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Stilbenophane Analogues of Deoxycombretastatin A-4

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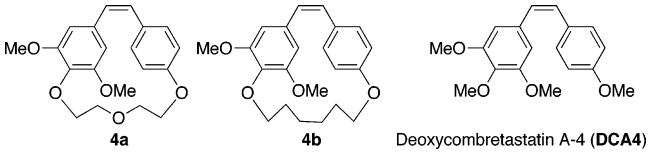
Received April 26, 2005



A new family of polyoxygenated stilbenophanes has been synthesized as conformationally restricted analogues of antimitotic combretastatins. By means of the McMurry olefination process, compounds derived from diethyleneglycol and 1,6-hexanediol were obtained, whereas Grubbs' catalyst failed in producing the ring-closing metathesis to this kind of macrocyclic products.

Diversely substituted paracyclophane derivatives are compounds of interest due to their structural features and properties.[1] Among the paracyclophanes, the so-called stilbenophanes[2] have two aromatic systems linked by an olefinic bridge. Polyether linkages between aromatic systems are found in interesting organic compounds such as the crown ethers, their main use being as complexing agents for cations (coronands[3] and other supramolecular hosts[4]). They have also been used as catalysts,[5] polymeric materials,[6] and molecular machines and switches.[7] However, less frequent are those displaying biological activity as in the use of rotaxanes as

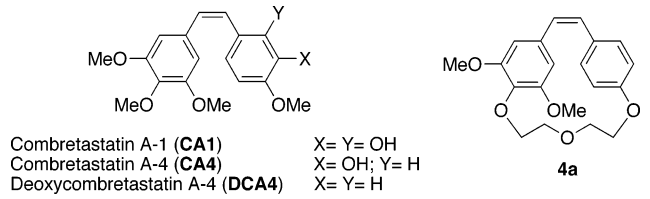


FIGURE 1. Structure of combretastatin A-1 (**CA1**), combretastatin A-4 (**CA4**), its 3′-deoxyanalogue (**DCA4**), and designed stilbenophane **4a**.

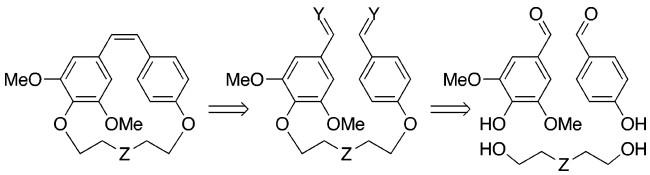


FIGURE 2. Retrosynthetic analysis of synthesized stilbenophanes. Ring-closing metathesis (Y = CH_2) or McMurry olefination (Y = O) was the methodology selected for the macrocyclization process.

cellular transport agents.[8] The combination of cyclophanes and crown ethers is known as crownophanes.[9]

During our research directed at the synthesis and evaluation of new cytotoxic agents based on natural products,[10] we designed several macrocyclic derivatives of the antimitotic agents combretastatin A-4 and related compounds (Figure 1).[11]

These compounds are polyoxygenated stilbenophanes macrocyclized through a polymethylene(polyether) chain sharing in part the structure of crownophanes. The presence of hexamethylene or 3-oxapentamethylene linkers restrict the conformational freedom of combretastatins, because they occupy the space between the two rings. This fact prevents the adoption of conformations in which the phenyl rings could be close to the coplanarity with the double bond. The synthesis of these derivatives and the study of the effect on their particular conformations and biological activities are very interesting in the search for new bioactive compounds. We planned the synthesis of title compounds as depicted in Figure 2. For synthetic simplicity and versatility, we selected the formation of the stilbenic double bond as the macrocy-

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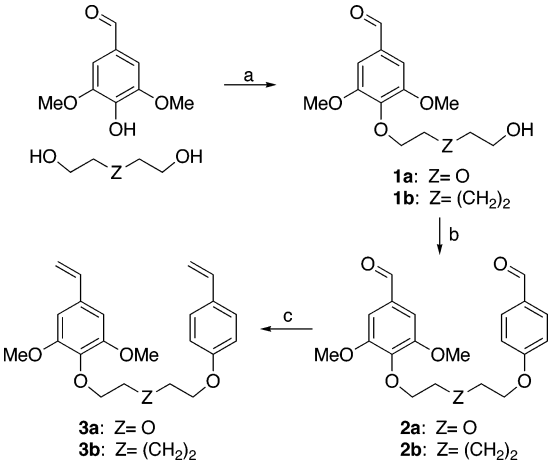
10.1021/jo0508393 CCC: $30.25
Published on Web 07/14/2005

SCHEME 1. Preparation of Synthetic Intermediates for Planned RCM and McMurry Macrocyclizations[a]



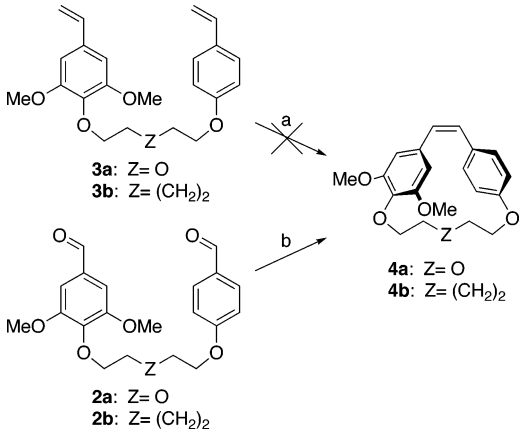
[a] Conditions (1 equiv = 1 mol/mol): (a) Diethyleneglycol or 1,6-hexanediol (2−10 equiv), DBAD (1.5−2 equiv), Ph_3P-resin (2 equiv), CH_2Cl_2 (dry), 48 h (70−80%); (b) 4-hydroxybenzaldehyde (1 equiv), DBAD (1 equiv), Ph_3P-resin (1 equiv), 70 h (55−80%); (c) $CH_3PPh_3^+I^-$(4−7 equiv), THF, −40 °C, ^{n}BuLi (1.6 M in hexane, 3.5−6 equiv), 50 min, then dialdehyde, −40 °C→ rt, 24 h (75−85%).

clization step, avoiding the formation of *Z*/*E* stereoisomers if the formation of the double bond was selected as the first step.

Ring-closing metathesis (RCM) of divinyl derivatives (Figure 2, Y = CH_2) was initially chosen due to its experimental simplicity and general utility for this kind of transformations. The McMurry reaction was envisaged as an alternative procedure, which could be directly applied to intermediate dialdehydes (Figure 2, Y = O) in a shorter synthetic sequence. However, the harsh conditions required, the low tolerance to functional groups, and the possibility of formation of undesired sideproducts (e.g., the dihydroxyderivatives) kept us from selecting it as our initial choice. Following this plan, the first results obtained during the synthesis of those stilbenophanes containing the diethyleneglycol bridge (Z = O) and the hexamethylene bridge (Z = $(CH_2)_2$) are now presented.

Compounds **1a** and **1b** were obtained in high yields by Mitsunobu[12] reaction of syringaldehyde with a large excess of either diethyleneglycol or 1,6-hexanediol (Scheme 1), to prevent the appearance of the dialkylation products that could result from the double Mitsunobu reaction of the diol. Subsequently, 4-hydroxybenzaldehyde was coupled to these compounds by a second Mitsunobu reaction, producing dialdehydes **2a** and **2b**. When they were to be used in the McMurry reaction, the use of solid-supported triphenylphosphine greatly improved the overall outcome of the synthetic route.[13] Divinyl derivatives **3a** and **3b** were prepared by Wittig olefination.

SCHEME 2. Synthesis of 4a and 4b[a]



[a] Conditions (1 equiv = 1 mol/mol): (a) Grubb's catalyst (0.05 equiv to excess) in $CHCl_3$ or CH_3OH, 12−4.5 × 10^3 h, rt to 80 °C (eventually ultrasound). (b) $TiCl_4$−Zn (5 equiv/10 equiv) in THF (dry) stirred for 30 min under reflux, then **2** in THF added dropwise and reacted 3−5 h (5−15% yield of **4** after purification).

We started by investigating the ring-closing metathesis[14] approach (Scheme 2). Under reaction conditions that demonstrated their utility for related macrocyclizations,[15] neither compound **3a** nor **3b** produced the expected stilbenophanes **4a** or **4b**. Chloroform, methanol, or benzene at either room temperature or reflux and the addition of catalyst up to equimolecular amounts and long periods of time were assayed,[16] but in no case was transformation of the starting material to cyclization products observed (no dimerization is produced under diluted conditions). As the activity of the catalyst had been checked with model compounds, we conclude that the tension required to approach both ends of the molecule is responsible for this lack of reactivity. The rigidity of the benzenic systems and the steric and torsional hindrance of the polymethylene bridge arising upon folding to the reaction intermediates seem to be the origin of such tension.

Once the RCM approach was discarded, we turned to the McMurry reaction[17] as an alternative procedure. Following the literature, several conditions were assayed. The reactions were carried out by slow addition of a solution of the dialdehyde to the reagent, under highly diluted conditions.[18] Reactions carried out at room temperature led to spectroscopically complex mixtures of polar compounds, which we believe correspond to the macrocyclic glycols. Reactions in refluxing THF favored the formation of olefinic products but had to be carefully controlled, as extended reaction times greatly reduced the reaction yields. In any case, the reactions produced

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(13) Absence of triphenyl phosphine or its oxide is an absolute requirement in the McMurry reaction, which did not work if minor amounts of this product were present. Due to the coelution of triphenyl phosphine oxide during the chromatographic purification of the Mitsunobu reaction products, use of the resin-supported reagent fully avoids this problem.

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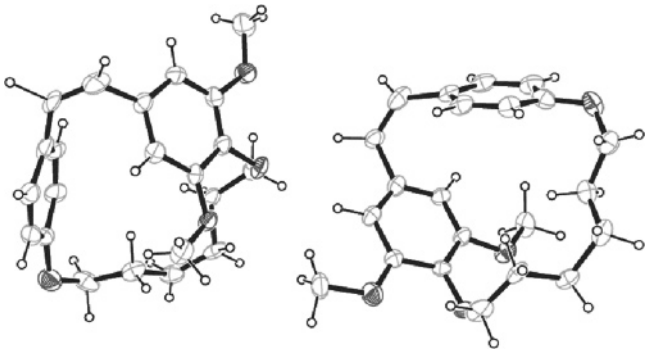

FIGURE 3. Ortep representation of the X-ray structure of compound **4b**, showing two molecules in the asymmetric unit.

TABLE 1. Comparison of ^{1}H NMR Shifts for Representative Protons of 4a,b and DCA4

	DCA4	4a	4b
3,5-OMe	3.69	3.62	3.63
2,6	6.51	5.93	6.09
2′,6′	7.25	6.69	6.80
3′,5′	6.80	6.67	6.63
olefinic	6.44/6.53	6.92/6.95	6.88/6.88

mixtures containing new olefinic and hydroxylated macrocyclic products. Careful separation by CC allowed us to isolate the final products **4a** or **4b**, although not in very high yields.

Compounds **4a** and **4b** showed simple NMR spectra, with a single signal for each chemically equivalent set of protons or carbons such as both methoxy groups, the 2,6, the 2′,6′, and the 3′,5′ aromatic proton pairs, or the potentially diastereotopic hydrogens of the methylene groups. The symmetry of the benzene rings and the absence of highly severe restrictions on the interconversion of both of the most stable (enantiomeric) conformations in the NMR spectra account for this fact. The NOEs between the 2,6 proton pair and 2′,6′ and 3′,5′ and the methylene bridge are the only ones observed. A comparison of the proton chemical shifts of the macrocycles with those described[19] for their noncyclized analogue deoxycombretastatin A-4 (**DCA4**, Figure 1) shows significant upfield shifting of all the aromatic protons and a downfield shift of the olefinic ones (Table 1), suggesting different conformational spaces for the macrocycles and the open analogues.

The structure of compound **4b** was confirmed by X-ray diffraction studies (Figure 3). The observed conformation in the solid state is the same calculated and in full agreement with the NMR data. We have compared this conformation with that obtained for the related combretastatin A-1.[20] The most noticeable difference is the close to parallel disposition of both aromatic rings, shifted to a situation that maintains the 2,6 (2′,6′) protons over the other aromatic ring, thus producing the strong shielding observed in **4a**,**b**. Combretastatin A-1, without the restrictions imposed by the bridge between positions 4 and 4′, has a nearly orthogonal disposition of both aromatic rings.

Once these compounds were prepared, we assayed them for their antimitotic activity, to check if the structural relationship between **4a**, **4b**, and combretastatin A-4 (**CA4**) or its deoxyanalogue **DCA4** is also reflected in their biological properties. Following the known methodology,[21] the inhibition of tubulin polymerization (ITP) IC_{50} values were >40 μM (**4a**) and about 40 μM (**4b**), far from the value (3 μM) obtained for **CA4** (and that described for **DCA4**, IC_{50} (ITP) = 2.2 μM[19]). The decrease in antimitotic activity, despite the structural similarity, could be attributed to either the presence of three (**4a**) or four (**4b**) additional atoms, in comparison to **DCA4**, or the conformational restrictions imposed on the phenyl rings by the bridge. Taking into consideration the relatively small increase of the molecular volume produced by these additional atoms, as well as the orthogonality between both aromatic rings in the related active compounds when bound to the target protein,[22] the second explanation is the most feasible.

In conclusion, the synthesis of a family of new stilbenophanes (crownophanes) has been completed and their activity as inhibitors of tubulin polymerization investigated. After these results, new members of this type of compound are being obtained in order to deduce the structure−activity relationships.

Experimental Section

General Procedure for the Mitsunobu Reactions Producing Hydroxyaldehydes 1 and Dialdehydes 2. A mixture of the PPh_3-resin (11.0 mmol), syringaldehyde (11.0 mmol), and a large excess of the diol (55.0 mmol) in dry CH_2Cl_2 (125 mL) was stirred for 1 h before the slow addition of DBAD or DIAD (12.1 mmol) at rt. After 48 h, the reactions were filtered, and the resin was washed with EtOAc. The combined organic layers were evaporated, dissolved in EtOAc, and washed with NaOH (4%) and water to neutrality. Once dried and evaporated, the crude reaction products were used in the next Mitsunobu reaction or purified by flash chromatography (Hex/EtOAc mixtures) for characterization purposes. Using the same procedure, the reaction products were reacted with an excess of 4-hydroxybenzaldehyde (1.1 mol/mol of **1**) to produce the dialdehydes (**2**).

4-[2-(2-Hydroxyethoxy)ethoxy]-3,5-dimethoxybenzaldehyde (1a). Oily compound. Yield: 73%. FTIR: 3401, 2736, 1683 cm $^{-1}$. ^{1}H NMR (200 MHz) δ: 3.60 (2H, m), 3.70 (2H, m), 3.80 (2H, m), 3.92 (6H, s), 4.20 (2H, m), 7.14 (2H, s), 9.86 (1H, s). ^{13}C NMR (50.3 MHz) δ: 56.3 (2)(CH_3), 61.5 (CH_2), 70.2 (CH_2), 72.4 (CH_2), 72.5 (CH_2), 106.7 (2)(CH), 131.8 (C), 142.5 (C), 153.7 (2)(C), 191.1 (CHO). GC-MS, *m/z*: 270 (M^+, 11%).

4-{2-[2-(4-Formylphenoxy)ethoxy]ethoxy}-3,5-dimethoxybenzaldehyde (2a). Oily compound. Yield: 70%. FTIR: 2738, 1693 cm $^{-1}$. ^{1}H NMR (200 MHz) δ: 3.80 (2H, m), 3.91 (6H, s), 4.00 (2H, m), 4.20 (4H, m), 7.01 (2H, d, J = 8.4), 7.12 (2H, s), 7.82 (2H, d, J = 8.4), 9.86 (1H, s), 9.88 (1H, s). ^{13}C NMR (50.3 MHz) δ: 56.2 (2) (CH_3), 67.9 (CH_2), 69.5 (CH_2), 70.8 (CH_2), 72.4 (CH_2), 106.7 (2)(CH), 114.9 (2)(CH), 130.0 (C), 130.9 (C), 131.9

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(2)(CH), 142.6 (C), 153.7 (2)(C), 163.9 (C), 190.9 (CHO), 191.1 (CHO). GC-MS, *m/z*: 374 (M^+, 32%).

General Procedure for Wittig Reactions Producing Diolefins 3. To a solution of methyltriphenylphosphonium iodide (5.8 mmol) in dry THF (80 mL) at −40 °C was added *n*BuLi 1.6 M in hexane (2,5 mL; 4.0 mmol), and the bright red solution was stirred for 30 min. After the addition of the dialdehyde **2** (0.6 mmol in dry THF, 20 mL), a pale yellow solution was obtained that was allowed to heat to room temperature and to react overnight. The reaction mixture was added to an ammonium chloride solution, extracted with EtOAc and purified by chromatography (SiO_2, hexane/EtOAc mixtures) to give the pure diolefins **3** in high yields.

1,3-Dimethoxy-5-vinyl-2-{2-[2-(4-vinylphenoxy)-ethoxy]ethoxy}benzene (3a). Oily compound. Yield: 83%. FTIR: 1606, 1582, 1509 cm^{-1}. ^1H NMR: 3.78 (6H, s), 3.80 (2H, m), 3.90 (2H, m), 4.10 (4H, m), 5.05 (1H, d, $J = 11.4$), 5.14 (1H, d, $J = 11.2$), 5.53 (1H, d, $J = 16.7$), 5.58 (1H, d, $J = 17.6$), 6.55 (2H, s), 6.57 (1H, dd, $J = 17.6$, $J = 11.2$), 6.58 (1H, dd, $J = 16.7$, $J = 11.4$), 6.80 (2H, d, $J = 8.4$), 7.20 (2H, d, $J = 8.4$). ^{13}C NMR: 56.2 (2)(CH_3), 67.7 (CH_2), 69.8 (CH_2), 70.8 (CH_2), 72.4 (CH_2), 103.4 (2)(CH), 111.7 (CH_2), 113.3 (CH_2), 114.7 (2)(CH), 127.4 (2)(CH), 130.6 (C), 132.1 (C), 133.5 (C), 136.3 (CH), 136.8 (CH), 153.5 (2)(C), 158.7 (C). GC-MS, *m/z*: 370 (M^+, 34%).

General Procedure for Ring-Closing Metathesis. The failed ring-closing metatheses were carried out in different solvents, under variable conditions (inert atmosphere, temperature from rt to reflux, time from overnight to several months) using Grubbs' catalyst (benzylidene-bis(tricyclohexylphosphine)dichlororuthenium; from 0.05 to 1.0 mol/mol). The reaction was checked by evaporation of the solvent, dissolution in CH_2Cl_2, and stirring in the presence of carbon black followed by ^1H NMR of the crude product. No transformation was detected in any of the assayed conditions.

General Procedure for McMurry Reactions Yielding Stilbenophanes 4. A mixture of $TiCl_4$·2THF 97% (32.0 mmol) and Zn (64.0 mmol) in dry THF (200 mL) was prepared at 0 °C and refluxed for 30 min; then, a solution of the dialdehyde **2** (6.4 mmol) in dry THF (30 mL) was added and maintained at reflux for 3 h. The reaction was poured onto a mixture of EtOAc and 2 M HCl; the aqueous layer was extracted, and the combined organic layers were worked up. By chromatography (SiO_2, hexane/EtOAc mixtures), the olefinic products **4** were separated from the mixture of hydroxylated products.

(2*Z*)-8,11,14-Trioxatricyclo[13.2.2.2^{4,7}]henicosa-1-(17),2,4,6,15,18,20-heptaene (4a). Oily compound. Isolated yield: 5% (plus 30−40% polyhydroxylated products). FTIR: 1603, 1578, 1505 cm^{-1}. ^1H NMR (400 MHz) δ: 3.56 (2H, t, $J = 3.9$), 3.62 (2H, m, overlapped), 3.62 (6H, s), 4.13 (2H, t, $J = 4.3$), 4.26 (2H, dd, $J = 5.3$, $J = 3.9$), 5.93 (2H, s), 6.67 (2H, d, $J = 8.8$), 6.69 (2H, d, $J = 8.8$), 6.92 (1H, d, $J = 9.9$), 6.95 (1H, d, $J = 9.9$). ^{13}C NMR (100.6 MHz) δ: 55.7 (2)(CH_3), 67.0 (CH_2), 73.2 (CH_2), 73.3 (CH_2), 73.4 (CH_2), 107.1 (2)(CH), 114.5 (2)(CH), 130.0 (2)(CH), 131.1 (C), 134.0 (CH), 134.3 (CH), 134.8 (C), 136.2 (C), 152.2 (2)(C), 156,9 (C). HRMS: calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1421. Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.16; H, 6.48. Found: C, 70.47; H, 6.74.

Acknowledgment. We thank the "Junta de Castilla y León" (Ref 073/02), Spanish MCyT (Ref PPQ-2001-1977), and MEC (Ref CTQ2004-00369/BQU) and the EU (Structural Funds) for financial support.

Supporting Information Available: Analytical and spectral characterization data of all compounds (**1a**−**4b**), ^1H and ^{13}C NMR spectra of **1a**−**3b**, and a crystallographic information file for **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

JO0508393