DOI: 10.1002/ejoc.200800957

A Novel Approach to Combretastatins: From *trans*-Epoxide to CA-4 and Its Dioxolane Derivative

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Keywords: Oxygen heterocycles / Ylides / Isomerization / Epoxidation

The *trans*-epoxide derivative of Combretastatin A-4 was stereoselectively prepared in good yield by sulfur ylide mediated epoxidation of silyl-protected isovanillin. From this key intermediate, a formal synthesis of CA-4, by stereoselective deoxygenation and photoisomerization, was achieved. Alternatively, a *trans*-dioxolane derivative was obtained by stereoselective acetone insertion.

Introduction

Combretastatin A-4 (**1**; Figure 1), a natural stilbene from the african *Combretum caffrum*, is a potent inhibitor of cancer cell growth, inducing irreversible vascular shutdown within solid tumors while leaving normal vasculature intact.[1] Its more bioavailable disodium phosphate analogue has shown promising results in human cancer clinical trials,[2] thus stimulating significant interest in a variety of CA-4 analogues. Extensive studies have been conducted to examine the structure–activity relationship (SAR) of CA-4 and its analogues. The model structure CA-4 has been modified in each of the three elements (ring A, ring B, and double bond), and all these results have been recently reviewed.[3]

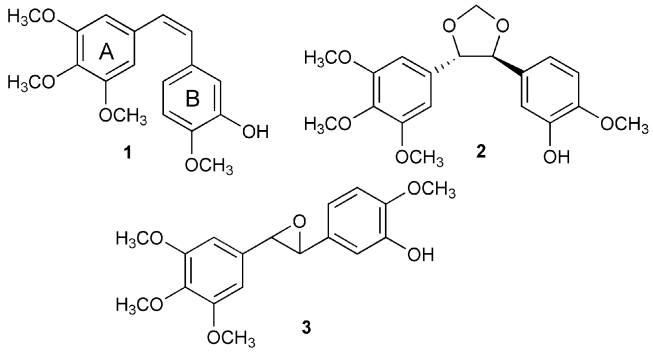

Figure 1. CA-4 and oxygenated derivatives.

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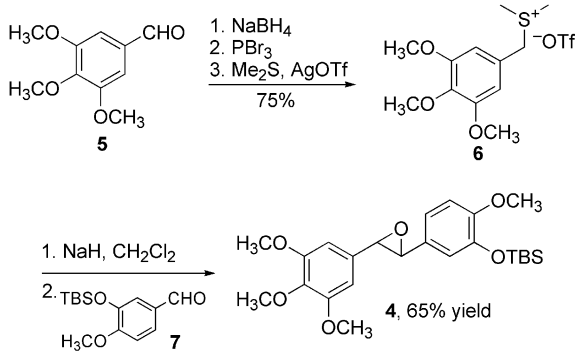
Novel stilbenic compounds are usually prepared by using two main reactions: Wittig and Perkin condensations. In the Wittig reaction, a mixture of the two geometrical isomers (*Z* and *E*) is always obtained.[1,4] In the Perkin reaction, the *Z* isomer predominates, but a high-temperature decarboxylative process is necessary to obtain the final product.[5] Among the hundreds of combretastatin derivatives synthesized so far, those bearing oxygenated functional groups on the ethylene chain have shown unusual properties with respect of their SARs. In particular, dioxolane-based *trans*-(*S*,*S*)-**2** and its enantiomer *trans*-(*R*,*R*)-**2** showed strong antitubulin activity,[6] whereas the corresponding *cis* isomers were inactive,[7] although the *Z* geometry of the two aromatic rings linked by the olefinic group has been claimed as an essential feature for the biological activity of CA-4.

Recently, stilbene epoxides were tested for cytotoxicity against the human leukaemia K562 cell line and *trans*-epoxide **3** of CA-4 showed good activity, although it was ineffective in the inhibition of the tubulin assembly. Nonetheless, its synthesis remains challenging, as attempts to oxidize combretastatins have failed, and catalytic ylide-mediated epoxidation of 3,4,5-trimethoxybenzaldehyde gave extremely poor yield of **3**.[8]

Results and Discussion

Here we describe an expeditious and efficient synthesis of silyl protected *trans*-epoxide **4** (Scheme 1) and its useful alternative transformations into either dioxolane derivatives or CA-4.

During our studies on the synthesis and elaboration of 2,3-diaryloxiranes[9] we took advantage of stoichiometric sulfur ylide mediated epoxidation of aryl aldehydes, and recently, structurally complex oxyfunctionalized aryl aldehydes were also efficiently transformed into the correspond-



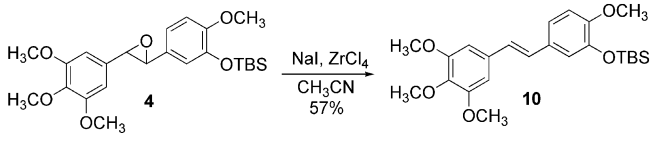
Scheme 1. Synthesis of *trans*-epoxide **4**.

ing *trans*-epoxides.[10] Although it appears of high substrate scope in both asymmetric and nonasymmetric versions, the reaction is particularly fine balanced if ylides bearing weakly anion-stabilizing groups such as substituted benzyl groups are used.[11] In general, the stereoselectivity is governed by both the electronic and steric properties of the reagents and electron-donating groups on either the ylide or aryl aldehyde lead to lower diastereocontrol. Thus, the stereoselective synthesis of polyphenolic diaryl epoxides appears particularly challenging. In principle, two alternative retrosynthetic approaches are always possible for epoxide **4**, depending on which aryl fragment is derived from the sulfur ylide and which one is derived from the aryl aldehyde. Initial studies on the transformation of either the commercially available isovanillin or 3,4,5-trimethoxybenzaldehyde **5** toward the corresponding sulfur ylide revealed the latter as the most suitable starting material. Thus, **5** was easily converted into the corresponding dimethylsulfonium triflate **6** in three steps and good overall yield.

The subsequent epoxidation reaction was performed with NaH as base to generate the ylide[12] and silyl-protected isovanillin **7** to afford the expected *trans*-epoxide **4** stereoselectively and in good isolated yield. In order to test the synthetic scope of such an intermediate we submitted epoxide **4** to our recently developed regio- and stereoselective ring-opening reactions, which were efficient on various *trans* 2,3-diarylepoxides.[13] In particular, the LiBr/Amberlyst 15 system[13b,14] afforded ketone **8** through acid-promoted rearrangement of the epoxide. In contrast, the direct conversion into *trans*-dioxolane **9** by the acetone/Amberlyst 15 system[13a] furnished the expected product stereospecifically and in good isolated yield (Scheme 2).

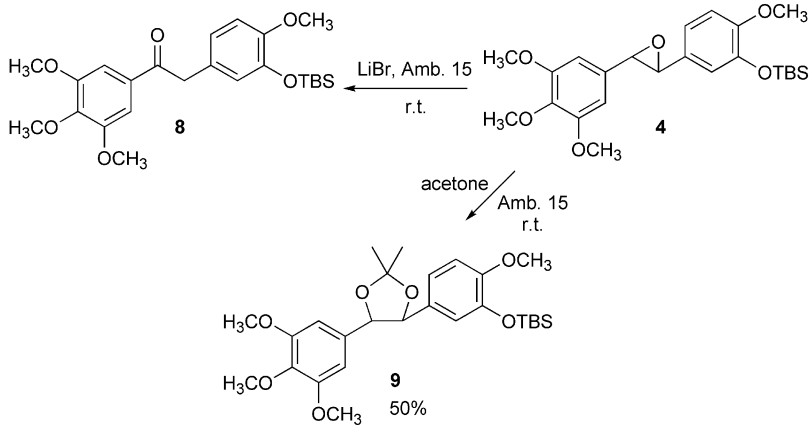
On the way to find a new access to Combretastatine A-4, we looked for an efficient deoxygenation method of epoxide **4**. Relatively few methods exist for removing oxygen atoms from epoxides, especially those with a stilbenic structure.[15] Many of them require expensive reagents and harsh reaction conditions, which may affect sensitive functional groups in the molecule.

Recently, $ZrCl_4$/NaI was described as a safe and highly efficient reagent for the chemoselective deoxygenation of various epoxides.[16] By using such a procedure, epoxide **4** was stereospecifically converted into *trans*-stilbene derivative **10** in good yield (Scheme 3).



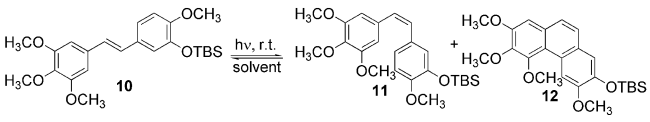
Scheme 3. Deoxygenation of *trans*-epoxide **4**.

The last step for obtaining *cis*-combretastatine derivative **11**, affording the formal synthesis of CA-4,[17] required the isomerization of the stilbenic double bond. Among the methods described, the photochemical isomerization appears, in principle, to be the best procedure in terms of selectivity, in particular when nonthermodynamic products are wanted.[18] Although photochemical isomerization of **10** to **11** at 254 nm in ethanol was described,[1] in our hands the reproduction of the same reaction conditions produced, rapidly, discrete quantities of phenanthrene **12**, which increased with prolonged reaction time. Thus, in order to find the best reaction conditions in terms of *cis*/*trans* ratio and chemical yield, the photoisomerization was run at 254 nm, at room temperature, in solvents with different polarities. The results are listed in Table 1.



Scheme 2. Elaboration of *trans*-epoxide **4**.

Table 1. Effect of the solvent on the formation of phenanthrene **12**.



Entry[a]	Solvent	Time [h]	**10** + **11**[b]	**12**[b]
1	*n*-hexane	11	96	4
2	*n*-hexane	17	93	7
3	*n*-hexane	48	73	27
4	benzene	5	93	7
5	benzene	8	91	9
6	benzene	14	78	22
7	acetone	44	100	0
8	CH_3CN	16	83	17
9	CH_3OH	4	85	15
10	CH_3OH	8	87	13

[a] All the reactions were performed by using a 15-W low-pressure Hg lamp (λ_{max} = 254 nm). [b] Product ratios were determined by the corresponding relative intensities of GC peaks.

In low-polar solvents (*n*-hexane, benzene), phenanthrene **12** was detected by GC–MS analysis after a few hours (11 h in *n*-hexane, 5 h in benzene) and increased as the olefins reached the photostationary ratio. In CH_3OH, **12** was formed even faster (15 mol-% after 4 h).[19] By using solvents at intermediate polarity, such as acetone and CH_3CN, **12** was practically absent even at prolonged reaction time, and only after 16 h in acetonitrile was 17 mol-% of this product detected.

The photostationary *cis*/*trans* ratio was also determined and the results are listed in Table 2.

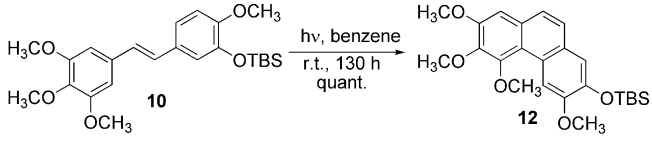
Table 2. Effect of the solvent in the *cis*/*trans* ratio.[a]

Entry	Solvent	*cis*/*trans* (**11** + **10**)	Time [h]
1	*n*-hexane	60:40	48
2	benzene	66:33	14
3	acetone	80:20	44
4	CH_3CN	80:20	16
5	CH_3OH	89:11	8

[a] All reactions were run until the constancy of relative GC peak intensities.

These results are not in agreement with those obtained with other substituted stilbenes. As an example, the photoisomerization of 4-methoxy-4′-nitrostilbene suffers from a strong solvent effect. The *Z*/*E* ratio upon excitation at 366 nm is 91:9 in petroleum ether and 17:83 in DMF.[20] For stilbene photoisomerization the Orlandi–Siebrand model is accepted.[21] On this basis, the [*cis*]/[*trans*] = ($\varepsilon_{trans}/\varepsilon_{cis}$)$k_{tp}/k_{cp}$, where k_{tp} and k_{cp} are the kinetic constants for the transition from the excited singlet state of the *trans* and *cis* isomers to a dipolar twisted "phantom" intermediate.[22] Compound **10** showed absorption maxima at λ = 331 and 350 nm (shoulder). Its fluorescence spectrum showed an emission at λ = 373 nm (λ_{exc} = 330 nm). Calculations performed by using TD-DFT/B3LYP/6-31G(d,p) on Gaussian 03[23] showed that the absorption at 331 nm is a π–π* transition between the HOMO at –0.192 H and the LUMO at –0.053 H (330 nm). However, another S_1 state can be populated corresponding to a transition HOMO → NLUMO: a π–π* is obtained with a more polar character than the first one, considering that the NLUMO orbital (–0.010 H) is restricted to the second aromatic ring. The increase in the *cis*/*trans* ratio with the polarity of the solvents can be explained assuming the inversion between the two excited states due to stabilization in polar solvents of the most polar excited state.[22] This stabilization can cause an increase in k_{tp} giving a higher concentration of the *cis* isomer in the photostationary state.

Although CH_3OH appears to be the best solvent for the high *cis*/*trans* ratio obtained in relatively short reaction times, the contemporary formation of phenanthrene **12** and other byproducts makes this procedure of low synthetic interest. In low-polar solvents, low *cis*/*trans* ratios were obtained, whereas in acetone and acetonitrile an interesting 80:20 *cis*/*trans* ratio was achieved, acetone being the solvent of choice for synthetic purposes as a result of the absence of any detectable byproduct. Phenanthrene **12** is also an interesting product, being the silyl-protected derivative of a natural product isolated from the above-cited *Combretum caffrum*[24] and *Combretum psidioides*.[25] Because this compound can be obtained by oxidative photocyclization from the parent stilbene derivative,[26] we investigated the possibility to achieve it by our photocyclization method. After a screening of solvents and reaction conditions we found that quantitative yield of **12** was obtained in 130 h from **10** performing the photochemical cyclization in benzene at room temperature (Scheme 4).



Scheme 4. Photochemical cyclization of *trans*-stilbene **10**.

Conclusions

We developed a new high-yielding stereoselective approach to oxygenated combretastatine derivatives, and we were also able to prepare *cis*-CA-4 and phenanthrene analogues from a common parent *trans*-stilbene derivative.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively. Mass spectra were recorded with a Hewlett–Packard 6890 chromatograph equipped with a HP 5973 mass detector. Commercially available reagents were used without further purification. All reactions were monitored by TLC on silica-gel-coated plates. Column chromatography was carried out by using 60–240 mesh silica gel at atmospheric pressure.

Dimethyl(3,4,5-Trimethoxybenzyl)sulfonium Triflate 6: To a solution of 3,4,5-trimethoxybenzyl bromide (900 mg, 3,45 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dimethyl sulfide (0.26 mL) and silver trifluoromethanesulfonate (1.49 g, 5.80 mmol) under an ar-

gon atmosphere. The reaction was stirred in the dark for 15 min. The silver bromide was filtered and washed with CH_2Cl_2 (20 mL), and the filtrate was concentrate in vacuo. To the dark oil was added anhydrous Et_2O (30 mL) and, after one hour, the formation of a white solid was observed. The solid was filtered to obtain 838 mg (62% yield) of pure salt **6**. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.91 (s, 6 H), 3.86 (s, 3 H), 3.87 (s, 6 H), 4.70 (s, 2 H), 6.74 (s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.9, 47.5, 56.3, 60.8, 105.7, 107.7, 121.6, 132.3, 154.0 ppm. $C_{13}H_{19}F_3O_6S_2$ (392.41): calcd. C 39.79, H 4.88; found C 39.70, H 4.90.

***trans*-3-(4-Methoxy-3-*tert*-butyldimethylsilyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)oxirane (4):** To a suspension of NaH (45 mg, 1.8 mmol) in CH_2Cl_2 (10 mL) was added a solution of sulfonium salt **6** (560 mg, 1.43 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After 1 h, a solution of 3-*tert*-butyldimethylsilyloxy-4-methoxybenzaldehyde (**7**; 400 mg, 1.5 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was stirred for 48 h at 0 °C. Cold water (20 mL) was added to the slurry, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic phase was dried with Na_2SO_4, filtered, and concentrated under vacuum. Chromatographic purification on silica gel (petroleum ether/diethyl ether, 6:4) gave 415 mg (65% yield) of pure epoxide **4** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17 (s, 6 H), 1.00 (s, 9 H), 3.72 (d, ^3J = 2.0 Hz, 1 H), 3.80 (d, ^3J = 2.0 Hz, 1 H), 3.82 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 6 H), 6.58 (s, 2 H), 6.83 (d, J = 2.0 Hz, 1 H), 6.85 (d, ^3J = 8.0 Hz, 1 H), 6.91 (dd, J = 8.0 Hz, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, 18.4, 25.6, 55.5, 56.0, 60.8, 62.6, 62.7, 101.9, 112.0, 117.9, 118.9, 129.3, 132.9, 137.7, 145.2, 151.1, 153.4 ppm. MS: *m*/*z* (%) = 446 (4) $[M]^+$, 417 (70), 389 (90), 345 (100). $C_{24}H_{34}O_6Si$ (446.61): calcd. C 64.54, H 7.67; found C 64.55, H 7.71.

***trans*-5-(3-*tert*-Butyldimethylsilyloxy-4-methoxyphenyl)-2,2-Dimethyl-4-(3,4,5-trimethoxyphenyl)-1,3-dioxolane (9):** To a solution of epoxide **4** (80 mg, 0,18 mmol) in acetone (2 mL) was added Amberlyst 15 (220 mg mmol^{-1}) at room temperature. After 16 h, solid $NaHCO_3$ was added, the mixture was filtered, and the solvent was removed under vacuum. Chromatographic purification on silica gel (petroleum ether/diethyl ether, 6:4) gave 45 mg (50% yield) of pure dioxolane **9** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.12 (s, 6 H), 0.97 (s, 9 H), 1.66 (s, 6 H), 3.77 (s, 3 H), 3.80 (s, 3 H), 3.83 (s, 6 H), 4.61 (d, ^3J = 8.5 Hz, 1 H), 4.66 (d, ^3J = 8.5 Hz, 1 H), 6.42 (s, 2 H), 6.78 (d, J = 2.0 Hz, 1 H), 6.82–6.83 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.7, 18.4, 25.6, 27.1, 55.5, 56.0, 60.8, 84.8, 85.2, 103.1, 109.1, 111.6, 119.5, 120.4, 129.1, 132.5, 137.5, 144.9, 151.0, 153.1 ppm. MS: *m*/*z* (%) = 504 (2) $[M]^+$, 447 (23), 251 (100), 209 (75). $C_{27}H_{40}O_7Si$ (504.69): calcd. C 64.26, H 7.99; found C 64.23, H 7.97.

(*E*)-5-(3-*tert*-Butyldimethylsilyloxy-4-methoxystyryl)-1,2,3-trimethoxybenzene (10): To a solution of epoxide **4** (200 mg, 0.45 mmol) in anhydrous CH_3CN (5 mL) was added $ZrCl_4$ (53 mg, 0.23 mmol) and NaI (135 mg, 0.90 mmol, previously dried under vacuum at 200 °C). The reaction mixture was stirred at room temperature for 2 h. Cold water (2 mL) and Et_2O (2 mL) were added, and the two phases were separated. The organic layer was washed with 10% aqueous $Na_2S_2O_3$ (10 mL) and water (10 mL) and then dried with anhydrous Na_2SO_4. The solvent was removed under vacuum. Chromatographic purification of the crude on silica gel (petroleum ether/diethyl ether, 6:4) gave 110 mg (57% yield) of pure **10** as an oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.19 (s, 6 H), 1.04 (s, 9 H), 3.83 (s, 3 H), 3.87 (s, 3 H), 3.92 (s, 6 H), 6.72 (s, 2 H), 6.84 (d, ^3J = 8.0 Hz, 1 H), 6.85 (d, ^3J = 16.0 Hz, 1 H), 6.91 (d, ^3J = 16 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H), 7.06 (dd, J = 8.5 Hz, J = 2.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.6, 18.4, 25.7, 55.4, 56.0, 60.9, 103.1, 112.0, 118.5, 120.4, 126.5, 127.8, 130.3, 133.4, 137.5, 145.1, 151.0, 153.3 ppm. MS: *m*/*z* (%) = 430 (32) $[M]^+$, 358 (100), 343 (40). $C_{24}H_{34}O_5Si$ (430.61): calcd. C 66.94, H 7.96; found C 66.90, H 7.89.

(*Z*)-5-(3-*tert*-Butyldimethylsilyloxy-4-methoxystyryl)-1,2,3-trimethoxybenzene (11): A solution of *trans*-stilbene **10** (50 mg; 0.1 mmol) in acetone (20 mL) was irradiated at λ = 254 nm at room temperature. After 44 h, the irradiation was stopped and the solvent was evaporated. Chromatographic purification of the crude on silica gel (petroleum ether/diethyl ether, 6:4) gave 39 mg (78% yield) of pure **11**. ^{1}H and ^{13}C NMR data were identical to those reported in the literature.[1] MS: *m*/*z* (%) = 430 (32) $[M]^+$, 358 (100), 343 (40). $C_{24}H_{34}O_5Si$ (430.61): calcd. C 66.94, H 7.96; found C 66.85, H 7.95.

7-*tert*-Butyldimethylsilyloxy-2,3,4,6-tetramethoxyphenanthrene (12): A solution of *trans*-stilbene **10** (50 mg; 0.1 mmol) in benzene (20 mL) was irradiated at λ = 254 nm at room temperature for 130 h. After evaporation of the solvent under vacuum, phenanthrene **12** (50 mg) was quantitatively obtained as the pure product. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.17 (s, 6 H), 1.00 (s, 9 H), 3.71 (s, 6 H), 4.04 (s, 3 H), 4.05 (s, 3 H), 7.08–7.39 (m, 3 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.54 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = –4.57, 18.5, 23.8, 25.6, 25.7, 25.9, 29.6, 55.2, 55.8, 60.4, 61.3, 105.1, 107.9, 118.0, 118.5, 124.3, 125.1, 126.0, 127.2, 128.3, 129.4, 142.3, 144.1, 150.9, 151.5, 151.7 ppm. $C_{24}H_{32}O_5Si$ (428.59): calcd. C 67.26, H 7.53; found C 67.15, H 7.60.

Supporting Information (see footnote on the first page of this article): Additional experimental procedures; selected ^{1}H and ^{13}C NMR spectra.

Acknowledgments

We thank the University of Basilicata for financial support.

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Received: September 30, 2008
Published Online: November 25, 2008

