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Tetrahedron Letters 47 (2006) 1101–1103
Tetrahedron Letters

Synthesis of combretastatins A-1 and B-1

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Received 12 October 2005; accepted 7 December 2005
Available online 27 December 2005

Abstract—Combretastatins A-1 and B-1 have been synthesized by coupling MOM-protected *p*-iodomethoxycatechol with 3,4,5-trimethoxyphenylacetylene in a Sonogashira reaction.

The combretastatins are a group of antimitotic agents isolated from the bark of an African tree, *Combretum caffrum*.[1] Biological studies of these compounds have revealed that they are among the most cytotoxic agents tested so far against several cancer cell lines.[2] They share a common binding site on tubulin with several other well-known antimitotic agents such as colchicine, podophyllotoxin, and steganacin. Combretastatins A-1 (**1**), B-1 (**2**), and A-4 (**3**) (Fig. 1) interact with and disrupt the vascular life support of tumors by inhibition of tubulin. This prevents metastasis and retards the cancer cells ability to grow new blood vessels by preventing microtubule assembly.[3] The high potency of the combretastatins together with their non-complex structures may offer a new approach to cancer treatment.

Structure–activity relationship analyses of combretastatins and their analogues have shown that the *cis*-olefin and the phenolic functional groups are important for antitumor activity.[4] Since tubulin inhibitors are of interest as potential anticancer drugs, synthesis, and biological testing of the combretastatins and their derivatives continue to attract interest.[5]

In the previously reported synthesis of combretastatin A-1, the biaryl moieties were combined using non-stereoselective Wittig reactions, which required chromatographic separation of the isomers.[6] Hudlicky and co-workers used biocatalytically generated *p*-bromomethoxycatechol that was coupled in a Suzuki reaction with 3,4,5-trimethoxyphenylacetylene in their synthesis of combretastatins A-1 and B-1.[7]

We have recently reported a one-pot *ortho*-formylation/Dakin-oxidation method for the synthesis of catechols[8] via *ortho*-formylation of substituted phenols.[9] The catechol moiety is present in combretastatins A-1 and B-1, and herein we report convergent synthesis of both **1** and **2** applying this methodology.

Accordingly, 5-bromo-2-methoxyphenol (**4**) was converted into *p*-bromomethoxycatechol (**5**), which was

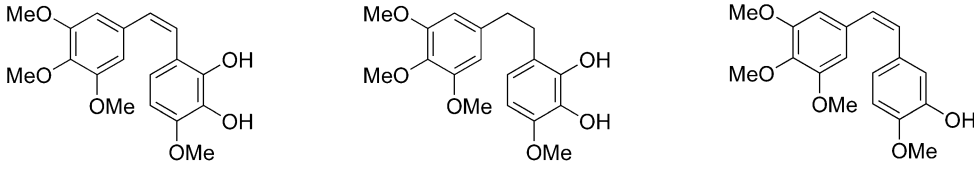

Figure 1.

Keywords: Combretastatins; Tubulin inhibitors; Sonogashira reaction.
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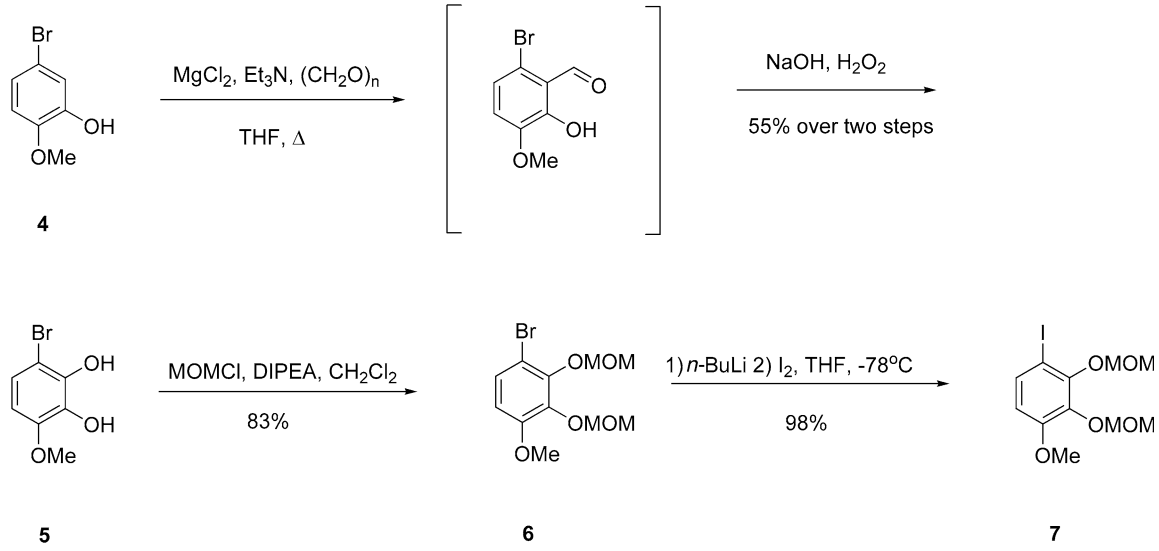
doi:10.1016/j.tetlet.2005.12.037



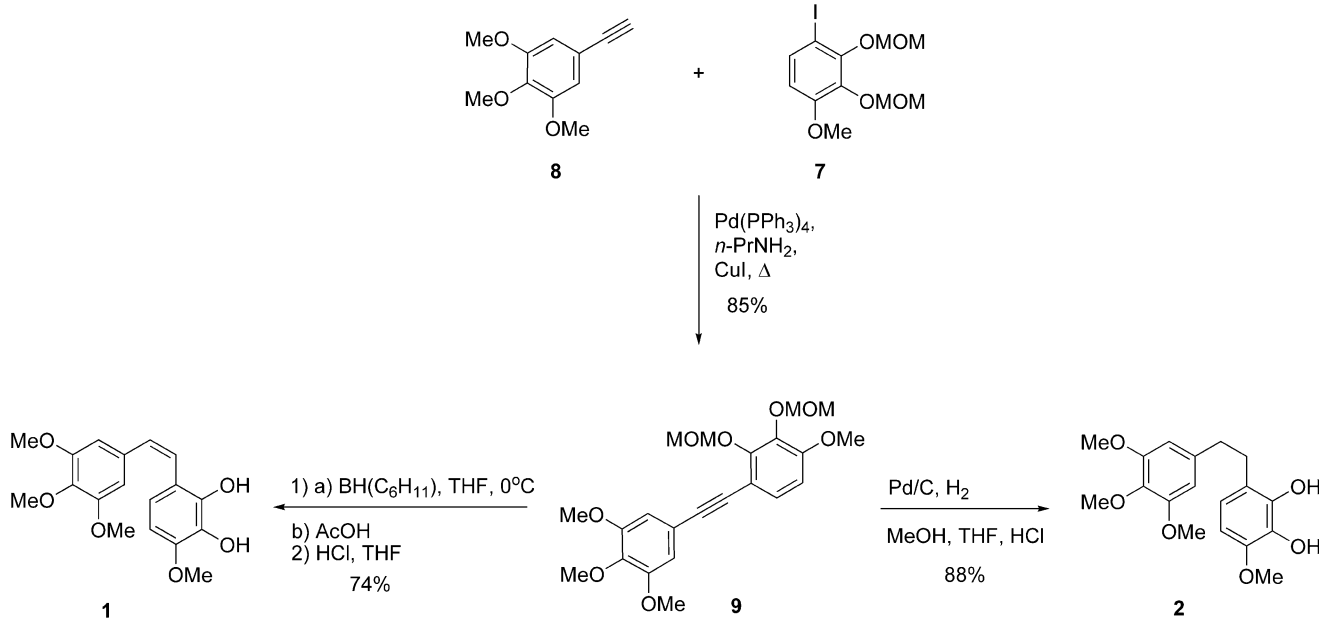
Scheme 1.

protected as the bis-(methoxymethyl)ether **6**.[10,11] The bromide was converted to the more reactive iodide **7** in 98% yield (Scheme 1).

3,4,5-Trimethoxyphenylacetylene (**8**), obtained from reaction of TMS–diazomethane and 3,4,5-trimethoxybenzaldehyde,[12] reacted with iodide **7** in a Sonogashira reaction affording alkyne **9** in 85% yield.[11,13] Hydrogenation and deprotection of alkyne **9** in a one-pot sequence afforded combretastatin B-1 (**2**) in 33% overall yield from **4** (Scheme 2).

Hydroboration has previously been reported[7] superior to the use of Lindlar's catalyst in the reduction of **9** to MOM-protected combretastatin A-1. Hydroboration under the reported conditions gave the desired *cis*-olefin. Final deprotection with diluted HCl yielded combretastatin A-1 (**1**) in 74% yield over two steps (Scheme 2). No isomerization of the *cis*-olefin was observed. The spectral data were in accord with those reported earlier.[1,11]

In conclusion, combretastatin A-1 and B-1 have been prepared from the phenol **4** in 28% and 33% overall yield, respectively. Our syntheses compare favorably with those previously reported with respect to yield and simplicity. Further work emphasis on synthesis and biological activity of novel analogues of these natural products as potential tubulin inhibitors. Results from this research will be reported in due course.



Scheme 2.

Acknowledgment

Financial support to K.O. from the School of Pharmacy, University of Oslo, is gratefully acknowledged.

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11. Spectral data of selected compounds: 3-bromo-6-methoxybenzene-1,2-diol (**5**): white solid; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.98 (d, *J* 8.9 Hz, 1H), 6.42 (d, *J* 8.9 Hz, 1H), 5.57 (s, 1H), 5.52 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.6, 141.0, 133.5, 122.2, 104.4, 101.6, 56.3; HRMS calcd for $C_7H_7BrO_3$ (M^+): 217.9579, found 217.9586; 1-bromo-4-methoxy-2,3-bis(methoxymethoxy)-benzene (**6**): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 (d, *J* 9.0 Hz, 1H), 6.59 (d, *J* 9.0 Hz, 1H), 5.18 (s, 2H), 5.11 (s, 2H), 3.82 (s, 3H), 3.64 (s, 3H), 3.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.3, 148.2, 140.0, 127.5, 108.9, 108.7, 99.4, 98.7, 58.1, 57.5, 56.1; HRMS calcd for $C_{11}H_{15}BrO_5$ (M^+): 306.0103, found 306.0112; 1-iodo-4-methoxy-2,3-bis(methoxymethoxy)benzene (**7**): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* 8.9 Hz, 1H), 6.51 (d, *J* 8.9 Hz, 1H), 5.19 (s, 2H), 5.11 (s, 2H), 3.83 (s, 3H), 3.67 (s, 3H), 3.58 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.4, 150.7, 139.1, 133.5, 110.0, 99.5, 98.7, 81.6, 58.6, 57.5, 56.1; HRMS calcd for $C_{11}H_{15}IO_5$ (M^+): 353.9964, found 353.9966; 1-methoxy-2,3-bis(methoxymethoxy)-4-((3,4,5-trimethoxyphenyl)-ethynyl)benzene (**9**): yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* 8.7 Hz, 1H), 6.74 (s, 2H), 6.68 (d, *J* 8.8 Hz, 1H), 5.31 (s, 2H), 5.14 (s, 2H), 3.87 (s, 3H), 3.86 (s, 9H), 3.66 (s, 3H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.3, 153.1, 151.7, 139.0, 138.7, 128.6, 118.5, 110.8, 108.6, 107.8, 99.2, 98.7, 92.0, 84.9, 60.9, 57.6, 57.4, 56.1, 56.0; HRMS calcd for $C_{22}H_{26}O_8$ (M^+): 418.1628, found 418.1629; combretastatin A-1 (**1**): ^{1}H NMR (300 MHz, $CDCl_3$): 6.76 (d, 1H, *J* 8.7 Hz), 6.59 (d, 1H, *J* 12.2 Hz), 6.53 (d, 1H, *J* 12.0 Hz), 6.52 (s, 2H), 6.38 (d, 1H, *J* 8.6 Hz), 5.41 (s, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.67 (s, 6H); 152.8, 146.3, 141.6, 137.3, 132.6, 132.5, 130.3, 124.0, 120.3, 117.8, 105.9, 102.9, 60.9, 56.2, 55.8; combretastatin B-1 (**2**): ^{1}H NMR (300 MHz, CD_3OD): 6.44 (s, 2H), 6.43 (d, *J* 8.4 Hz, 1H), 6.35 (d, *J* 8.4 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 6H), 3.71 (s, 3H), 2.80 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): 154.1, 148.0, 144.8, 140.2, 137.0, 135.0, 122.8, 120.8, 106.9, 103.8, 61.1, 56.6, 56.5, 37.7, 33.3.
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