effects (Figure 1).[8−10] Later dubbed *trans*-rodgersinine A (**1**), *cis*-rodgersinine A (**2**), *trans*-rodgersinine B (**3**), and *cis*-rodgersinine B (**4**),[11] these four lignans are of particular interest due to not only the unusual 2,4-dihydroxy substitution on the aromatic ring found in all members but also the acetylenic group in the side chains of *trans*- and *cis*-rodgersinine B, **3** and **4**. These compounds are the first lignans to be isolated containing an acetylenic group.[8,11]

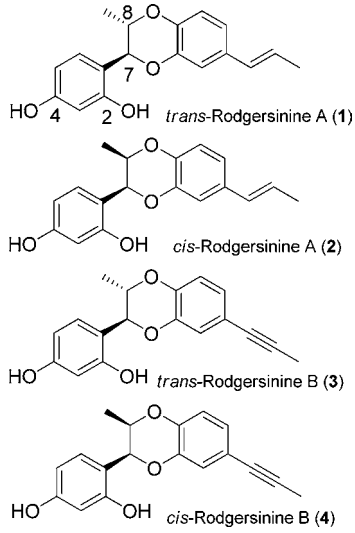


Figure 1. Published structures of the rodgersinines, isolated by Chin et al.[8]

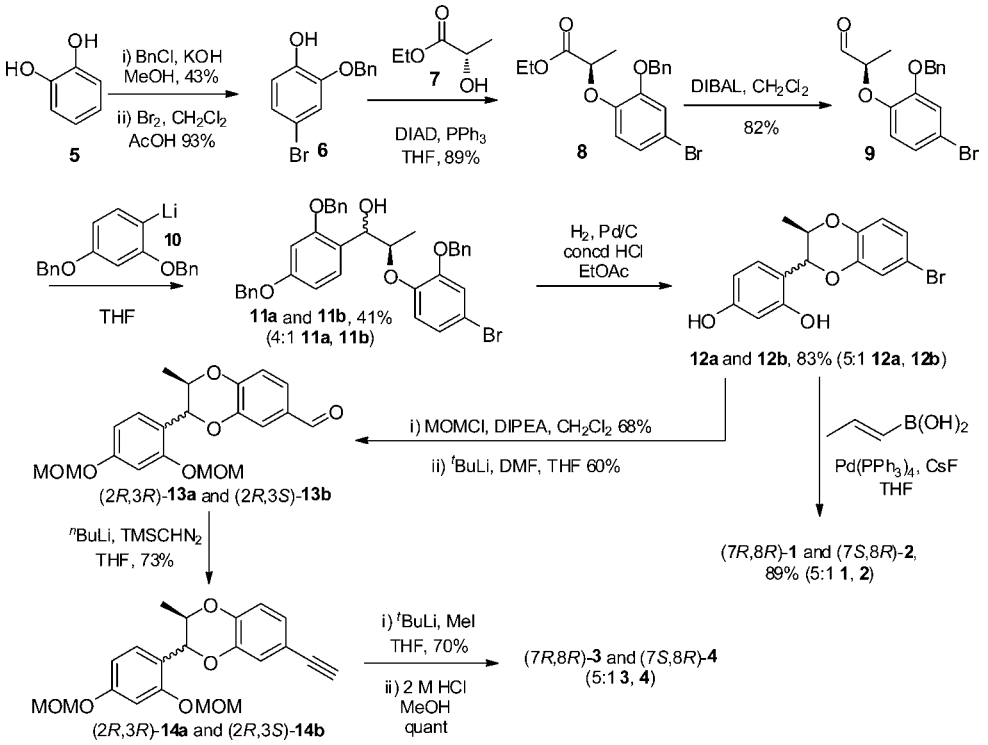
The *trans*/*cis* configuration of these compounds was determined by examination of the coupling constants between H-7 and H-8. The absolute stereochemistry was suggested using comparison of their electronic circular dichroism (ECD)

Received: January 20, 2015
Published: February 11, 2015

ACS Publications © 2015 American Chemical Society

DOI: 10.1021/acs.orglett.5b00189
Org. Lett. 2015, 17, 1046−1049

Scheme 1. Synthesis of (7*R*,8*R*)-Rodgersinine A and B and (7*S*,8*R*)-Rodgersinine A and B



curves with model 1,4-benzodioxanes and other BNLs that were assigned according to a study by Arnoldi et al.[7,8,12]

trans-Rodgersinines **1** and **3** were assigned a (7*S*,8*S*) configuration, and *cis*-rodgersinines **2** and **4** a (7*S*,8*R*) configuration by Chin et al. (further discussed below). In our previous work on the asymmetric synthesis and CD investigation of members of the eusiderins,[13] we were able to determine trends in the ECD spectra of this family, specifically that, for the eusiderins, the stereochemistry of C-7 had little impact on the overall trend, which was mainly affected by the stereochemistry at C-8; when *R*, the main peak in the ECD spectrum at ∼250 nm was negative, while an *S* configuration gave a positive peak. This matched the previous conclusions of the natural product based on a model study.[7] Interestingly, the reported values for the rodgersinines did not appear to follow this trend. We also reported that 1,4-benzodioxanes with additional conjugation due to the side chain were difficult to assign using ECD alone. This uncertainty prompted us to synthesize and investigate the absolute stereochemistry of all proposed rodgersinine natural products and enantiomers through chiroptical analysis of the synthesized compounds.

To begin, catechol **5** was monobenzyl protected and brominated to give phenol **6** which underwent a Mitsunobu reaction with (*S*)-ethyl lactate **7** to give ether **8** which was reduced to give aldehyde **9** (Scheme 1).

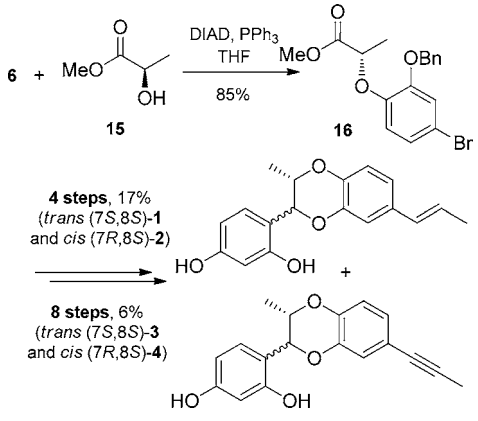
Initially the synthesis was attempted using methyl ethers as protecting groups for the phenols in **1**−**4**. Unfortunately, all attempts at methyl deprotection of the subsequent benzodioxanes were unsuccessful.[14]

Subsequently, lithiate **10** was added to aldehyde **9** to give a mixture of diastereomeric alcohols **11a** and **11b**. Hydrogenolysis of **11a** and **11b** and concomitant cyclization under the acidic conditions gave diphenolic 1,4-benzodioxanes **12a** and **12b**. Installation of the alkene group provided (7*R*,8*R*)-*trans* and (7*S*,8*R*)-*cis* rodgersinine A, (7*R*,8*R*)-**1** and (7*S*,8*R*)-**2**.

Various transition-metal-based methods to install the alkyne side chain in rodgersinine B directly from bromides **12** were unsuccessful.[14] Consequently, diols **12a** and **12b** were MOM-protected and the bromide converted to a formyl group through lithiation of the bromide and addition of DMF. Corey−Fuchs procedures with aldehydes **13a** and **13b** were unsuccessful; however, the terminal alkyne **14a** and **14b** was alternatively formed using lithium trimethylsilyldiazomethane. Formation of the propyne and removal of the protecting groups yielded (7*R*,8*R*)-*trans* and (7*S*,8*R*)-*cis* rodgersinine B, (7*R*,8*R*)-**3** and (7*S*,8*R*)-**4**.

To produce the enantiomers of **1**−**4**, (*R*)-methyl lactate **15** was coupled with phenol **6** in a Mitsunobu reaction to give **16** (Scheme 2). Following the synthetic procedure previously described, *trans*-(7*S*,8*S*)- and *cis*-(7*R*,8*S*)-rodgersinine A (**1** and **2**) were formed in 4 steps from **16** with an overall yield of 17%, and *trans*-(7*S*,8*S*)- and *cis*-(7*R*,8*S*)-rodgersinine B (**3** and **4**)

Scheme 2. Synthesis of (7*S*,8*S*)-*trans*-Rodgersinine A and B and (7*R*,8*S*)-*trans*-Rodgersinine A and B



DOI: 10.1021/acs.orglett.5b00189
Org. Lett. 2015, 17, 1046−1049

were formed in 6% yield, over 8 steps. All final products were initially obtained as isomeric *trans*/*cis* mixtures and then separated using HPLC.

When the rodgersinine family was first isolated, both optical rotation and ECD measurements of the pure compounds were measured (Tables 1 and 2). Chin et al. compared the ECD

Table 1. Chiroptical Data for the *trans*-Rodgersinine Natural Products and Both Synthetic Enantiomers

compd	$[\alpha]_D$	sign of peak ~250 nm
reported *trans*-A (**1**)[7]	+24.8	negative
(7*R*,8*R*)-**1**	+20.0	negative
(7*S*,8*S*)-**1**	−19.7	positive
reported *trans*-B (**3**)[7]	+18.7	negative
(7*R*,8*R*)-**3**	+18.0	negative
(7*S*,8*S*)-**3**	−16.0	positive

spectra of the isolated rodgersinines, with those of eusiderin BNLs reported by da Silva et al., who in turn had assigned the absolute stereochemistry of their compounds based on a paper by Arnoldi et al.[7,8,12] The main point of comparison was the sign of the major peak in the range of 240−260 nm.

The optical rotation and ECD spectra of both enantiomers of *trans*-A (**1**) and *trans*-B (**3**) were measured (Table 1, Figure 2).

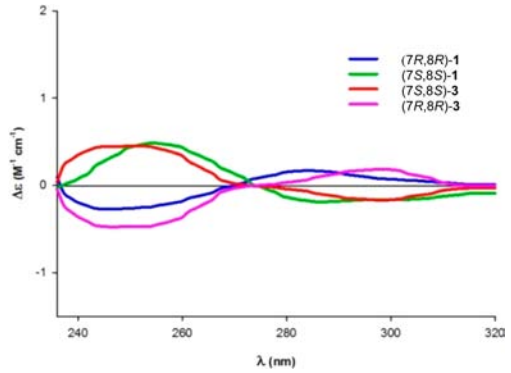


Figure 2. ECD spectra of both synthesized enantiomers of *trans*-rodgersinine A and B, **1**, and **3**.

When looking at the ECD spectra of the *trans* compounds, in particular the peak at ~250 nm, it was discovered that the assigned absolute stereochemistry of (7*S*,8*S*) for both *trans*-A **1** and *trans*-B **3** was incorrect and should in fact be (7*R*,8*R*); the peaks at ~250 nm for the (7*S*,8*S*) compounds were positive (Figure 2, green and red), while the natural products were negative in that region, as shown in the (7*R*,8*R*) enantiomers (Figure 2, blue and pink). This was further verified by comparison of the optical rotations of the synthesized and natural compounds (Table 1).

The ECD spectra and optical rotations of (7*S*,8*R*)-*cis*-A **2** and (7*S*,8*R*)-*cis*-B **4** matched those for the natural products **2** and **4** (Table 2, Figure 3, blue and pink respectively), while (7*R*,8*S*)-**2** and (7*R*,8*S*)-**4** compounds showed chiroptical data opposite to those of the natural product (Table 2, Figure 3, green and red). This confirmed the natural products to have a (7*S*,8*R*) configuration.

Interestingly, when looking at the model study and references used to initially assign the rodgersinines, it appears that these *cis* compounds do not follow the trends observed in previous 1,4-benzodioxane ECD studies. Arnoldi et al.

Table 2. Chiroptical Data for the *cis*-Rodgersinine Natural Products and Both Synthetic Enantiomers

compd	$[\alpha]_D$	sign of peak ~250 nm
reported *cis*-A (**2**)[7]	+79.9	positive
(7*S*,8*R*)-**2**	+67.8	positive
(7*R*,8*S*)-**2**	−79.0	negative
reported *cis*-B (**4**)[7]	+62.0	positive
(7*S*,8*R*)-**4**	+66.7	positive
(7*R*,8*S*)-**4**	−50.0	negative

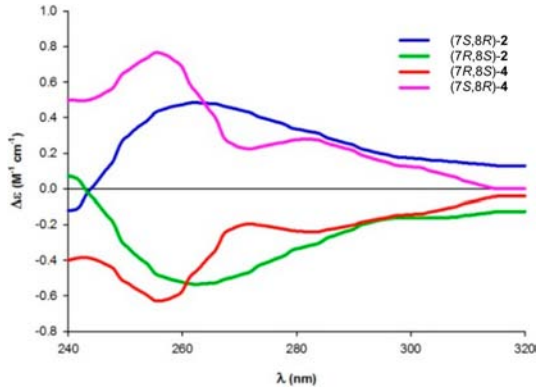


Figure 3. ECD spectra of both synthesized enantiomers of *cis*-rodgersinine A and B, **2**, and **4**.

measured the ECD spectra of two model compounds, one *trans* compound, **17**, with a known (7*S*,8*S*) absolute configuration and the other, *cis*-1,4-benzodioxane **18**, with (7*R*,8*S*) stereochemistry (Figure 4).

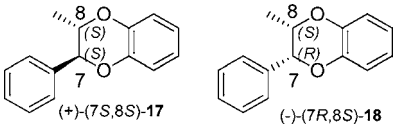


Figure 4. Model 1,4-benzodioxanes studied by Arnoldi et al.

The ECD spectrum of **18** with a (7*R*,8*S*) configuration showed a positive peak at 242 nm. Given this information, one would expect, with a positive peak in the corresponding region, the natural products **2** and **4** to have a (7*R*,8*S*) configuration.[15] Our results, however, indicate otherwise; the absolute stereochemistry of natural *cis* rodgersinine products is (7*S*,8*R*).

Assignation of absolute stereochemistry through comparison of ECD spectra can be difficult, especially when there are differences in substitution; there are previous examples where this discrepancy has led to incorrect assignments.[16] *cis*-Rodgersinine compounds **2** and **4** do not follow the trend observed for the model study, which has also been used in the stereochemical assignment of many other 1,4-benzodioxane natural products.[17−21] As we have shown ECD is not always appropriate in the determination of the absolute stereochemistry of 1,4-benzodioxanes, there stands the possibility that if this is the sole indicator used to determine the absolute stereochemistry of these natural products, they may not be correct.

The verified structures of the rodgersinine compounds are as shown (Figure 5).

BNLs have been suggested to demonstrate hepaprotective activities.[2,22] However, this has been due to their similarity in

DOI: 10.1021/acs.orglett.5b00189
Org. Lett. 2015, 17, 1046−1049

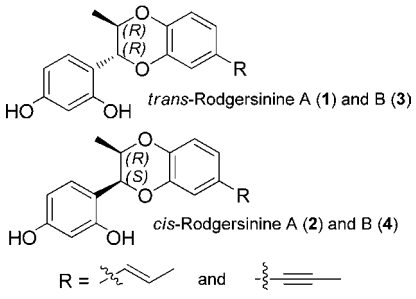


Figure 5. Structures of the rodgersinine family.

structure to silybin; there has been no study of their activity. Both enantiomers of **1** and **3** were tested for anti-Hepatitis C Virus (HCV) activity, an action exhibited by silybin,[23] by analyzing the reduction in expression of HCV nonstructural proteins NS3 and NS5A, critical proteins in the lifecycle of HCV.[24,25] All showed anti-HCV activity; (7*R*,8*R*)-**1** had much weaker activity, with an IC_{50} of ∼125 μM, than the others that had an estimated IC_{50} of ∼15 μM for (7*S*,8*S*)-**1** and (7*S*,8*S*)-**3** and ∼10 μM for (7*R*,8*R*)-**3** which was slightly more potent. Antiviral activity was independent of cytotoxicity.[14] This was the first time that both enantiomers of a BNL have been studied, and the first study of neolignans in relation to anti-HCV activity.

In summary, the enantioselective synthesis of both enantiomers of all members of the rodgersinine family was achieved. Both ECD and optical rotation measurements determined that *trans*-rodgersinines **1** and **3** have a (7*R*,8*R*) configuration and that the original (7*S*,8*S*) assignment was incorrect. It was also verified that *cis* rodgersinines A (**2**) and B (**4**) have a (7*S*,8*R*) configuration; this indicates that the *cis* rodgersinines do not follow the same trend as observed for other 1,4-benzodioxanes. This highlights that ECD spectral comparison of BNLs to model compounds alone is not reliable enough to assign absolute stereochemistry, and although there are notable trends, they are not applicable to all 1,4-benzodioxanes. The only way to confirm the absolute stereochemistry beyond doubt is through synthesis of the natural product and comparison of chiroptical data with those of the isolated product. All rodgersinine natural products showed anti-HCV activity, with considerably lower toxicity profiles compared to silybins.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra for all compounds, individual ECD spectra and data comparison tables for final compounds, and biological testing data are supplied. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: d.barker@auckland.ac.nz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Auckland for funding this project and a doctoral scholarship to L.I.P.

■ REFERENCES

(1) Tanaka, H.; Kato, I.; Ito, K. *Chem. Pharm. Bull.* **1987**, *35*, 3603−3608.
(2) Antus, S.; Gottsegen, Á.; Baitz-Gács, E.; Bauer, R.; Seligmann, O.; Wagner, H. *Liebigs Ann. Chem.* **1989**, *1989*, 1147−1151.
(3) Avakyan, A. S.; Vartanyan, S. O.; Markaryan, É. A.; Martirosyan, O. M.; Avakyan, O. M. *Pharm. Chem. J.* **1988**, *22*, 448−451.
(4) Nelson, W. L.; Wennerstrom, J. E.; Dyer, D. C.; Engel, M. *J. Med. Chem.* **1977**, *20*, 880−885.
(5) Quaglia, W.; Pigini, M.; Tayebati, S. K.; Piergentili, A.; Giannella, M.; Leonardi, A.; Taddei, C.; Melchiorre, C. *J. Med. Chem.* **1996**, *39*, 2253−2258.
(6) Pelter, A.; Hänsel, R. *Tetrahedron Lett.* **1968**, *9*, 2911−2916.
(7) Arnoldi, A.; Merlini, L. *J. Chem. Soc. Perkin Trans. 1* **1985**, 2555−2557.
(8) Chin, Y.-W.; Kim, J. *Tetrahedron Lett.* **2004**, *45*, 339−341.
(9) Kim, Y. L.; Chin, Y.-W.; Kim, J. *Chem. Pharm. Bull.* **2005**, *53*, 103−104.
(10) Chin, Y.-W.; Kim, J. *Chem. Pharm. Bull.* **2006**, *54*, 234−236.
(11) Miao, Q.; Xie, X.-G.; Zhang, J.-Y.; She, X.-G.; Pan, X. *J. Chin. Pharm. Sci.* **2007**, *16*, 41−42.
(12) Da Silva, M. S.; Barbosa-Filho, J. M.; Yoshida, M.; Gottlieb, O. R. *Phytochemistry* **1989**, *28*, 3477−3482.
(13) Pilkington, L. I.; Barker, D. *J. Org. Chem.* **2012**, *77*, 8156−8166.
(14) See Supporting Information for further details.
(15) Although the original stereochemical assignment was correct, it could not have been predicted by the referenced paper.[7]
(16) Clive, D. L. J.; Stoffman, E. J. L. *Org. Biomol. Chem.* **2008**, *6*, 1831−1842.
(17) Kamiya, K.; Tanka, Y.; Endang, H.; Umar, M.; Satake, T. *J. Agric. Food Chem.* **2004**, *52*, 5843−5848.
(18) Bae, J.-S.; Kim, T. H. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 793−796.
(19) Sawasdee, K.; Chaowasku, T.; Lipipun, V.; Dufat, T.-H.; Michel, S.; Likhitwitayawuid, K. *Tetrahedron Lett.* **2013**, *54*, 4259−4263.
(20) Nguyen, P.-H.; Yang, J.-L.; Uddin, M. N.; Park, S.-L.; Lim, S. I.; Jung, D.-W.; Williams, D. R.; Oh, W. K. *J. Nat. Prod.* **2013**, *76*, 2080−2087.
(21) Yang Kuo, L.-M.; Zhang, L.-J.; Huang, H.-T.; Lin, Z.-H.; Liaw, C.-C.; Cheng, H.-L.; Lee, K.-H.; Morris-Natschke, S. L.; Kuo, Y.-H.; Ho, H.-O. *J. Nat. Prod.* **2013**, *76*, 580−587.
(22) Jing, X.-B.; Gu, W.; Bie, P.; Ren, X.; Pan, X. *Chin. Chem. Lett.* **2000**, *11*, 875−878.
(23) Polyak, S. J.; Morishima, C.; Lohmann, V.; Pal, S.; Lee, D. Y. W.; Liu, Y.; Graf, T. N.; Oberlies, N. H. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 5995−5999.
(24) Huang, Y.; Staschke, K.; De Francesco, R.; Tan, S.-L. *Virology* **2007**, *364*, 1−9.
(25) Raney, K. D.; Sharma, S. D.; Moustafa, I. M.; Cameron, C. E. *J. Biol. Chem.* **2010**, *285*, 22725−22731.

DOI: 10.1021/acs.orglett.5b00189
Org. Lett. 2015, 17, 1046−1049