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Total Synthesis and Stereochemical Revision of Acortatarins A and B

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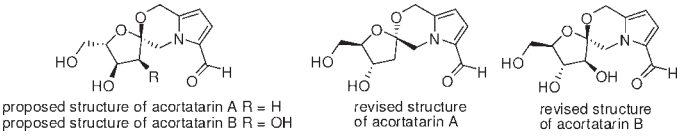
ABSTRACT



A first total synthesis of acortatarins A, B, and an enantiomer of the proposed structure of acortatarin B is described by using readily available D-sugars. This convergent total synthesis revealed the revision of the absolute configuration of acortatarin A and structural revision of acortatarin B. The key steps involved are regioselective epoxide opening with deprotonated 2,5-disubstituted pyrrole and spiroketalization.

Recently, Hou and co-workers isolated two novel spirocyclic alkaloids, acortatarin A and B (Figure 1),[1] with a naturally unusual morpholine motif from the rhizome of *Acorus tatarinowii*, which is used as a traditional Chinese medicine for treating central nervous system disorders.[2] They found that acortatarin A significantly inhibits reactive oxygen species production in high-glucose-stimulated mesangial cells in a dose- and time-dependent manner. The relative stereochemistry of these compounds was proposed on the basis of extensive spectroscopic analysis. In addition, the relative and absolute configurations of acortatarin A were determined by using X-ray crystallographic diffraction analysis and Mosher's method, respectively. The relative configuration of acortatarin B was assigned via ROESY experiments and assumed that from the biogenetic point of view it may have the same absolute configuration as that of acortatarin A.[1]

The novel spiroalkaloids contain a unique tricyclic structural skeleton in which the morpholine motif, a common pharmacophore present in many inhibitors, is embodied by a spiro fused sugar ring. The interesting structure combined with an impressive biological profile attracted us to develop a synthetic strategy that could be used to access structural analogues in addition to the

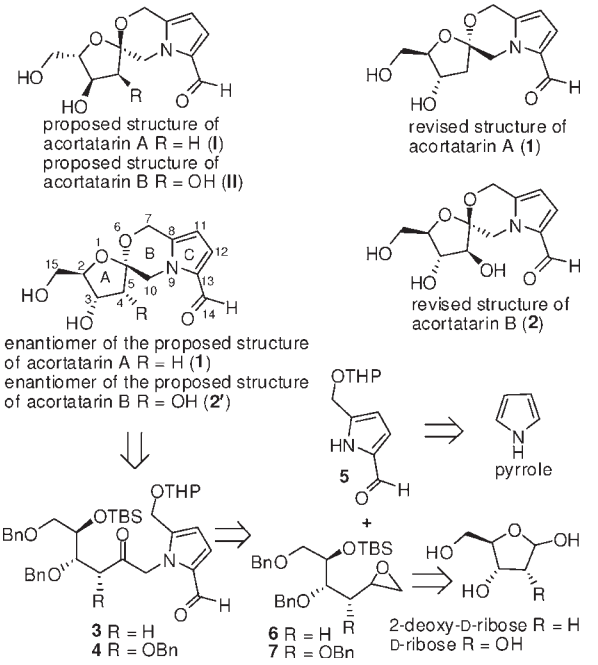


Figure 1. Originally proposed and revised structures of acortatarins A and B. Retrosynthetic analysis for **1** and **2′**.

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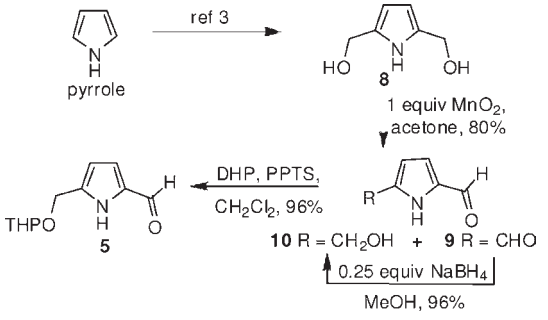
larger quantities of natural products required for further biological studies. We envisioned that the sugar moiety present in the acortatarins could be accessed from the L-sugars, but we found that the stereochemistry of acortatarins A (**I**) and B (**II**) was misassigned when in the course of our total synthesis effort using readily available D-sugars as starting materials to accomplish enantiomers of acortatarins natural products resulted. The revised stereochemical assignments are shown as acortatarins A (**1**) and B (**2**) (Figure 1).

Our retrosynthetic analysis for **1** and **2′** was based on the spiroketalization of suitably protected ketones **3** and **4**, respectively, followed by deprotection of benzyl ethers (Figure 1). Ketones **3** and **4** could be prepared by reacting epoxides **6** and **7**, respectively, with 2,5-disubstituted pyrrole **5** which in turn is, easily, accessible from pyrrole. Epoxide fragments **6** and **7** could be derived from chiral pool starting materials 2-deoxy-D-ribose and D-ribose, respectively.

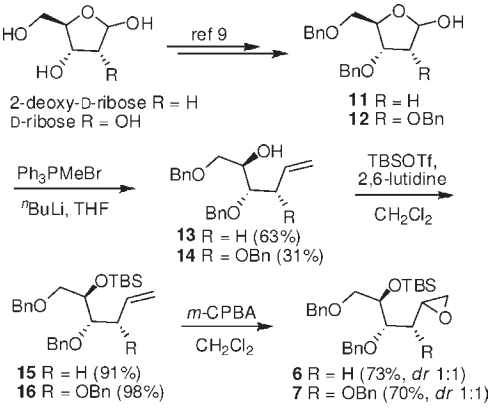
Scheme 1. Synthesis of Pyrrole Fragment **5**



Initial efforts were focused on the synthesis of the pyrrole fragment **5** as shown in Scheme 1. The 2,5-bis-(hydroxymethyl)pyrrole (**8**) was prepared from pyrrole according to the known procedure.[3] Controlled oxidation of diol **8** using 1 equiv of MnO_2 resulted pyrrole-2,5-dicarbaldehyde (**9**) and 5-hydroxymethylpyrrole-2-carbaldehyde (**10**)[4] in 29% and 51% yield, respectively. The dicarbaldehyde **9** was reduced to **10**[5] in 96% yield by using 0.25 equiv of $NaBH_4$. Because of the poor stability of the diol **8**,[6] we have synthesized dicarbaldehyde **9** by following another reported procedure[7] and converted it to monoaldehyde **10**.[8] Subsequently, primary hydroxyl group of **10** was protected as THP ether to give the pyrrole fragment **5** in 96% yield.

The synthesis of appropriately protected epoxides **6** and **7** (Scheme 2) was started from the known 3,5-di-*O*-benzyl-2-deoxy-D-ribofuranose (**11**) and 2,3,5-tri-*O*-benzyl-D-ribofuranose (**12**), respectively, which in turn were prepared from their corresponding sugars by following the reported procedure in three steps.[9] The lactols **11** and **12** were reacted with methylenetriphenylphosphorane to give the alkenes **13**[10] (63%) and **14**[9d] (31%), respectively, and the resulting secondary hydroxyl group was transformed to *O*-silyl ethers **15** (91%) and **16** (98%) by using TBSOTf in the presence of 2,6-lutidine. Terminal olefins **15** and **16** were treated with *m*-CPBA to give the anticipated epoxides **6** (73%) and **7** (70%), respectively.

Scheme 2. Synthesis of Fragments **6** and **7**



With both key fragments in hand, after having examined several conditions,[11,8] the deprotonation of substituted pyrrole[12] **5** with NaH in DMF followed by *N*-alkylation

(1) Tong, X. G.; Zhou, L. L.; Wang, Y. H.; Xia, C.; Wang, Y.; Liang, M.; Hou, F. F.; Cheng, Y. X. *Org. Lett.* **2010**, *12*, 1844–1847. (b) Tong, X. G.; Zhou, L. L.; Wang, Y. H.; Xia, C.; Wang, Y.; Liang, M.; Hou, F. F.; Cheng, Y. X. *Org. Lett.* **2011**, *13*, 4478–4478.

(2) Hu, J. G.; Gu, J.; Wang, Z. W. *Pharmacol. Clin. Chin. Mater. Med.* **1999**, *15*, 19–21.

(3) (a) Taniguchi, S.; Hasegawa, H.; Nishimura, M.; Takahashi, M. *Synlett* **1999**, 73–74. (b) Taniguchi, S.; Hasegawa, H.; Yanagiya, S.; Tabeta, Y.; Nakano, Y.; Takahashi, M. *Tetrahedron* **2001**, *57*, 2103–2108.

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(5) (a) Cin, Y. W.; Lim, S. W.; Kim, S. H.; Shin, D. Y.; Suh, Y. G.; Kim, Y. B.; Kim, Y. C.; Kim, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 79–81. (b) Chiou, W. F.; Shen, C. C.; Yu, H. J.; Chiang, C. H.; Chen, C. C.; Chang, W.; Don, M. J. *Heterocycles* **2005**, *65*, 1215–1220.

(6) The diol **8** became unstable in our hands, leading to quick polymerization or decompostion to unidentified compounds. Its worth mentioning that when the diol **8** was converted to monoaldehyde **10** it attained great stability, indicating that the aldehyde may play a key role in the stability of C ring of these natural products.

(7) Knizhnikov, V. A.; Borisova, N. E.; Yurashevich, N.Ya.; Popova, L. A.; Chernyad'ev, A. Yu.; Zubreichuk, Z. P.; Reshetova, M. D. *Russ. J. Org. Chem.* **2007**, *43*, 855–860.

(8) See the Supporting Information.

(9) (a) Alexander, V.; Choi, W. J.; Chun, J.; Kim, H. O.; Jeon, J. H.; Tosh, D. K.; Lee, H. W.; Chandra, G.; Choi, J.; Jeong, L. S. *Org. Lett.* **2010**, *12*, 2242–2245. (b) Xu, G.; Moeller, K. D. *Org. Lett.* **2010**, *12*, 2590–2593. (c) Adamo, M. F. A.; Pergoli, R. *Org. Lett.* **2007**, *9*, 4443–4446. (d) Hekking, K. F. W.; Moelands, M. A. H.; van Delft, F. L.; Rutjes, F. P. J. T. *J. Org. Chem.* **2006**, *71*, 6444–6450. (e) Takahashi, T.; Hirose, Y.; Iwamoto, H.; Doi, T. *J. Org. Chem.* **1998**, *63*, 5742–5743.

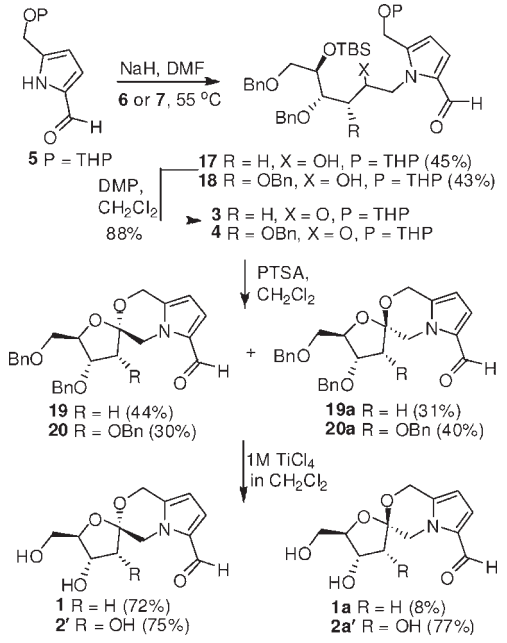
(10) Hossain, N.; Blaton, N.; Peeters, O.; Rozenski, J.; Herdewijn, P. A. *Tetrahedron* **1996**, *52*, 5563–5578.

(11) Initial efforts were undertaken to furnish **17a** and **18a** from **5a** (P = TBS) to avoid complexity in the NMR specrtra of **17** and **18** (P = THP) because of the diastereomeric mixture from the THP group in addition to the secondary hydroxyl stereocenter. But **6** or **7** with **5a** and NaH under heating conditions in DMF or THF consistently gave **17a** and **18a** in low yields (10−20%) due to the falling of TBS.

(12) (a) Rudolph, A.; Rackelmann, N.; Savard, M. O. T.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 289–297. (b) Ludwig, J.; Bovens, S.; Brauch, C.; Elfringhoff, A. S.; Lehr, M. *J. Med. Chem.* **2006**, *49*, 2611–2620. (c) Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J. L.; Sleight, A. J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762–2769.

via regioselective opening of terminal epoxides **6** and **7** at 55 °C led to the secondary alcohol in each case as a inseparable diastereomeric mixture of **17** (45%) and **18** (43%), respectively, in moderate yield on the basis of recovered starting material (Scheme 3). However, stereochemistry of this hydroxyl group is inconsequential as it would be oxidized to the corresponding ketone in the next step.

Scheme 3. Total Synthesis of Acortatarin A (**1**) and Enantiomer of the Proposed Structure of Acortatarin B (**2′**)



Oxidation of the secondary hydroxyl group of **17** and **18** with DMP[13] furnished ketones **3** and **4** each in 88% yield. Treatment of **3** and **4** with PTSA in CH_2Cl_2 effected, as expected, deprotection of the THP and TBS groups and simultaneous intramolecular spiroketalization to give chromatographically separable mixture of anomers at the C-5 position. The ratio is 1.4:1 in the case of **19** and **19a** in 75% combined yield and 1:1.3 for **20** and **20a** in 70% combined yield (Scheme 3).[14,8] Anomers **19** and **19a** were independently subjected to deprotection[15] of benzyl groups by using 1 M $TiCl_4$ that accomplished,[16] interestingly, in both cases again anomeric mixture **1** and **1a** in the ratio of 9:1 in 80% combined yield. Comparison of the ^1H and ^{13}C NMR spectra revealed that the **1** (major) represented the desired natural product acortatarin A.

However, the specific rotation of the synthesized compound [$[\alpha]^{27}_D$ +191.4 (*c* 0.27, MeOH)] is of similar magnitude and the same sign as reported for acortatarin A [$[\alpha]^{27}_D$ +178.4 (*c* 0.4, MeOH)]. This result surprised us as the synthesis was planned for the enantiomer of acortatarin A (based on the proposed structure) from the D-sugar. With this unexpected result, we synthesized and compared spectral data of MTPA-esters of **1**[8] with the Mosher esters which were used in determining the absolute configuration of acortatarin A in the isolation paper.[1] We found that the same absolute configuration of MTPA-Cl was carried over to the MTPA-ester;[17] as a result, the absolute configuration of acortatarin A was misassigned.[1] Thus, the compound synthesized is the natural enantiomer and the revised absolute configuration of acortatarin A (**1**) is C-2 (*R*), C-3 (*S*), and C-5 (*R*) (Figure 1).

In a similar manner, **20** and **20a** were independently subjected to debenzylation to give **2′** (75%) and **2a′** (77%). We expected that the NMR spectra of one of the **2′** or **2a′** should be identical with the spectra of acortatarin **B**, nevertheless, the synthesis was planned for the enantiomer of acortatarin **B** (based on the proposed structure) from D-ribose. Unfortunately, the ^1H and ^{13}C NMR spectral data of **2′** and **2a′** did not match the data reported for acortatarin B,[18,8] indicating that the structure was misassigned. The ^1H NMR spectrum of **2a′** is similar to the one reported for acortatarin B except for the major chemical shift discrepancies at C-2 and C-3 protons. However, extensive NMR experiments[14,8] of **2′** and **2a′** established that **2′** had an enantiomeric relationship with the structure proposed to acortatarin B.

To find out the correct structure of acortatarin B by its total synthesis, one of each of the possible eight enantiomeric pairs needs to be synthesized as it has four asymmetric centers. Formation of anomeric mixture at spirocyclization stage is advantageous as it gives access to both the diastereomers required for confirmation of acortatarin B. Thus, the synthesis of another three diastereomers of ketone **4** is, indeed, needed. These three diastereomers can be accessed from the same D-sugar series, arabinose, lyxose, and xylose, as **4** was already derived from D-ribose.

We have started with D-xylose owing to the major chemical shift differences at C-2 and C-3 protons in the ^1H NMR spectrum of **2a′** and acortatarin B. The lactol **21** (Scheme 4), synthesized from D-xylose following the known procedure,[19] was treated with methylenetriphenylphosphorane to give alkene **22**.[20] Transformation of free alcohol to *O*-silyl ether followed by epoxidation of the terminal olefin with *m*-CPBA resulted epoxide **23** in 85% yield over two steps. The key reaction between pyrrole

(13) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(14) Compounds **19**, **19a**, and all spirocyclic compounds at the final stage have been fully characterized by using 2D NMR experiments.

(15) Our attempts to deprotect benzyl groups by conventional hydrogenolysis in the presence of Pd/C resulted no reaction or at higher catalyst loading led to complex mixture of compounds.

(16) (a) Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903–2905. (b) Gurjar, M. K.; Nagaprasad, R.; Ramana, C. V. *Tetrahedron Lett.* **2003**, *44*, 2873–2875.

(17) (a) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458. (b) Joshi, B. S.; Pelletier, S. W. *Heterocycles* **1999**, *51*, 183–184.

(18) We were unsuccessful in obtaining crystals of **2a′** (derived from major isomer **20a**) or its bromobenzoyl derivative.

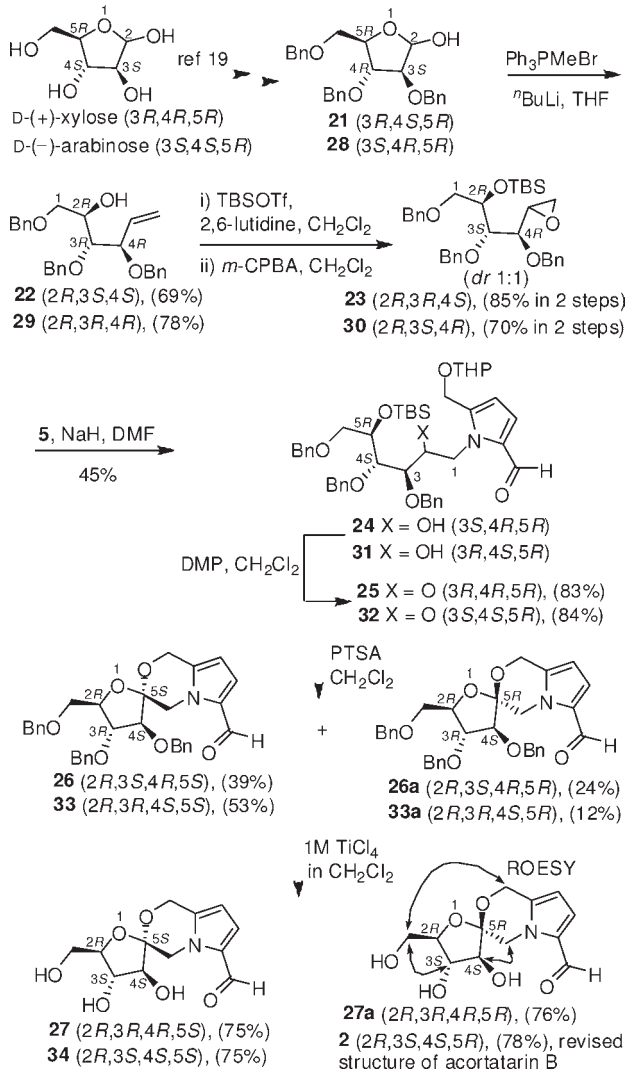
(19) (a) Barker, R.; Fletcher, H. G., Jr. *J. Org. Chem.* **1961**, *26*, 4605–4609. (b) Tejima, S.; Fletcher, H. G., Jr. *J. Org. Chem.* **1963**, *28*, 2999–3004.

(20) Yu, C. Y.; Huang, M. H. *Org. Lett.* **2006**, *8*, 3021–3024.

(21) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785–5793.

(22) Maryanoff, B. E.; Nortey, S. O.; Inners, R. R.; Campbell, S. A.; Reitz, A. B.; Liotta, D. *Carbohydr. Res.* **1987**, *171*, 259–278.

Scheme 4. Synthesis of **27**, **27a**, **34**, and Total Synthesis of Acortatarin B (**2**)



fragment **5** and epoxide **23** was executed under the same conditions to give **24**, which was oxidized to **25** in 37% yield over two steps. Subsequent treatment with PTSA resulted chromatographically separable anomers at C-5 position **26** and **26a** in the ratio 1.6:1 in 63% combined yield. Finally, cleavage of benzyl ethers of both the anomers independently furnished **27** (75%) and **27a** (76%). Disappointingly, comparison of the NMR spectra of **27** and **27a** with the one reported for acortatarin B revealed that neither **27** nor **27a** represented the correct structure of acortatarin B.

The additional hydroxyl group at C-4 stereocenter in acortatarin B, which only differs from acortatarin A, suggested that D-arabinose could be the better choice of starting material than D-lyxose. Accordingly, terminal alkene **29**[21] (Scheme 4) was subjected to a similar sequence of reactions such as TBS protection[22] and epoxidation to deliver **30** in 70% yield over two steps. *N*-Alkylation of the deprotonated pyrrole **5** with epoxide **30** resulted in **31** which was oxidized to the ketone **32** in 37% yield over two steps. Exposure of the ketone to PTSA resulted separable mixture of anomers **33** and **33a** in the ratio 4.6:1 in 65% combined yield. Subsequent benzyl groups deprotection of both the anomers independently resulted **34** (75%) and **2** (78%). To our pleasure and surprise the ^{1}H and ^{13}C NMR spectra of **2**, obtained from minor anomer **33a**, are identical with the one reported for acortatarin B. The specific rotation [$[\alpha]^{27}_{D}$ −94.4 (*c* 0.04, MeOH); lit.[1b] $[\alpha]^{27}_{D}$ −92.7 (*c* 0.10, MeOH)] indicated the compound synthesized is the natural enantiomer. The stereochemistry at C-5 was established by using ROESY experiments and found cross peaks H-3↔H-15, H-4↔H-10, and H-7↔H-15; hence, the revised structure and absolute configuration of acortatarin B are as shown in Scheme 4.

In conclusion, the first total synthesis of acortatarins A, B and an enantiomer of the proposed structure of acortatarin B revealed the revision of stereochemical assignment and suggested D-sugars could be the biosynthetic precursors for these natural products. In addition, the developed synthetic strategy is short, efficient, and practically applicable, which is apparent from the synthesis of various diastereomers to unambiguously reassign the stereochemistry of acortatarin B. The synthesis of further acortatarin analogues and their biological evaluation is in progress in our laboratory and will be reported in due course.

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Supporting Information Available. Experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.