Organic LETTERS

Letter

pubs.acs.org/OrgLett

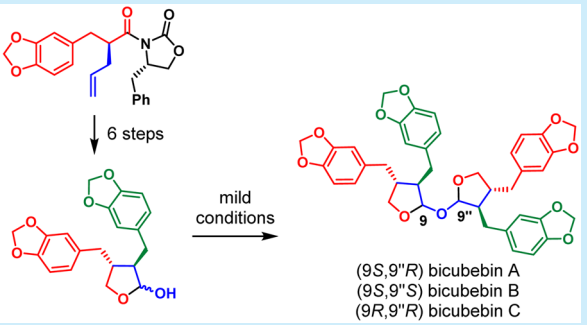
Total Synthesis of (−)-Bicubebin A, B, (+)-Bicubebin C and Structural Reassignment of (−)-*cis*-Cubebin

Samuel J. Davidson, A. Norrie Pearce, Brent R. Copp, and David Barker*

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland 1010, New Zealand

Supporting Information

ABSTRACT: The first total synthesis of (−)-bicubebin A, and two previously unreported dilignans, (−)-bicubebin B and (+)-bicubebin C has been achieved through the dimerization of (−)-cubebin, confirming the structure and absolute stereochemistry of (−)-bicubebin A. Analysis of the data for (−)-bicubebin B showed it matched that of reported compound (−)-*cis*-cubebin. The NMR data of the subsequently synthesized proposed structure of *cis*-cubebin confirmed that its original proposed structure was incorrect.



Dilignans are an uncommon subset of the lignan family of natural plant products. They are dimers of lignans and have been isolated in a variety of forms, including tetrahydrofuran rings, e.g., cynarinine **1**,[1] 1,4-dioxanes, e.g., strebluslignanol F (**2**),[2] Diels−Alder products, e.g., ramonanin A (**3**),[3] and lactol dimers, e.g., (−)-bicubebin A (**4**) (Figure 1).[4]

Bicubebin A (**4**), isolated from *Aristolochia pubescens* and *Aristolochia lagesiana* alongside its monomeric unit (−)-cubebin **5**,[4] contains six contiguous chiral centers and is the only reported lignan dimer containing this structural motif.

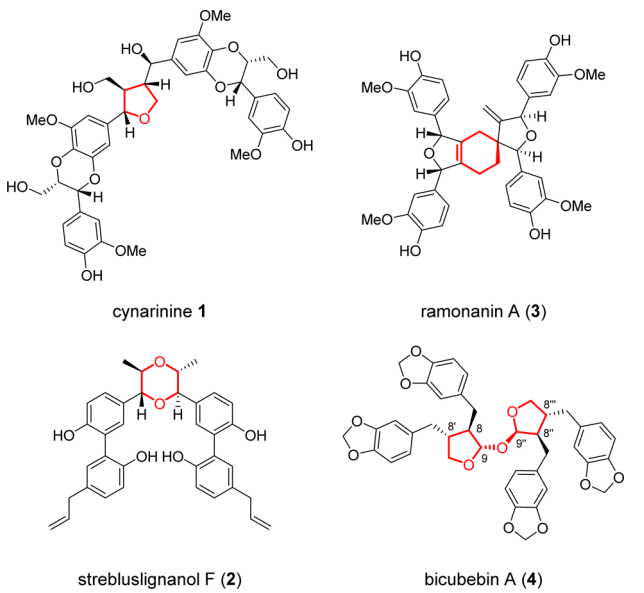


Figure 1. Structures of dilignans **1**−**4**.

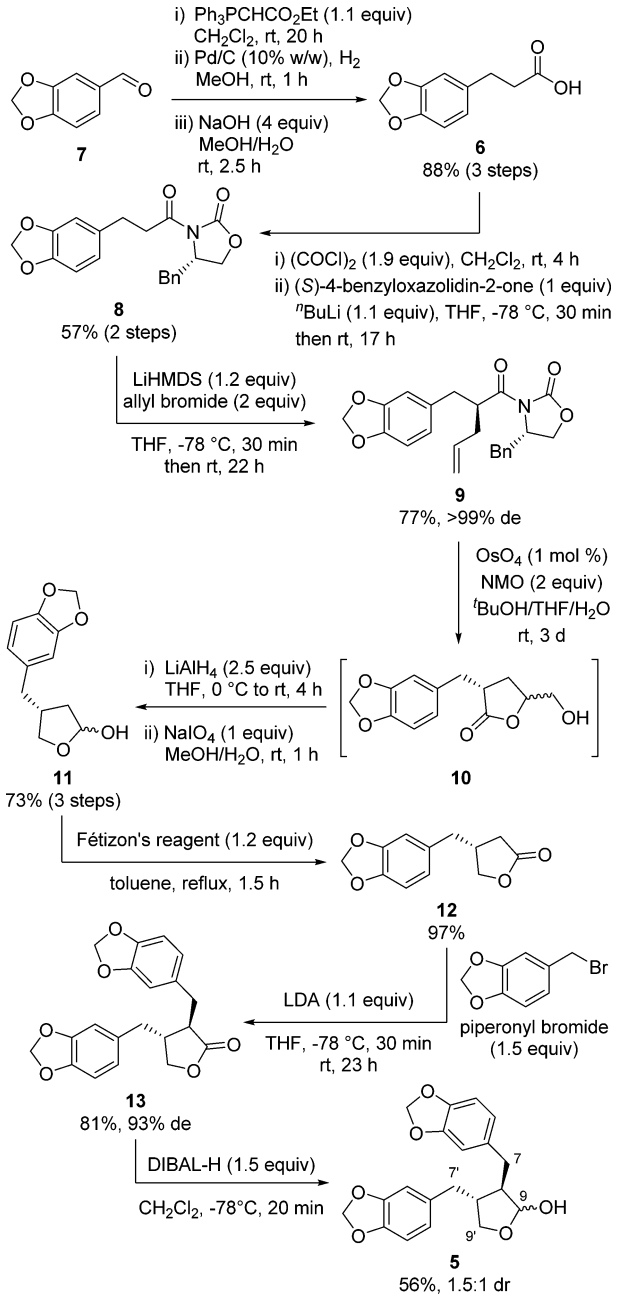
Due to the unique structure, it was decided to explore an approach to bicubebin A (**4**) using the putative biological precursor (−)-cubebin **5** to confirm the unusual structure and determine the absolute stereochemistry of **4**. The synthesis of (−)-cubebin **5** began with the coupling of (*S*)-4-benzyloxazolidin-2-one to carboxylic acid **6**, which itself was synthesized over three steps from piperonal **7** (Scheme 1). This was done through the use of a stabilized Wittig reaction, followed by hydrogenation of the resultant *α*,*β*-unsaturated ester and subsequent hydrolysis which gave the desired carboxylic acid **6** in 88% yield over three steps. Carboxylic acid **6** was converted to the acid chloride, using oxalyl chloride, prior to addition to the lithium salt of (*S*)-4-benzyloxazolidin-2-one to give the desired oxazolidinone **8** in 57% over two steps. A stereoselective allylation was then performed using a sterically hindered base and low temperatures to control facial selectivity,[5,6] which gave (+)-(*S*,*S*)-**9** in 77% yield with greater than 99% de (as determined by ^{1}H NMR). The chiral auxiliary was then removed through use of 1 mol % OsO_4 in *tert*-butanol−water with NMO as the co-oxidant, resulting in simultaneous dihydroxylation and cyclization to form lactone **10**. Subsequent $LiAlH_4$ reduction of lactone **10** followed by $NaIO_4$ oxidative cleavage gave lactol **11** in 73% yield over three steps.

Lactol **11** was then oxidized using Fétizon's reagent[7,8] (Ag_2CO_3/Celite) giving lactone **12** in 97% yield (Scheme 1). Piperonyl bromide (prepared from piperonal in two steps[9]) was then added to the lithium enolate of lactone **12** to yield (−)-hinokinin **13** in 81% yield. Reduction of (−)-hinokinin **13** with di-isobutyl aluminum hydride gave (−)-cubebin **5** in 56% yield as a 1.5:1 ratio of diastereomers at the anomeric carbon,

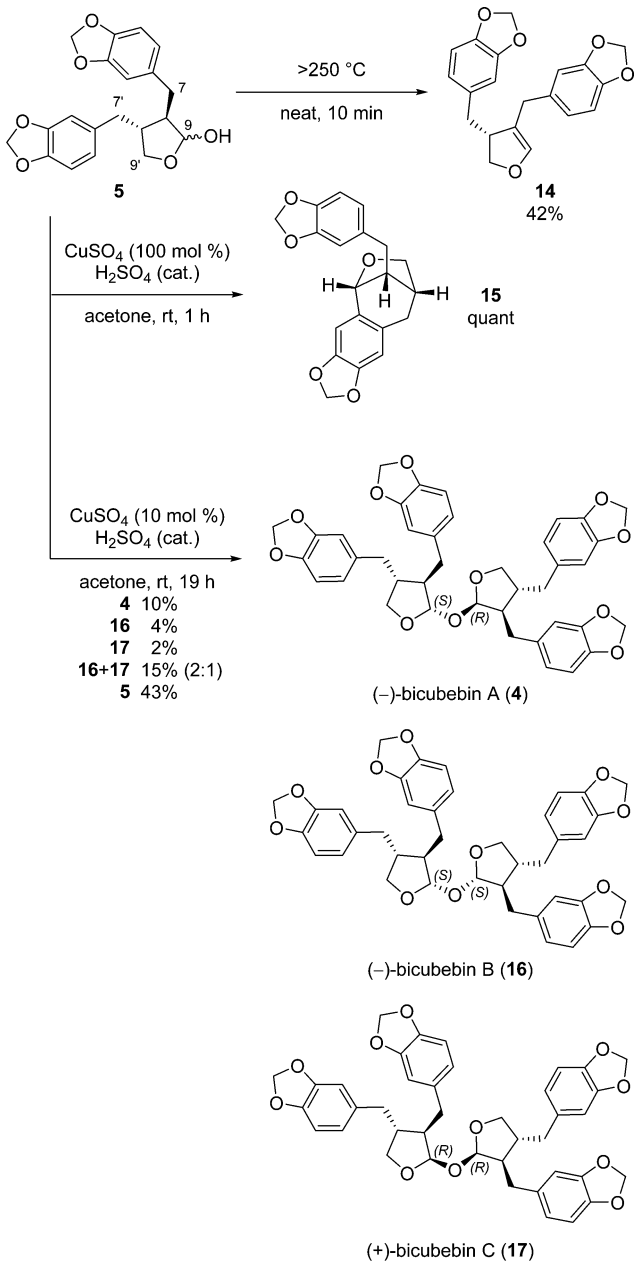
Received: August 25, 2017

DOI: 10.1021/acs.orglett.7b02644
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of (−)-Cubebin



Scheme 2. Dimerization of (−)-Cubebin



C-9. With the synthesis of (−)-cubebin **5** completed, dimerization to form bicubebin A (**4**) was then attempted. Thermal dimerization was first attempted. However, heating at 125 °C resulted in no reaction and heating at temperatures over 250 °C resulted in dehydration to form the dihydrofuran **14** (Scheme 2). Next, anhydrous $CuSO_4$ with catalytic H_2SO_4 in acetone was evaluated, as Cubero et al. had shown these conditions were able to dimerize simple lactols.[10]

Using stoichiometric amounts of $CuSO_4$ resulted in cyclization forming isocubebinic ether[11] **15** in quantitative yield. Fortunately, reducing the $CuSO_4$ to substoichiometric amounts resulted in dimerization of cubebin with three bicubebins being isolated; the unsymmetrical dimer (−)-bicubebin A (**4**), and two previously unreported symmetrical bicubebins which were named (−)-bicubebin B (**16**) and (+)-bicubebin C (**17**) (Scheme 2).

The spectroscopic data of synthetic **4** was then compared with literature values.[4] It was found that the ^1H and ^{13}C NMR spectra of **4** were almost identical (see Table 1 for selected NMR peaks and Supporting Information (SI) data for full details) and the mass spectrum of this compound confirmed that it was a dimer ($M + Na^+$: 717). As the sign of the optical rotation for synthetic **4** (−14.5, *c* 0.19, $CHCl_3$) was the same to that of the isolated compound **4** (−54.8, *c* 0.36, $CHCl_3$),[4] this therefore confirms the absolute stereochemistry of (−)-bicubebin A (**4**) as (8*R*,9*S*,8′*R*,8″*R*,9″*R*,8‴*R*)-**4** (see Figure 1 for atom numbering).

Upon further inspection of the experimental data for synthetic (−)-bicubebin B (**16**), it was discovered that ^1H and ^{13}C NMR data (Table S1) and optical rotation values matched that of previously reported (−)-*cis*-cubebin **18**, which was isolated alongside **4**. De Pascoli et al. reported that **18** was isolated as a single lactol anomer which was unusually unable to

DOI: 10.1021/acs.orglett.7b02644
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Selected ^{1}H and ^{13}C NMR Comparison of Synthetic ($CDCl_3$, 400 MHz) and Isolated (−)-Bicubebin A (4) ($CDCl_3$, 500 MHz)

	^{1}H NMR (δ ppm)		^{13}C NMR (δ ppm)	
	synthetic[a]	reported[4]	synthetic[a]	reported[4]
7	2.34 *dd* (13.8, 8.1)	2.32 *dd* (13.5, 8.0)	38.5	38.5
	2.46−2.51 *m*	2.47 *dd* (13.5, 7.5)		
7′	2.52 *d* (7.7)	2.51 *d* (8.0)	39.4	39.4
7″	2.43 *dd* (13.8, 6.0)	2.43 *dd* (13.5, 6.5)	33.9	33.9
	2.46−2.51 *m*	2.49 *dd* (13.5, 8.5)		
7‴	2.36 *dd* (13.3, 9.1)	2.36 *dd* (13.5, 9.5)	39.4	39.4
	2.61 *dd* (13.3, 4.9)	2.60 *dd* (13.5, 5.0)		
9	4.77 *d* (1.6)	4.76 *d* (2.0)	108.6	108.6
9′	3.63 *dd* (8.4, 7.7)	3.62 *dd* (8.5, 7.5)	72.4	72.4
	3.93 *dd* (8.4, 7.8)	3.92 *t* (8.5)		
9″	4.81 *d* (4.6)	4.81 *d* (5.0)	104.2	104.2
9‴	3.52 *dd* (8.3, 6.9)	3.51 *dd* (8.5, 7.0)	72.5	72.4
	4.01 *t* (8.3)	4.00 *t* (8.5)		

[a]Chemical shifts are reported relative to the solvent peak of chloroform (δ 7.2 for ^{1}H and δ 77.16 for ^{13}C) for comparison to literature[4] values.

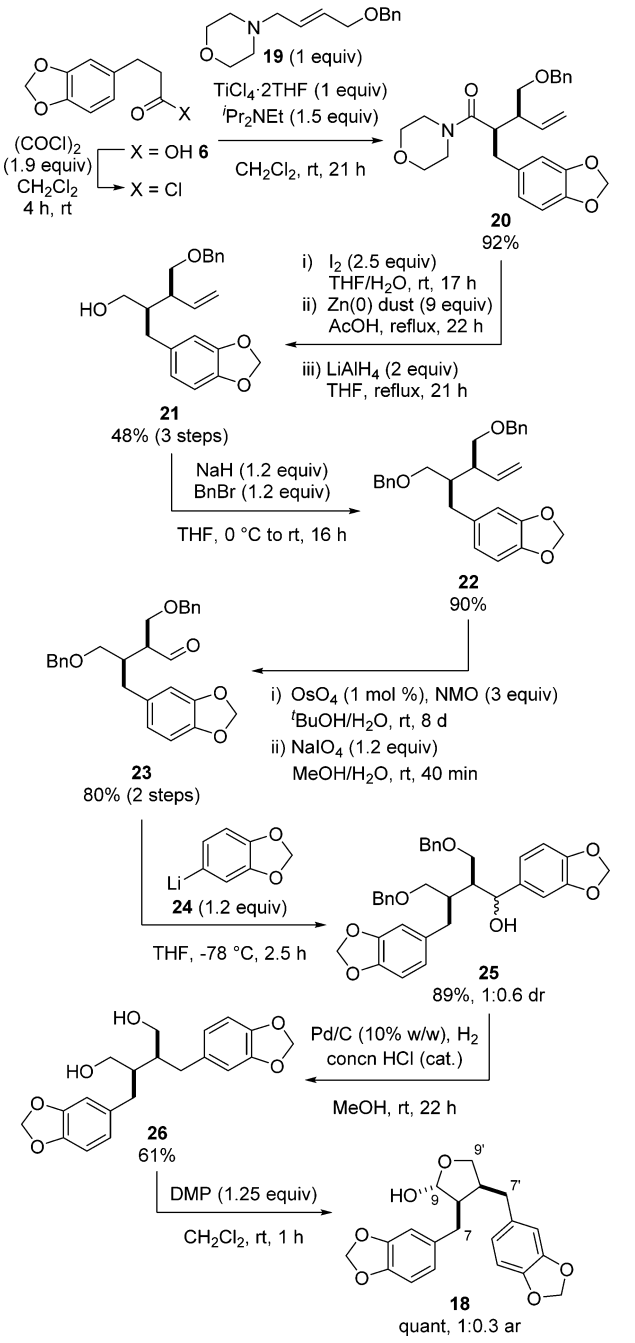
be oxidized to the lactone *cis*-hinokinin.[4] This led us to the belief that the natural product given the structure *cis*-cubebin was in fact a symmetrical dimer and not the lactol reported.

A third bicubebin, (+)-bicubebin C (**17**) which was also isolated alongside bicubebin A (**4**) and B (**16**), is also a symmetrical dimer varying only in the stereochemistry at C-9 with comparison to **16**. The structure of **17** was confirmed using mass spectrometry which concluded that this is in fact a dimer, 2D NMR (Figure S2) and coupling constants to determine the stereochemistry. An 8−9-H coupling constant of 1.5 Hz for bicubebin B (**16**) relates to a *trans*-relationship between vicinal protons whereas an 8−9-H coupling constant of 5.0 Hz for bicubebin C (**17**) is indicative of a *cis*-relationship.[12,13] Therefore, the absolute stereochemistry for the symmetrical dimer (−)-bicubebin B is (8*R*,9*S*,8′*R*)-**16** and (+)-bicubebin C is (8*R*,9*R*,8′*R*)-**17**.

To unequivocally confirm the data attributed to (−)-*cis*-cubebin **18** was in fact an alternative bicubebin; (−)-bicubebin B (**16**), it was decided to prepare the reported structure of **18**. The synthesis began with an acyl-Claisen rearrangement[14−20] of the acid chloride formed from acid **6** and allylic morpholine **19** giving *syn*-substituted morpholine amide **20** in 92% yield (Scheme 3). Iodo-lactonization followed by zinc mediated reductive cleavage gave a carboxylic acid which underwent $LiAlH_4$ reduction giving alcohol **21** in 48% yield over three steps. Alcohol **21** was then protected using benzyl bromide giving bis-benzyl ether **22** in 90% yield. The olefin of **22** was then oxidatively converted to aldehyde **23** in 80% yield over two steps.

To complete the synthesis, aryl lithium **24** was added to aldehyde **23** to yield the desired secondary alcohol **25** in 89% yield as a 2:1 mixture of diastereomers at the newly formed stereocenter (Scheme 3). Hydrogenolysis, in the presence of catalytic acid, removed both benzyl protecting groups and the benzylic alcohol giving the *meso*-diol **26** in 61% yield. Finally, Dess−Martin periodinane oxidation of **26** gave lactol **18** in quantitative yield as a 1:0.3 mixture of diastereomers at the anomeric carbon, C-9. The spectroscopic data for synthetic lactol **18** was then compared with that reported for *cis*-cubebin and was found to be significantly different. Most notably the ^{1}H

Scheme 3. Synthesis of *cis*-Cubebin



signals for synthetic *cis*-cubebin were shifted downfield and the methylenedioxy signals had a distinctive pattern of two singlets compared to the reported four doublets (Table S2). It can therefore be confirmed that the lactol structure reported as *cis*-cubebin is in fact a second dimeric lignin (−)-bicubebin B (**16**).

In conclusion, the first total synthesis of the unique dimeric lignan (−)-bicubebin A has been completed alongside the synthesis of the symmetric dimers (−)-bicubebin B and (+)-bicubebin C. Comparison of the experimental data for synthetic bicubebin B as well as the synthesis of the proposed structure for *cis*-cubebin has confirmed the corrected structure of *cis*-cubebin as bicubebin B.

DOI: 10.1021/acs.orglett.7b02644
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02644.

Experimental procedures, NMR spectra for all compounds, data comparison tables for final compounds, and mass spectra of dilignans (PDF)

■ AUTHOR INFORMATION

Corresponding Author

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

ORCID

Brent R. Copp: 0000-0001-5492-5269
David Barker: 0000-0002-3425-6552

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Auckland for funding this project and a doctoral scholarship to S.D. We thank Prof. L. M. X. Lopes (São Paulo State University) for providing copies of original spectra of the natural products.

■ REFERENCES

(1) Koubaa, I.; Damak, M. *Fitoterapia* **2003**, *74*, 18−22.
(2) Li, J.; Meng, A.-P.; Guan, X.-L.; Li, J.; Wu, Q.; Deng, S.-P.; Su, X.-J.; Yang, R.-Y. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2238−2244.
(3) Chavez, K. J.; Feng, X.; Flanders, J. A.; Rodriguez, E.; Schroeder, F. C. *J. Nat. Prod.* **2011**, *74*, 1293−1297.
(4) de Pascoli, I. C.; Nascimento, I. R.; Lopes, L. M. X. *Phytochemistry* **2006**, *67*, 735−742.
(5) So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura, A. *J. Org. Chem.* **2012**, *77*, 4017−4028.
(6) Allais, F.; Pla, T. J. L.; Ducrot, P.-H. *Synthesis* **2011**, *2011*, 1456−1464.
(7) Kakis, F. J.; Fetizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. *J. Org. Chem.* **1974**, *39*, 523−533.
(8) Fétizon, M.; Golfier, M.; Louis, J.-M. *J. Chem. Soc. D* **1969**, *0*, 1118−1119.
(9) Aslam, S. N.; Stevenson, P. C.; Phythian, S. J.; Veitch, N. C.; Hall, D. R. *Tetrahedron* **2006**, *62*, 4214−4226.
(10) Cubero, I. I.; Plaza Lopez-Espinosa, M. T.; Gonzalez, D. G. *Carbohydr. Res.* **1986**, *148*, 209−219.
(11) Batterbee, J.; Burden, R.; Crombie, L.; Whiting, D. *J. Chem. Soc. C* **1969**, *0*, 2470−2477.
(12) Wei-Ming, C.; Mayer, R.; Rücker, G. *Arch. Pharm.* **1987**, *320*, 374−376.
(13) Cambie, R. C.; Clark, G. R.; Craw, P. A.; Jones, T. C.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1985**, *38*, 1631−1645.
(14) Yoon, T. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 2911−2912.
(15) Rye, C. E.; Barker, D. *J. Org. Chem.* **2011**, *76*, 6636−6648.
(16) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726−9727.
(17) Davidson, S. J.; Barker, D. *Tetrahedron Lett.* **2015**, *56*, 4549−4553.
(18) Davidson, S. J.; Barker, D. *Angew. Chem., Int. Ed.* **2017**, *56*, 9483−9486.
(19) Dittrich, N.; Jung, E.-K.; Davidson, S. J.; Barker, D. *Tetrahedron* **2016**, *72*, 4676−4689.
(20) Davidson, S. J.; Rye, C. E.; Barker, D. *Phytochem. Lett.* **2015**, *14*, 138−142.

DOI: 10.1021/acs.orglett.7b02644
Org. Lett. XXXX, XXX, XXX−XXX