

Stereoselective Synthesis of the  
Atropisomers of Myristinin B/C

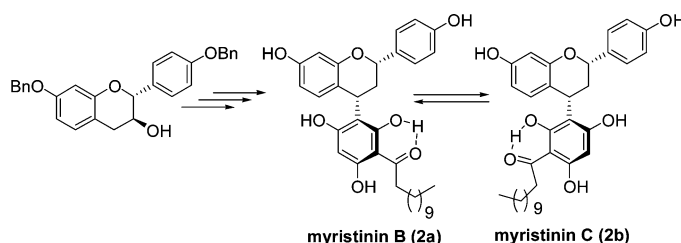
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## ABSTRACT



The first stereoselective synthesis of a potent DNA damaging agent, (–)-myristinin B/C, has been accomplished. This efficient synthesis allowed for unambiguous confirmation of the structure and absolute stereochemistry of the atropisomeric natural product. The antipode, (+)-myristinin B/C, was also synthesized, providing ample material for biological evaluation of both enantiomers.

Our laboratory has long been interested in the isolation and biological evaluation of compounds which possess activity as DNA damaging agents or polymerase  $\beta$  inhibitors.<sup>1</sup> The myristinins (Figure 1) were first isolated by Sawadajoon and

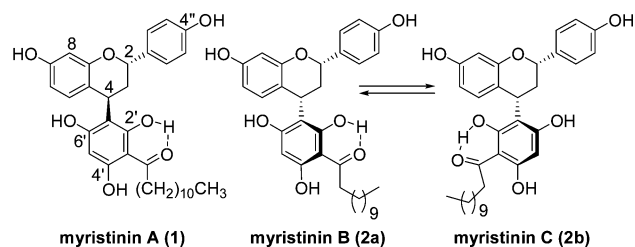


Figure 1. Structures of the myristinins.

co-workers from *Myristica cinnamomea*<sup>2</sup> and more recently isolated by our laboratory from *Knema elegans*.<sup>3</sup> These compounds exhibit impressive dual biochemical activity both

as potent DNA damaging agents and as DNA polymerase  $\beta$  inhibitors.<sup>3,4</sup> Additionally, they have demonstrated strong potentiation of the cytotoxicity of bleomycin. Given the intriguing biological activity of these compounds, it was of interest to synthesize these compounds to gain access to material sufficient for detailed biological evaluation. Initial studies focused on the synthesis of myristinin A (**1**) as preliminary biochemical assays revealed this to be the more potent DNA damaging agent. Ultimately, these efforts culminated in the first synthesis of **1**, providing structural confirmation and absolute stereochemistry determination.<sup>4</sup> With the completion of the synthesis of the 2,4-trans isomer **1**, we sought to gain synthetic access to the 2,4-cis isomer myristinin B/C (**2a,b**) which exists naturally as an inseparable mixture of atropisomers.<sup>2</sup> In this account, we report the successful synthesis of both enantiomers of **2a,b**, permitting the absolute stereochemistry of the natural product to be

(2) Sawadajoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtaranonth, Y. *J. Org. Chem.* **2002**, *67*, 5470. Compound **1** has also been isolated from *Horsfieldia amygdaline*. See: Katuhiko, H.; Akio, K.; Hirokazu, Y.; Akira, M.; Akira, I.; Akinori, S.; Shengji, P.; Yanhui, L.; Chun, W. Patent WO 9208712, 1992.

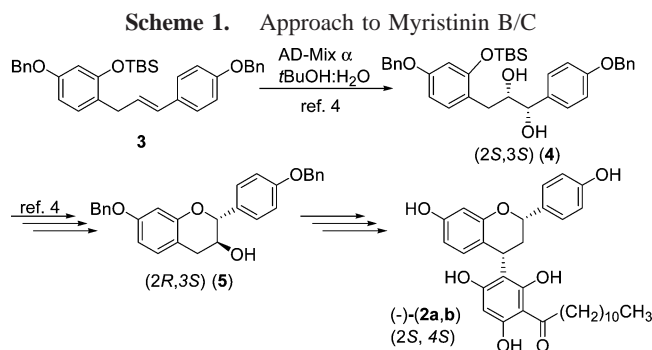
(3) Deng, J.-Z.; Starck, S. R.; Li, S.; Hecht, S. M. *J. Nat. Prod.* **2005**, *68*, 1625.

(4) Maloney, D. J.; Deng, J.-Z.; Starck, S. R.; Gao, Z.; Hecht, S. M. *J. Am. Chem. Soc.* **2005**, *127*, 4140.

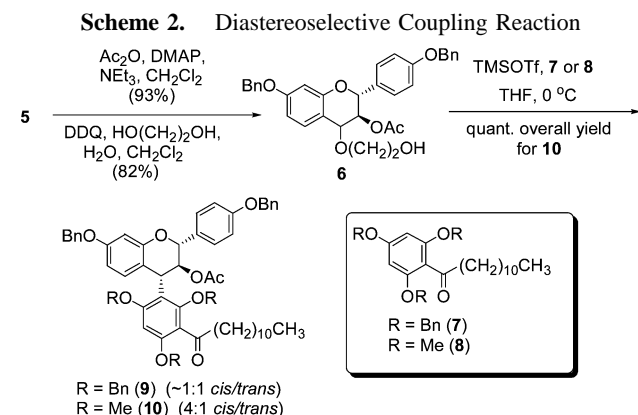
(1) (a) Hecht, S. M. *J. Nat. Prod.* **2000**, *63*, 158. (b) Hecht, S. M. *Pharm. Biol.* **2003**, *41*, S68 and references therein.

determined unambiguously. A key step involved a Lewis acid promoted condensation,<sup>5</sup> and the synthesis also provided an opportunity to investigate the factors controlling this diastereoselective reaction.

Although the absolute stereochemistry of the 2,4-trans isomer (**1**) was determined previously,<sup>4</sup> the absolute configuration of naturally occurring **2a,b** could not be inferred from that study. Thus, the synthesis of both enantiomers seemed prudent. The approach utilized (2*R*,3*S*)-flavan-3-ol **5**<sup>6</sup> which is accessible in six steps from the substituted 1,3-diphenyl-propene derivative **3**<sup>4</sup> shown in Scheme 1.<sup>7</sup> The absolute



stereochemistry of **5** was confirmed using circular dichroism as previously described by van Rensburg et al.<sup>8</sup> Subsequent acetylation of **5** followed by C-4 oxidation using DDQ and ethylene glycol gave **6** in yields of 93% and 82%, respectively (Scheme 2).<sup>5</sup> In our approach to myristinin A (**1**), the



C-3 hydroxyl group of **5** was inverted to facilitate the desired

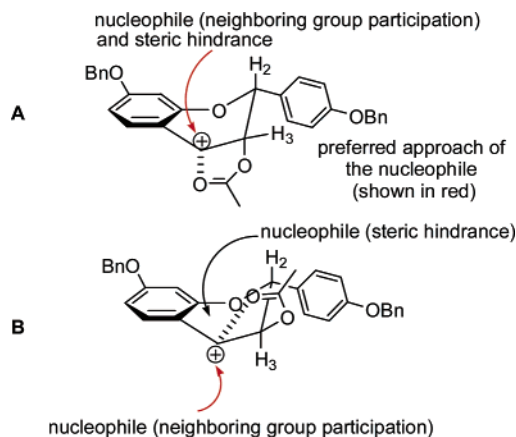
(5) (a) Tückmantel, W.; Kozikowski, A. P.; Romanczyk, L. J., Jr. *J. Am. Chem. Soc.* **1999**, *121*, 12073. (b) Saito, A.; Nakajima, N.; Tanaka, A.; Ubukata, M. *Tetrahedron* **2002**, *58*, 7829. (c) Kozikowski, A. P.; Tückmantel, W.; Hu, Y. *J. Org. Chem.* **2001**, *66*, 1287.

(6) Notably, the enantiomer of **5** (i.e., having the 2*S*,3*R* configuration) can be obtained by using AD-Mix β in the asymmetric dihydroxylation<sup>7</sup> reaction of **3**.

(7) Sharpless, K. B.; Amberg, W.; Beller, M.; Chen, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* **1991**, *56*, 4585.

(8) van Rensburg, H.; Steynberg, P. J.; Burger, J. F. W.; van Heerden, P. S.; Ferreira, D. *J. Chem. Res., Synop.* **1999**, 450.

neighboring group participation effect from the acetate, yielding the 2,4-trans coupled product in a stereoselective manner (Figure 2A). Thus, for the synthesis of myristinin

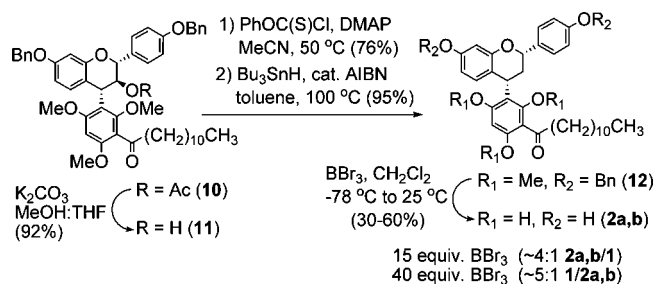


**Figure 2.** Approach of the nucleophile in the Lewis acid promoted condensation reaction.

B/C, it seemed logical to anticipate that the 2,3-trans configuration of the phenyl and OAc groups would favor approach of the nucleophile from the bottom face in the Lewis acid promoted condensation reaction<sup>5</sup> (Figure 2B). Nonetheless, it was anticipated that the steric interaction of the incoming nucleophile from the bottom face with the C-2 phenyl group might result in reduced diastereoselectivity. In fact, the coupling of **6** with the tri-*O*-benzyl-protected acetophenone derivative **7**<sup>4</sup> used in the synthesis of **1** gave **9**, albeit as an unsatisfactory 1:1 mixture of *cis/trans* isomers with respect to C-2 and C-4. Reasoning that the benzyl protecting groups were too large, we changed these to a smaller protecting group to limit this steric interaction.<sup>9</sup> Thus, the tri-*O*-methyl-protected acetophenone derivative **8** was synthesized from commercially available 1,3,5-trimethoxybenzene via acid-catalyzed acylation with lauroyl chloride. Gratifyingly, the diastereoselectivity of the condensation reaction was improved to 4:1 *cis/trans* (100% overall yield); however, attempts to improve this ratio using TiCl<sub>4</sub>, SnCl<sub>4</sub>, BF<sub>3</sub>·OEt<sub>2</sub>, or varying reaction conditions failed. Although the selectivity was not as high as had been hoped, the 2,4-*cis* product could be separated easily from the undesired 2,4-*trans* isomer by column chromatography. Removal of the C-3 hydroxyl group proceeded as planned (Scheme 3). Deacetylation of **10** using K<sub>2</sub>CO<sub>3</sub> in 1:1 THF–MeOH gave alcohol **11** in 92% yield. Subsequent deoxygenation of the C-3 hydroxyl group was carried out in a manner analogous to that reported for the synthesis of **1** using phenyl chlorothionoformate, DMAP in MeCN followed by treatment with Bu<sub>3</sub>SnH, and catalytic AIBN to afford **12** in 72% yield over two steps.<sup>10</sup> Notably, formation of the thioester precursor

(9) Initially, the use of MOM ethers was planned as they are generally more easily removed as compared to methyl ethers. However, all attempts to protect the three phenolic OH groups led to significant C-alkylation of the electron-rich aromatic ring.

**Scheme 3.** Completion of (–)-(2a,b) Synthesis



on the hindered alcohol required the use of rather forcing conditions, whereas the radical deoxygenation was facile. With the fully protected myristinin B/C (**2a,b**) in hand, a method to remove all of the protecting groups in one step was sought. BBr<sub>3</sub> was chosen, given its ability to remove methyl ethers and the known sensitivity of benzyl ethers to this reagent. Although epimerization at the doubly benzylic C-4 position was anticipated, the extent to which this would happen was unclear. Initial attempts at complete deprotection using minimal amounts of BBr<sub>3</sub> (i.e., 1.1 equiv per protecting group) led to incomplete deprotection and very complex product mixtures. After several attempts at optimizing reaction conditions, complete deprotection was finally accomplished using 15 equiv of BBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub>. As anticipated, some epimerization at the C-4 position was observed, yielding an approximately 4:1 mixture of cis/trans isomers as judged by HPLC analysis. The isomeric compounds **1** and **2a,b** have the same mobility on silica gel yet could be separated by C<sub>18</sub> reversed-phase HPLC (retention times: 22.5 min for **1** and 23.4 min for **2a,b**). Interestingly, treatment of **12** with 40 equiv of BBr<sub>3</sub> yielded approximately a 1:5 mixture of cis/trans isomers, essentially inverting the ratio of the products.<sup>11</sup> The fact that increasing the amount of BBr<sub>3</sub> (which should favor the thermodynamic product) results in the formation of more **1** argues that this species is the more energetically stable isomer.<sup>12</sup> Comparison of the synthetic **2a,b** with the natural sample revealed that the absolute

(10) Robins, M. J.; Wilson, J. S.; Hansske, F. *J. Am. Chem. Soc.* **1983**, *105*, 4059.

stereochemistry of authentic (–)-myristinin B/C is 2*S*,4*S* and exists as a 1.2:1 mixture of atropisomers myristinin B (**2a**) and myristinin C (**2b**), respectively.<sup>13</sup> To gain further insight into the biological activity of these compounds, the enantiomer (2*R*,4*R*)-(+)-myristinin B/C was also synthesized in comparable yields starting from the antipode of **5** (Scheme 1).<sup>14</sup>

In summary, both enantiomers of myristinin B/C (**2a,b**) were synthesized in a facile manner permitting unequivocal determination of the absolute stereochemistry of (–)-myristinin B/C as 2*S*,4*S*. Both enantiomers were identical with the authentic sample as judged by comparisons of <sup>1</sup>H NMR, <sup>13</sup>C NMR, HRMS, and mobility on C<sub>18</sub> reversed-phase HPLC.<sup>15</sup> With the syntheses of both enantiomers of **2a,b** completed, a detailed biochemical and biological evaluation of these interesting compounds is currently underway.

**Acknowledgment.** This work was supported by NIH Research Grant CA50771, awarded by the National Cancer Institute.

**Supporting Information Available:** Experimental procedures and characterization data for all new compounds. <sup>1</sup>H and <sup>13</sup>C NMR for compounds **2a,b** and **5–12** are also available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) In addition to observing epimerization of **2a,b** to **1**, we also observed the formation of what appears to be a conformational isomer of **1**. This compound has mass (by HRMS) and retention time on C<sub>18</sub> reversed HPLC identical to **1**. However, the <sup>1</sup>H NMR spectra of the two compounds are quite different (see Supporting Information). The possibility that this species is a constitutional isomer of **1** formed under the forcing conditions cannot presently be excluded.

(12) Attempts to measure the relative energies of compounds **1** and **2a,b** using molecular modeling techniques led to inconsistent results.

(13) The ratio was determined by integration of H-4 and 2'-OH in the <sup>1</sup>H spectrum of **2a,b** as these protons possess different resonances due to the restricted rotation about the substituents on C-4 and C-3'. Sawadajoon and co-workers<sup>2</sup> reported the same ratio and assigned the structures of atropisomers **2a** and **2b** through NOESY spectral data by observing a cross-peak with the chelated hydroxyl (2'-OH) of **2a** with the pseudoaxial H-4. In comparison, this correlation was absent in **2b**.

(14) See Supporting Information for the optical rotations of intermediates from the enantiomeric series.

(15) The optical rotation of synthetic **2a,b**, [α]<sub>D</sub><sup>19</sup> –48.3 (c 0.4, MeOH), had the same sign as that of the authentic sample, [α]<sub>D</sub><sup>22</sup> –55.3 (c 0.5, MeOH); (+)-myristinin B/C, [α]<sub>D</sub><sup>23</sup> +44.6 (c 0.6, MeOH).