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Total Synthesis of Tedarene A

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Abstract : Tedarene A is a macrocyclic diaryl ether heptanoid isolated from the marine sponge *Tedania ignis* and showing an inhibitory effect against nitric oxide production. The first total synthesis of tedarene A was achieved starting from the commercially available 3-(4-methoxyphenyl)propan-1-ol in 9 steps and 15.3% overall yield. The synthetic sequence featured an *E,Z*-dienic bond introduction and a macrocyclization under Ullman conditions. During the synthesis, the *E,E*-isomer of tedarene A was also obtained and fully characterized.

Natural and synthetic macrocycles have attracted growing attention in drug discovery and medicinal chemistry due to their favorable pharmacological properties.^{1,2,3} Among them, the cyclic diarylheptanoids have been reported to mediate diverse remarkable biological activities including antioxidant, anti-inflammatory, antiviral and anticancer ones.^{4,5,6} Diarylheptanoids are typical secondary metabolites widely distributed in plants that possess a 1,7-diphenylheptane structural skeleton. Three subgroups can be distinguished *i.e.* linear diarylheptanoids from which the most known is curcumin,⁷ cyclic biphenyl ([7,0]-metacyclophanes) such as myricanone,⁸ and cyclic diphenylethers that harbor a 14-oxa-[7,1]-metaparacyclophane architecture with acerogenin A⁹ or C¹⁰ as examples (Figure 1). Among the cyclic diaryletherheptanoid (DAEH) family, tedarene A (Figure 1) was recently isolated¹¹ from the marine sponge *Tedania ignis*, commonly named the fire sponge. It is the first DAEH extracted from a marine organism. Tedarene A shows an inhibitory activity on nitric oxide production¹¹ that may have therapeutic utility to treat inflammatory pathologies. In view of its pharmacological activity, the total synthesis of tedarene A represents an attractive challenge for chemists as a way to provide sufficient amounts of pure product for further biological assays. The unique structure of tedarene A comprises a 15-membered diaryl ether macrocycle displaying a phenol ring and an *E,Z*-conjugated diene unit in the seven-membered aliphatic chain. Herein, the first total synthesis of tedarene A is described. The key steps involve macrocyclization based on Ullmann coupling conditions and the regio- and stereoselective introduction of the two conjugated *E,Z*-alkene bonds by sequentially controlled reduction and elimination steps.

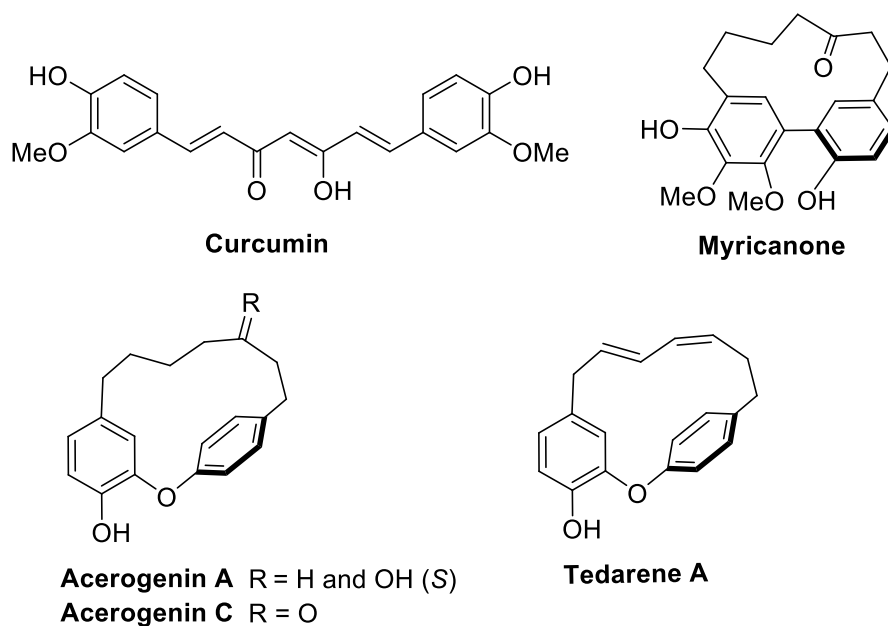
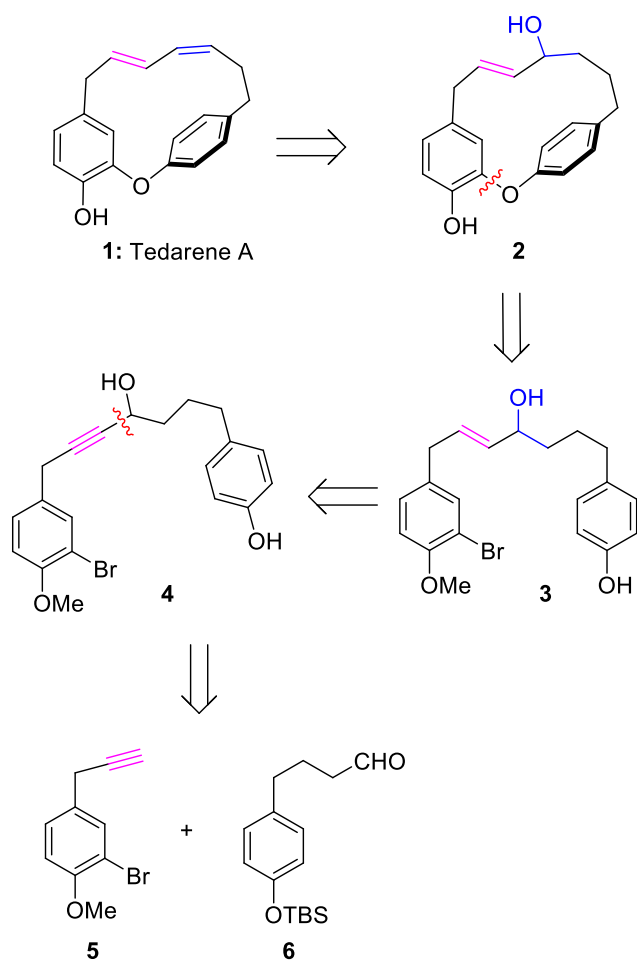


Figure 1. Representative diarylheptanoid natural products.

RESULTS AND DISCUSSION

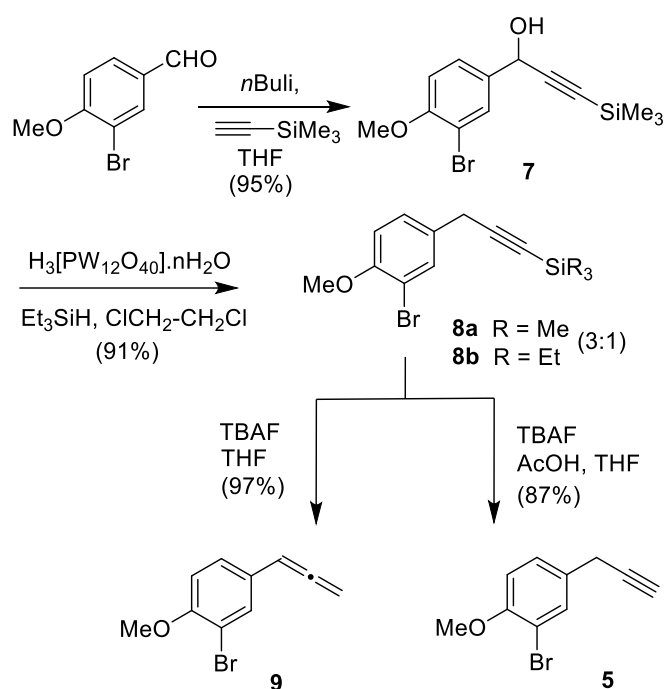
As shown in the retrosynthetic analysis outlined in Scheme 1, we envisioned that tedarene A (**1**) could be obtained by a stereocontrolled dehydration of *E*-allylic alcohol **2** giving rise to the conjugated *E,Z*-diene moiety. The macrocyclic core of **2** could result from an intramolecular Ullmann condensation of the linear bromophenol **3**. In turn, the *E*-double bond of **3** could stem from the controlled trans-hydrogenation of the propargyl alcohol **4**. The latter could be readily accessed by condensation of the acetylide anion of alkyne **5** on the protected aldehyde **6**.

Scheme 1. First Retrosynthetic Approach to Tedarene A (**1**)



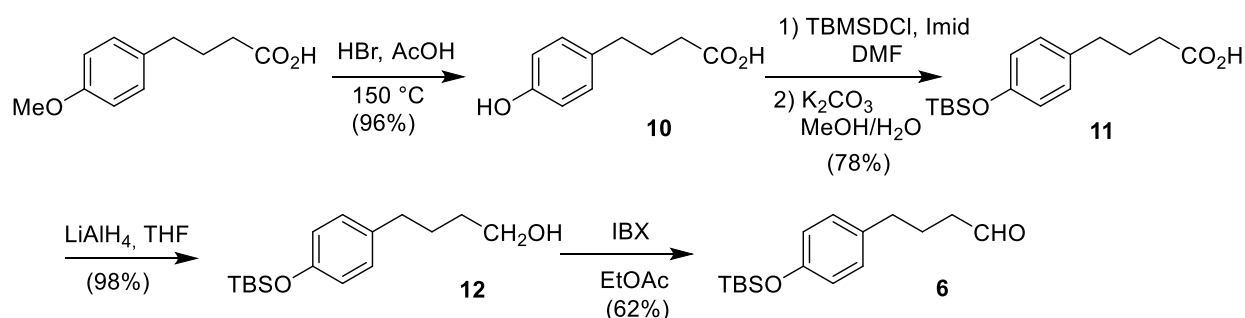
Our synthesis of the propargyl compound **5** started with 3-bromo-4-methoxybenzaldehyde as shown in Scheme 2. Ethynylation by the acetylide anion of propargyltrimethylsilane provided alcohol **7** in 95% yield. Deoxygenation was readily achieved in 91% yield by treatment with catalytic heteropolyacid $\text{H}_3[\text{PW}_{12}\text{O}_{40}]\cdot n\text{H}_2\text{O}$ in the presence of triethylsilane in dichloroethane.¹² It is of note that the trimethylsilyl alkyne **8a** was obtained in mixture with the unexpected triethylsilyl analogue **8b** (75/25 ratio) in 91% overall yield. This result was of no consequence on the synthesis as the next step consisted of a desilylation reaction. Initial treatment of a mixture of **8a** and **8b** with TBAF in THF at 0 °C led to allene **9** quantitatively. Alternative treatment with K_2CO_3 in MeOH at 0 °C afforded a mixture of the expected compound **5** along with allene **9** and the starting triethylsilane **8b** in a 60/20/20 ratio. Fortunately, addition of acetic acid in the presence of TBAF allowed circumvention of the formation of allene **9**.¹³ After optimization of the reaction conditions (3 additions of the reactants TBAF and AcOH spread over 6 days), the expected alkyne **5** was obtained in 87 % yield.

Scheme 2. Synthesis of Alkene 5



The required aldehyde **6** (Scheme 3) was obtained starting with the demethylation of 4-(4-methoxyphenyl)butanoic acid using hydrobromic acid in acetic acid at 150 °C to give rise to phenol **10** in 96% yield as previously described.¹⁴ The regioselective protection of the phenol function as a *t*-butyldimethylsilyl ether was achieved by reaction with TBDMSCl in the presence of imidazole in DMF followed by treatment with K₂CO₃ in a MeOH/H₂O mixture.¹⁵ Acid **11** obtained in 78% yield was then reduced to alcohol **12** using LiAlH₄ in 98% yield. Subsequent oxidation with IBX finally gave aldehyde **6** in 62% yield.

Scheme 3. Synthesis of Aldehyde 6

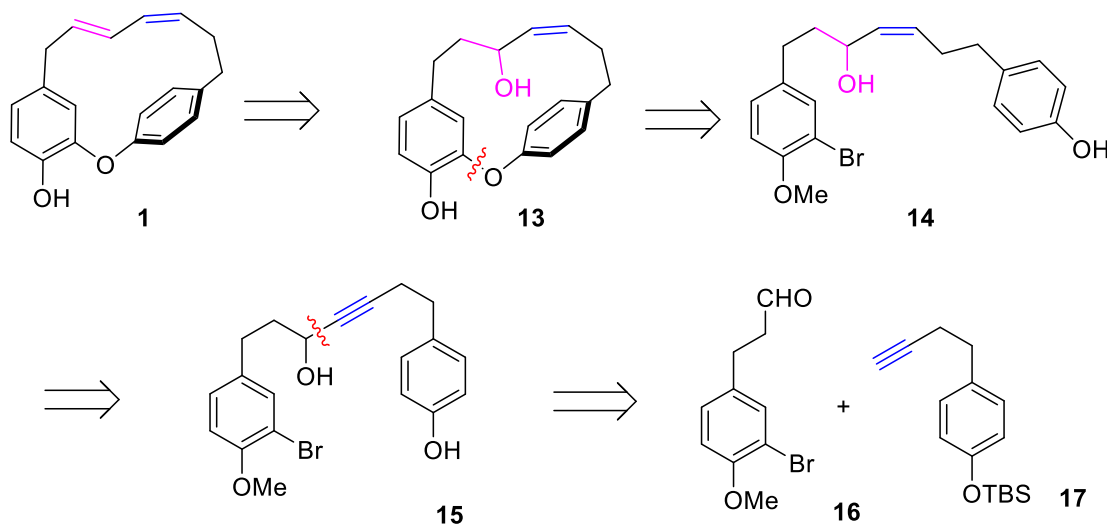


With compounds **5** and **6** in hand, we next examined the addition of the acetylide anion of **5** on aldehyde **6**. We first carried out the reaction in the presence of EtMgBr in THF.¹⁶ No addition product was formed. The use of Carreira conditions (Zn(OTf)₂, NEt₃ in toluene)¹⁷ equally failed to deliver the target compound. In both cases, starting materials were totally recovered. We next

conducted the reaction using LDA as the base at $-78\text{ }^{\circ}\text{C}$.¹⁸ Attempts were made by varying the reaction temperature, reaction time and the order of addition of the reagents. Unfortunately, this reaction was found to be not reproducible with the formation of trace amounts of the expected compound along with various amounts of allene **9**.

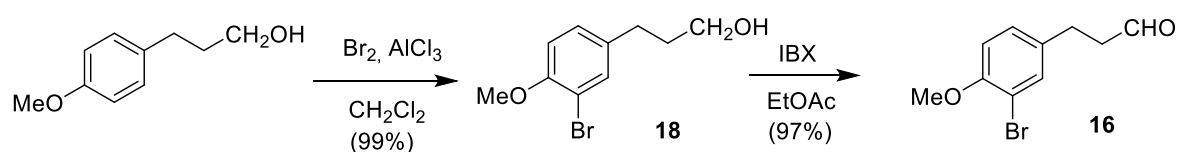
To overcome this failure due to the presence of acidic benzylic protons in alkyne **5**, we turned our attention to an alternative strategy for the synthesis of tedarene A as depicted in Scheme 4. The retrosynthetic strategy was still based on an intramolecular Ullmann cyclization. However, the timing of the formation of the double bonds was reversed. So, the *E*-alkene bond was envisioned to result from dehydration of the macrocyclic allylic alcohol **13** obtained by an Ullmann cyclization on bromophenol **14**. The *Z*-double bond of **14** would arise from a stereocontrolled hydrogenation of the propargyl alcohol **15**. The latter derivative was to be obtained more efficiently by condensing the acetylide anion of alkyne **17** onto aldehyde **16**. This strategy overcomes the problems arising from the acidic benzylic protons of alkyne **5** under basic conditions and was expected to efficiently lead to the target tedarene A.

Scheme 4. Second Retrosynthetic Approach to Tedarene A (1)



Bromoaldehyde **16** was synthesized in two steps starting from 3-(4-methoxyphenyl)propan-1-ol (Scheme 5). The regioselective monobromination of the aromatic ring by treating with bromine and aluminium chloride in CH_2Cl_2 and subsequent IBX oxidation of the resulting alcohol **18** led to the expected aldehyde **16** in 96% yield over two steps.

Scheme 5. Synthesis of Aldehyde 16

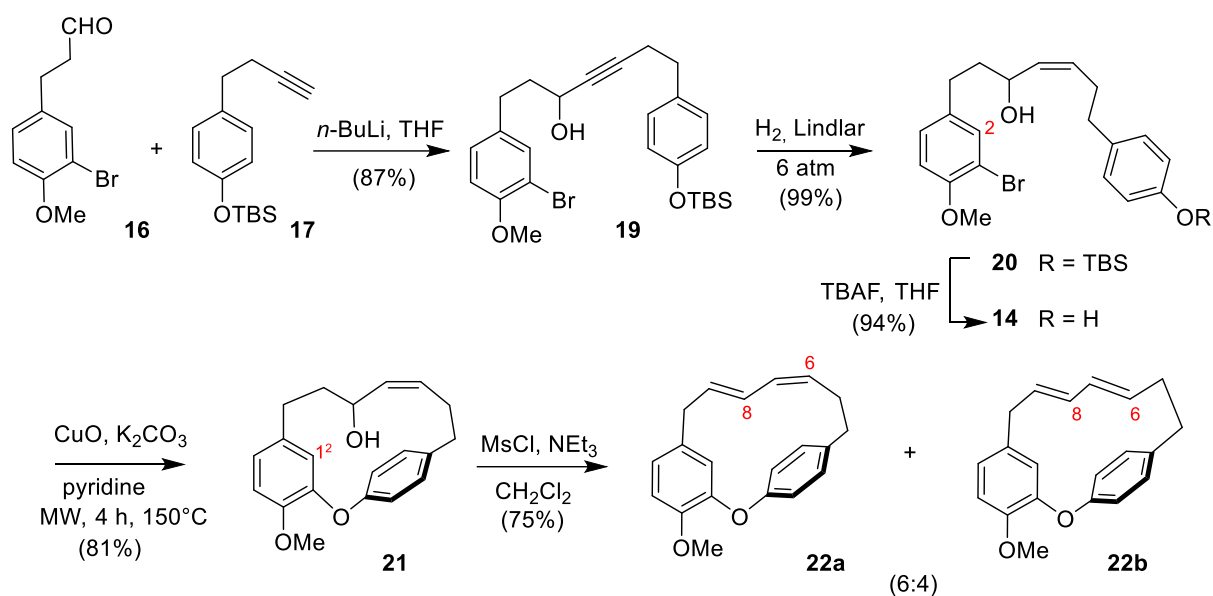


Alkyne **17** was readily obtained from the commercially available 4-hydroxybenzaldehyde *via* a known three-step sequence.¹⁹

The acetylide anion of compound **17**, efficiently formed by action of *n*-BuLi, was then condensed onto aldehyde **16** in THF to afford the expected propargyl alcohol **19** in 87% yield (Scheme 6). The controlled and stereospecific hydrogenation of the alkyne bond to a *Z*-double one was first envisioned by using 15% w/w Lindlar catalyst in the presence of 6% quinoline at 1 atm, in MeOH for 12 h.²⁰ Under these conditions, the starting material was fully recovered. The expected transformation was then carried out under the same conditions without quinoline. The observed conversion rate (evaluated by ¹H NMR) was 31%. Increasing the reaction time to 24 h enhanced the conversion rate to 50%. However, the hydrogenation efficiency was not improved by increasing the reaction time up to 90 h or the catalyst amount up to 30% w/w. Raising the hydrogen pressure to 3 atm for 24 h increased the conversion to 81%. Finally, optimized conditions (6 atm for 18 h) led to *Z*-alkene **20** in 99% isolated yield.

Cleavage of the TBS group of **20** was readily accomplished in 94% yield by treatment with TBAF in THF. Subsequent intramolecular Ullman cyclization on bromophenol **14** was achieved in the presence of CuO and K₂CO₃ in refluxing pyridine for 48 h.²¹ Under these conditions, ring closure afforded macrocyclic compound **21** in good 70% yield. In order to reduce the reaction time, the cyclization was carried out under microwave heating.²² The reaction was complete at 150 °C in 4 h and **21** was obtained in 81% an improved yield. The cyclic structure of **21** was confirmed by the typical shield shift of the H1² resonance (Scheme 6) shown in the ¹H NMR spectrum as a result of the anisotropic effect of the neighboring aromatic ring²¹ ($\delta\text{H1}^2 = 5.38$ ppm in **21** vs. $\delta\text{H2} = 7.33$ ppm in **14**).

Scheme 6. Synthesis of the Macrocyclic Core of Tedarene A



At this point, the required *E*-alkene bond was expected to result from the stereospecific dehydration of the allylic alcohol **21**. Treatment with mesyl chloride in the presence of NEt_3 in CH_2Cl_2 from 0°C to room temperature directly afforded²³ a 60/40 mixture of two diene derivatives (as estimated by ^1H NMR), in 75% overall yield. The use of preparative HPLC in direct phase conditions using a chiral phase column allowed the separation of the two isomers in respectively 44% and 13% isolated yields.

The ^1H and ^{13}C NMR spectra of the major isomer **22a** appeared similar to those described for tedarene A along with some missing or hardly detectable signals at room temperature. The slow interconversion rate near the NMR time scale between the two enantiomeric conformations causes coalescence of some NMR signals at 25°C .²⁴ The configurations of the double bonds, supposed to be identical to those of tedarene A *i.e.* *6Z,8E*, was confirmed by single crystal X-ray diffraction analysis of **22a** (Figure 2). The NMR data of the minor isomer **22b** are consistent with a *6E,8E* configuration of the diene system with a rapid interconversion of the two enantiomeric conformations at room temperature. Regarding the coupling constant for alkenes protons, *E* ($J = 14.7$ Hz) and *Z* ($J = 7.5$ Hz) configurations are undoubted. Macrocycle **22b** afforded needle crystals that were submitted to single crystal X-ray diffraction analysis (Figure 2). The resulting data confirmed the assigned configurations, which suggest a partial isomerization of the pre-established *Z*-double bond presumably *via* a carbocation intermediate.

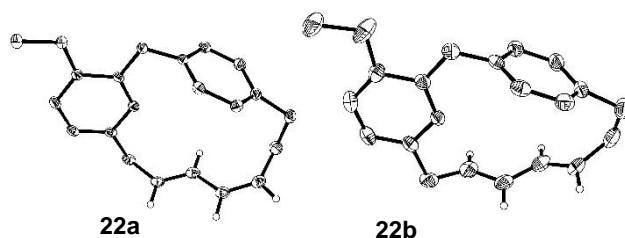
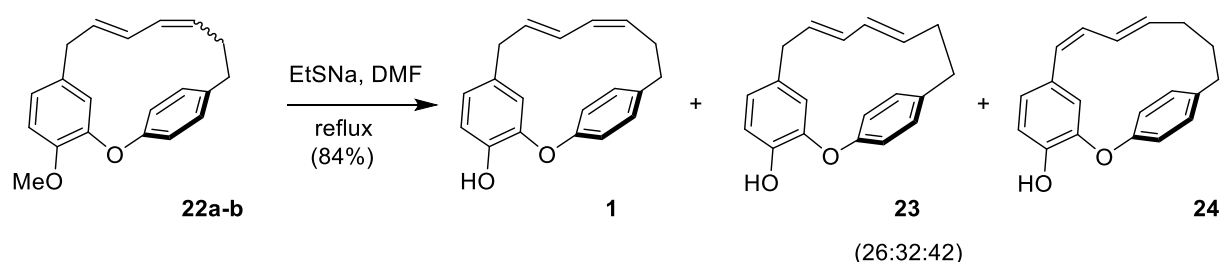


Figure 2. X-ray crystal structure of **22a** and **22b**. Thermal ellipsoids represent 30% probability level. For clarity, disordered atoms and H atoms are omitted except the dienic and phenolic ones.²⁵

In order to complete the synthesis of tedarene A, the last O-demethylation step was then attempted using standard Lewis acid conditions as already described for diarylheptanoid derivatives. Unfortunately, the use of AlCl₃ in refluxing CH₂Cl₂²⁶ or of BBr₃ in CH₂Cl₂ at lower temperature (-78 °C²⁷ to -40 °C²⁸), led to the degradation of the starting material due to the high reactivity of the diene heptanoid moiety under these Lewis acid conditions.

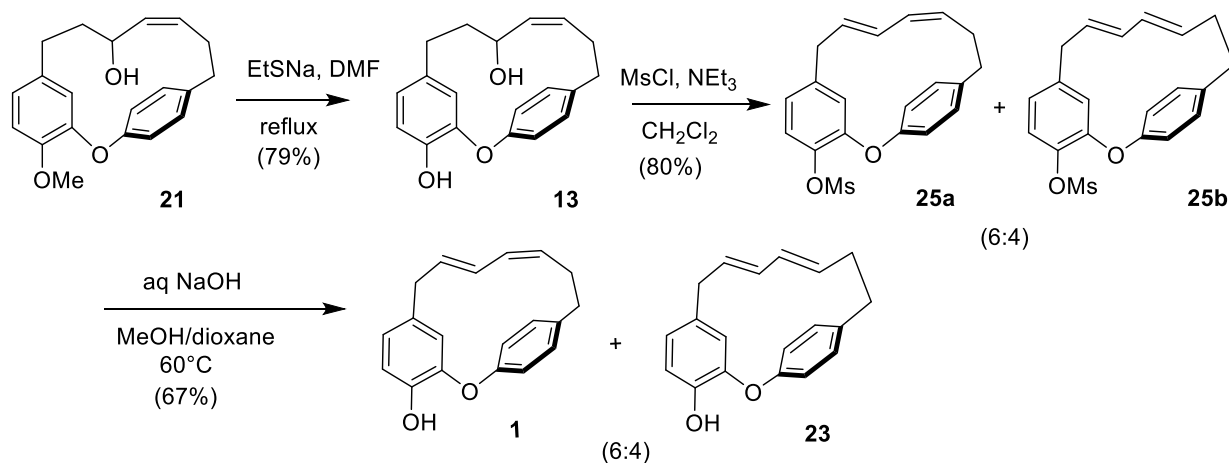
Alternatively, the isomeric mixture **22a-b** was treated in the presence of sodium thioethanolate in refluxing DMF²⁹ (Scheme 7). This procedure effectively allowed the expected O-demethylation. Beside a mixture of the expected phenols **1** and **23**, a third isomer was detected, in a 26/32/42 ratio according to ¹H NMR. Flash chromatography allowed us to isolate the undesired compound **24** along with an inseparable mixture of **1** and **23**. The spectroscopic data of **24** was in accordance with a 7*E*,9*Z* conjugated diene phenol structure, resulting from the deprotonation of the benzylic protons followed by the migration of the diene system under basic conditions.

Scheme 7. Demethylation of Macrocyces **22a-b**



The formation of the unwanted derivative **24** prompted us to conduct the demethylation step earlier in the synthesis starting from the macrocyclic allylic alcohol **21** that does not contain any acidic benzylic protons (Scheme 8). When submitted to the previous demethylation conditions (EtSNa, DMF, reflux), macrocycle **21** cleanly afforded the expected phenol **13** in 79% yield.

Scheme 8. Synthesis of Tedarene A (**1**) and its Isomer **23**



Treatment of phenolic allylic alcohol **13** with mesyl chloride in the presence of NEt₃ from 0 °C to room temperature allowed the elimination reaction to proceed along with the unavoidable mesylation of the phenol leading to a mixture of diene *E,Z* and *E,E*-isomers **25a** and **25b** in 60/40 ratio (as determined by ¹H NMR), as previously observed for the mixture of **22a-b**, in 80% overall yield. Hydrolysis of the mesylates was finally accomplished by action of aqueous sodium hydroxide³⁰ in an optimized 1:1 MeOH-dioxane mixture at 60 °C, in 67 % overall yield. This led to a mixture of isomers *E,Z*-**1** and *E,E*-**23** in the same ratio as the initial mixture and with no trace of double bond migration. A challenging preparative HPLC chromatography of this mixture due to the minor structure differences, using a chiral phase column in direct phase allowed the separation of the two macrocycles **1** and **23** in 38.5% and 23% respective isolated yields. The spectroscopic data of **1**, in particular the ¹H and ¹³C NMR spectra in CD₃OD recorded at 25 °C and -40 °C, were in full agreement with those published for the naturally occurring tedarene A.¹¹ Moreover, both isomers crystallized from CH₂Cl₂ to give colorless crystals that were suitable for single crystal X-ray diffraction analysis (Figure 3). Their respective configurations was unambiguously confirmed by this analysis.

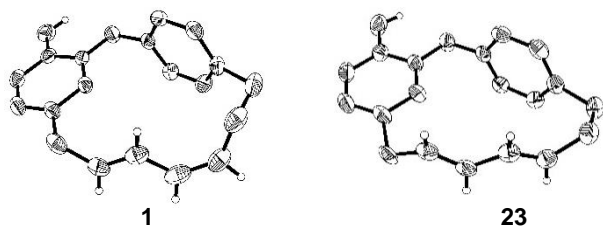


Figure 3. X-ray structures of **1** and **23**. Thermal ellipsoids represent 30% probability level. The asymmetric unit contains two independent molecules, only one is shown here. For clarity, disordered atoms and H atoms are omitted except the diene and phenolic ones.²⁵

In summary, we have completed the first total synthesis of the natural product tedarene A. The envisioned optimized strategy proceeded in nine steps and 15.3% overall yield from commercially available 3-(4-methoxyphenyl)propan-1-ol. The regio- and stereocontrol of the dienic system as well as the intramolecular Ullmann macrocyclization represent the key features of this total synthesis. The previously unknown *E,E*-isomer of tedarene A was also prepared and fully characterized. This efficient synthesis provides convenient access to tedarene A for further biological assays and paves the way for the preparation of analogues for further SAR studies.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise noted, all experiments were carried out under a nitrogen atmosphere. Solvents (CH₂Cl₂ and THF) were dried *via* a purification solvent system MB-SP- 800 (MBRAUN). Melting points (mp) were obtained on a Buchi apparatus and are uncorrected. Measurements above 200°C were not possible with this apparatus. UV spectra were recorded in MeOH on a Hewlett Packard 8453 spectrometer at 25°C. IR spectra were recorded on a Thermo Nicolet Nexus spectrometer. NMR spectra were recorded on Bruker Avance 300 and 500 MHz spectrometers. The NMR spectra were acquired in CDCl₃ and CD₃OD, and the chemical shifts were reported in parts per million referring to CHCl₃ (δ_{H} 7.26 for proton and δ_{C} 77.0 for carbon) and MeOH (δ_{H} 3.34 for proton and δ_{C} 49.0 for carbon), respectively. Signals are described as follow: s, singlet; brs, broad signal; d, doublet; t, triplet; m, multiplet. HRMS data were recorded on a Xevo G2 QTOF (Waters) instrument. Reactions were monitored by TLC on silica gel Alugram® Xtra SIL G/UV₂₅₄. Column chromatography were performed on Machery-Nagel silica gel 0.063-0.2 mm. Flash chromatography purification was performed on Puriflash 430 (Interchim) equipped with a 30 μm silica gel column PF-30SIHP-JP (Interchim). HPLC purification was performed using a system equipped with an UV detector. The column used was a ChiralPak IA for SFC (250×20 mm, 5 μm). Reactions utilizing microwave technology were conducted in a CEM Discover Benchmate microwave reactor (model no. 908010).

1-(3-Bromo-4-methoxyphenyl)-3-(trimethylsilyl)prop-2-yn-1-ol (7). To a solution of propargyl trimethylsilane (854 μL , 6.05 mmol) in dry THF (30 mL) at $-78\text{ }^\circ\text{C}$ under a N_2 atmosphere was added dropwise *n*-BuLi (1.6 M in hexanes, 3.78 mL, 6.05 mmol). The reaction mixture was stirred for 45 min and a solution of 3-bromo-4-methoxybenzaldehyde (1 g, 4.65 mmol) in THF (10 mL) was added dropwise. The reaction was allowed to warm to $0\text{ }^\circ\text{C}$ and quenched with satd aq NH_4Cl solution. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with satd aq NH_4Cl solution, H_2O , brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/PE = 1:9) to provide propargyl alcohol **7** (1.39 g, 95%) as a light yellow oil. $R_f = 0.41$ (EtOAc/PE = 2:8); IR (neat) 3370, 2173 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.73 (d, 1H, $J = 1.8$ Hz), 7.44 (dd, 1H, $J = 8.4, 1.8$ Hz), 6.89 (d, 1H, $J = 8.4$ Hz), 5.38 (d, 1H, $J = 6$ Hz), 3.90 (s, 3H), 2.23 (d, 1H, $J = 6$ Hz), 0.21 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 155.9, 134.1, 132.0, 127.1, 111.8, 111.7, 104.7, 92.0, 63.9, 56.4, -0.1; HRMS (ESI) : m/z 295.0150 $[\text{M}+\text{H}-\text{H}_2\text{O}]^+$ (calcd for $\text{C}_{13}\text{H}_{16}\text{BrOSi}$, 295.0154).

(3-(3-Bromo-4-methoxyphenyl)prop-1-yn-1-yl)trimethylsilane (8a) and *(3-(3-bromo-4-methoxyphenyl)prop-1-yn-1-yl)triethylsilane (8b)*. To solution of propargyl alcohol **7** (1.2 g, 3.85 mmol) in 1,2-dichloroethane (12 mL) was added $\text{H}_3\text{PW}_{12}\text{O}_4 \cdot n\text{H}_2\text{O}$ (111 mg, $3.95 \cdot 10^{-2}$ mmol) then Et_3SiH (0.92 mL, 5.77 mmol). The reaction mixture was heated at $50\text{ }^\circ\text{C}$ for 2 h. After cooling to room temperature, the mixture was quenched with satd aq NaHCO_3 solution. The aqueous layer was extracted CH_2Cl_2 . The combined organic layers were washed with satd aq NaHCO_3 solution, H_2O , brine, dried over Na_2SO_4 , and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/PE = 3:97) to provide an inseparable (73/27) mixture of trimethyl and triethylsilyl compounds **8a** and **8b** (0.95 g, 91%) as colorless oil. $R_f = 0.65$ (EtOAc/PE = 2:8); IR (neat) 2176 cm^{-1} ; For **8a** (From a mixture) ^1H NMR (CDCl_3 , 300 MHz) δ 7.51 (d, 1H, $J = 2.2$ Hz), 7.24 (dd, 1H, $J = 8.4, 2.2$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 3.88 (s, 3H), 3.57 (s, 2H), 0.19 (s, 9H); ^{13}C NMR (CDCl_3 , 75 MHz) δ . 154.7, 132.8, 130.0, 127.9, 112.0, 111.7, 104.0, 87.4, 56.4, 25.0, 0.17; For **8b** (From a mixture) ^1H NMR (CDCl_3 , 300 MHz) δ 7.55 (d, 1H, $J = 2.2$ Hz), 7.24 (dd, 1H, $J = 8.4, 2.2$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 3.88 (s, 3H), 3.60 (s, 2H), 1.01 (t, 9H, $J = 7.8$ Hz), 0.62 (qd, 6H, $J = 7.8, 0.8$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.6, 132.8, 130.2, 127.8, 111.9, 111.6, 104.9, 84.8, 56.4, 25.1, 7.6, 4.6.

2-Bromo-1-methoxy-4-(propa-1,2-dienyl)benzene (9). A 73/27 mixture of derivatives **8a-8b** (232 mg, 0.78 mmol) was dissolved in dry THF (10 mL) and cooled to 0 °C. A TBAF solution (1M in THF, 1.56 mL, 1.56 mmol) was added dropwise. The reaction mixture, which turned red immediately, was warmed to rt and stirred for 1 h. Water was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with H₂O, brine and dried over Na₂SO₄. Concentration under reduced pressure provided allene **9** (171 mg, 97%) as a yellow oil which was pure enough for use without further purification. $R_f = 0.32$ (EtOAc/PE = 5:95); IR (neat) 1941 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.49 (d, 1H, $J = 2.1$ Hz), 7.17 (dd, 1H, $J = 8.4, 2.1$ Hz), 6.84 (d, 1H, $J = 8.4$ Hz), 6.06 (t, 1H, $J = 6.8$ Hz), 5.16 (d, 2H, $J = 6.8$ Hz), 3.88 (s, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 209.5, 154.9, 131.4, 127.9, 126.8, 112.2, 112.1, 92.6, 79.4, 56.34; HRMS (DCI, CH₄) : m/z 224.9912 [M]⁺ (calcd for C₁₀H₉BrO, 223.9837).

2-Bromo-1-methoxy-4-(prop-2-ynyl)benzene (5). A 73/27 mixture of derivatives **8a-8b** (1.26 g, 4.07 mmol) was dissolved in dry THF (40 mL) and cooled to 0 °C. AcOH (1.16 mL, 20 mmol) and TBAF solution (1M in THF, 16.3 mL, 16.3 mmol) were added dropwise and the reaction mixture was allowed to warm to rt. Two supplementary additions of AcOH (0.7 mL, 12.2 mmol) and TBAF solution (8.15 mL, 8.15 mmol) were realized after stirring for 48 h and 96 h. After 6 days of reaction time at rt, H₂O was added and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with satd aq NaHCO₃ solution, H₂O, brine, dried over Na₂SO₄, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/PE = 5:95) to provide alkyne **5** (772 mg, 87%) as a yellow oil. $R_f = 0.38$ (EtOAc/PE = 1:9); IR (neat) 3271 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.54 (d, 1H, $J = 1.9$ Hz), 7.24 (dd, 1H, $J = 8.4, 1.9$ Hz), 6.85 (d, 1H, $J = 8.4$ Hz), 3.88 (s, 3H), 3.53 (d, 2H, $J = 2.75$ Hz), 2.20 (t, 1H, $J = 2.75$ Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 154.8, 132.8, 129.7, 127.9, 112.0, 111.7, 81.7, 70.9, 56.4, 23.7; HRMS (DCI, CH₄) : m/z 224.9915 [M+H]⁺ (calcd for C₁₀H₁₀BrO, 224.9912).

4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)butanoic acid (11). To an ice cooled solution of acid **10** (100 mg, 0.55 mmol) in dry DMF (5 mL) under N₂ were added imidazole (227 mg, 3.33 mmol) and TBDMSCl (251 mg, 1.66 mmol). The reaction mixture was stirred at 0 °C for 1 h and allowed to warm to rt. The reaction was quenched with aq 1M KHSO₄ solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with 1M KHSO₄ solution, satd aq NaHCO₃ solution, H₂O and brine, dried over Na₂SO₄ and

concentrated under reduced pressure. K_2CO_3 (115 mg, 0.83 mmol) in H_2O (1.5 mL) was added to a solution of the obtained crude disilylate in THF (3 mL) and MeOH (1.5 mL). The mixture was stirred at rt for 12 h. After dilution with EtOAc, the organic layer was extracted with satd aq Na_2CO_3 solution. The aqueous layer was extracted with EtOAc, acidified with conc HCl solution to pH = 1, and re-extracted with EtOAc. The combined organic layers were washed with H_2O , brine, dried over Na_2SO_4 and concentrated under reduced pressure to yield acid **11** (128 mg, 78%) pure enough to be used without further purification. The physical data and NMR spectra were in agreement with the literature.³¹

4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)butan-1-ol (12). To a suspension of LiAlH_4 (33 mg, 0.87 mmol) in dry THF (5 mL) at 0 °C under N_2 was added dropwise a solution of aldehyde **11** (128 mg, 0.43 mmol) in THF (5 mL). The reaction mixture was allowed to warm to rt and quenched with aq 3M HCl solution. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with satd aq NaHCO_3 solution, brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Alcohol **12** (119 mg, 98%) was obtained as yellow oil with no further purification. The physical data and NMR spectra were in agreement with the literature.³¹

4-(4-((tert-Butyldimethylsilyl)oxy)phenyl)butanal (6). To a solution of alcohol **12** (1.27 g, 4.53 mmol) in EtOAc (30 mL) was added IBX (2.54 g, 9 mmol). The reaction mixture was refluxing for 3 h then cooled to rt and filtered over a Celite pad. The filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (EtOAc/PE = 1:9) to provide aldehyde **6** (787mg, 62%) as a colorless oil. The physical data and NMR spectra were in agreement with the literature.³²

3-(3-Bromo-4-methoxyphenyl)propan-1-ol (18). To a solution of 3-(4-methoxyphenyl) propan-1-ol (4.4 g, 26.47 mmol) in CH_2Cl_2 (100 mL) were added AlCl_3 (3.53 g, 26.47 mmol) and Br_2 (1.35 mL, 26.47 mmol) dropwise at 0 °C under N_2 . The reaction was allowed to stir at 0 °C for 30 min and was quenched with ice water. The aqueous layer was extracted with CH_2Cl_2 . The combined organic layers were washed with H_2O , satd aq NaHCO_3 solution, brine, dried over Na_2SO_4 , and concentrated under reduced pressure. Alcohol **18** (6.45 g, 99%) was obtained as a colorless oil with no further purification. $R_f = 0.23$ (EtOAc/EP = 2:3). IR (neat) ν_{max} 3300 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) δ 7.39 (d, 1H, $J = 2.1$ Hz), 7.09 (dd, 1H, $J = 8.4, 2.1$ Hz), 6.82 (d,

1H, $J = 8.1$ Hz), 3.87 (s, 3H), 3.66 (t, 2H, $J = 6.3$ Hz), 2.64 (t, 2H, $J = 7.5$ Hz), 1.90-1.81 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.2, 135.6, 133.3, 128.4, 112.1, 111.6, 62.1, 56.4, 34.3, 30.9. HRMS (DCI, CH_4): m/z 245.0177 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{10}\text{H}_{14}\text{BrO}_2$, 245.0162).

3-(3-Bromo-4-methoxyphenyl)propanal (16). To a solution of alcohol **18** (2 g, 8.16 mmol) in EtOAc (75 mL) was added IBX (8 g, 28.57 mmol). The reaction mixture was refluxing for 3h then cooled to rt and filtered over a Celite pad. The filtrate was concentrated under reduced pressure to provide aldehyde **16** (1.92 g, 97 %) as colorless oil pure enough to be used without further purification. $R_f = 0.37$ (EtOAc/PE = 3:7); IR (neat) ν_{max} 1720 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 9.80 (t, 1H, $J = 1.2$ Hz), 7.37 (d, 1H, $J = 2.1$ Hz), 7.09 (dd, 1H, $J = 2.4, 8.4$ Hz), 6.82 (d, 1H, $J = 8.4$ Hz), 3.86 (s, 3H), 2.90-2.85 (m, 2H), 2.78-2.72 (m, 2H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 201.3, 154.5, 134.1, 133.1, 128.4, 112.1, 111.7, 56.4, 45.3, 26.9; HRMS (DCI, CH_4): m/z 243.0022 $[\text{M}+\text{H}]^+$ (calcd for $\text{C}_{10}\text{H}_{12}\text{BrO}_2$, 243.0021).

1-(3-Bromo-4-methoxyphenyl)-7-(4-(tert-butyldimethylsilyloxy)phenyl)hept-4-yn-3-ol (19). To a stirred solution of alkyne **17** (0.385 g, 1.48 mmol) in dried THF (15 mL) at -78 °C under N_2 was added dropwise $n\text{-BuLi}$ (1.6 M in hexane, 1.11 mL, 1.78 mmol). After stirring for 45 min at -78 °C a solution of aldehyde **16** (0.359 g, 1.48 mmol) in dry THF (5 mL) was added. The resulting mixture was allowed to warm up to rt and was stirred for another 90 min, then quenched with satd aq NH_4Cl solution and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with satd aq NH_4Cl solution, H_2O and brine then dried over Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/PE = 1:9) to provide propargyl alcohol **19** (0.65 g, 87 %) as a light yellow oil. $R_f = 0.38$ (EtOAc/PE = 3:7); IR (neat) ν_{max} 3390, 1500, 1260 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.38 (d, 1H, $J = 2.1$ Hz), 7.07 (dd, 1H, $J = 8.4, 2.1$ Hz), 7.07 (d, 2H, $J = 8.7$ Hz), 6.54 (d, 1H, $J = 8.4$ Hz), 6.76 (d, 2H, $J = 8.7$ Hz), 4.31 (tt, 1H, $J = 6.3, 1.9$ Hz), 3.87 (s, 3H), 2.76 (t, 2H, $J = 7.5$ Hz), 2.66 (t, 2H, $J = 7.8$ Hz), 2.48 (td, 2H, $J = 7.5, 1.9$ Hz), 1.98-1.87 (m, 2H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.3, 154.2, 135.3 (2C), 133.4, 129.4, 128.5, 120.0, 112.1, 111.6, 85.6, 81.7, 61.9, 56.4, 39.6, 34.3, 30.3, 25.8, 21.2, 18.3, -4.3. HRMS (DCI, CH_4): m/z 501.1442 $[\text{M}-\text{H}]^+$ (calcd for $\text{C}_{26}\text{H}_{34}\text{BrO}_3\text{Si}$, 501.1461).

(4Z)-(3-Bromo-4-methoxyphenyl)-7-(4-(tert-butyldimethylsilyloxy)phenyl)hept-4-en-3-ol (20). To a solution of alkyne **19** (52 mg, 0.1 mmol) in EtOH (3.3 mL) was added Lindlar catalyst

(7.8 mg, 15% w/w) and the reaction mixture was subjected to 6 atm of hydrogen at rt for 18h. Filtration over a Celite pad and concentration under vacuum yield alkene **20** (53 mg, 99%) as a light yellow oil pure enough to be used in the next step without further purification. $R_f = 0.32$ (EtOAc/PE = 2:8); IR (neat) ν_{\max} 3360, 1610 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.35 (d, 1H, $J = 2.1$ Hz), 7.05 (dd, 1H, $J = 8.1, 2.1$ Hz), 6.99 (d, 2H, $J = 8.7$ Hz), 6.80 (d, 1H, 8.1 Hz), 6.76 (d, 2H, $J = 8.7$ Hz), 5.52 (dtd, 1H, $J = 10.8, 7.8, 0.9$ Hz), 5.39 (ddt, 1H, $J = 10.8, 8.4, 1.2$ Hz), 4.22 (dt, 1H, $J = 8.4, 6.6$ Hz), 3.87 (s, 3H), 2.69-2.45 (m, 4H), 2.41-2.25 (m, 2H), 1.79 (dtd, 1H, $J = 13.5, 6.9, 8.4$ Hz), 1.58 (dtd, 1H, $J = 13.5, 6.9, 9.3$ Hz), 0.97 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.0, 153.8, 135.6, 134.1, 133.2, 133.1, 131.1, 129.5, 128.3, 119.9, 111.9, 111.4, 66.5, 56.2, 38.6, 34.9, 30.4, 29.8, 25.7, 18.2, -4.4. HRMS (DCI, CH_4): m/z 504.1682 $[\text{M}]^+$ (calcd for $\text{C}_{26}\text{H}_{37}\text{BrO}_3\text{Si}$, 504.1695).

(Z)-4-(7-(3-Bromo-4-methoxyphenyl)-5-hydroxyhept-3-enyl)phenol (**14**). To a solution of silylether **20** (0.698 g, 1.38 mmol) in dry THF (15 mL) was added dropwise TBAF (1M solution in THF, 2.76 mmol). After stirring for 30 min at 0 °C, the reaction mixture was quenched with sat aq NaHCO_3 (5 mL), and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with satd aq NaHCO_3 , H_2O and brine, then dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (1% MeOH in CH_2Cl_2) to provide aldehyde **14** (0.51g, 94%) as a colorless gum. $R_f = 0.22$ (1% MeOH in CH_2Cl_2); IR (neat) ν_{\max} 3315, 1610, 1510 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 7.33 (d, 1H, $J = 2.1$ Hz), 7.04 (dd, 1H, $J = 8.4, 2.1$ Hz), 7.00 (d, 2H, $J = 8.7$ Hz), 6.80 (d, 1H, $J = 8.4$ Hz), 6.75 (d, 2H, $J = 8.7$ Hz), 5.53 (dt, 1H, $J = 10.9, 7.7$ Hz), 5.40 (dd, 1H, $J = 10.9, 9$ Hz), 4.17 (dt, 1H, $J = 8.7, 7.2$ Hz), 3.87 (s, 3H), 2.71-2.47 (m, 4H), 2.36-2.28 (m, 2H), 1.76 (dtd, 1H, $J = 13.4, 8.6, 6.9$ Hz), 1.53 (ddt, 1H, $J = 13.4, 9.4, 6.9$ Hz); ^{13}C NMR (CDCl_3 , 75 MHz) δ 154.5, 154.1, 135.6, 133.3, 133.2, 132.9, 131.8, 130.0, 128.4, 115.3, 112.0, 111.5, 66.8, 56.4, 38.2, 34.6, 30.4, 30.1; HRMS (DCI, CH_4) m/z 390.0838 $[\text{M}]^+$ (calcd for $\text{C}_{20}\text{H}_{23}\text{BrO}_3$, 390.0831).

(Z)-1⁶-Methoxy-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphan-6-en-8-ol (**21**).

By conventional heating: To a solution of phenol **20** (406 mg; 1.04 mmol) in anhydrous pyridine (53 mL) was added K_2CO_3 (287 mg; 2.08 mmol). The mixture was warmed to 90 °C and CuO (207 mg; 2.6 mmol) was added. After heating was for 48 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. The residue was dissolved in EtOAc and neutralized by addition of 10% aq NaHSO_3 solution. The aqueous layer was extracted with

EtOAc and the combined organic layers were washed with 10% aq NaHSO₃ solution, water and brine, then dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (EtOAc/pentane = 3:7) to provide compound **21** (226 mg, 70%) as a gum.

By microwave heating: A mixture of **20** (31 mg, 7.92 10⁻⁵ mol), K₂CO₃ (22 mg, 1.58 10⁻⁴ mol) and CuO (16 mg, 1.98 10⁻⁴ mol) in pyridine (4 mL) was heated at 150°C under microwave irradiation in a sealed tube for 4 h. The reaction mixture was treated as described above to yield, after column chromatography, the expected compound **21** (20 mg, 81%). R_f = 0.21 (EtOAc/PE = 3:7); IR (neat) ν_{max} 3400, 1590, 1520, 1500, 1220 cm⁻¹; RMN ¹H (CDCl₃, 300 MHz) δ 7.31 (dd, 1H, J = 8.1, 2.1 Hz), 7.07-6.98 (m, 3H), 6.77 (d, 1H, J = 8.4 Hz), 6.62 (dd, 1H, J = 8.1, 2.1 Hz), 5.53 (dddd, 1H, J = 11.1, 10.8, 4.8, 0.9 Hz), 5.43 (ddd, 1H, J = 10.8, 7.1, 0.9 Hz), 5.38 (d, 1H, J = 2.1 Hz), 3.94 (s, 3H), 3.59 (ddd, 1H, J = 9.9, 7.2, 2.7 Hz), 3.04 (ddd, 1H, J = 12.9, 5.7, 2.1 Hz.), 2.67 (dd, 1H, J = 16.2, 9.3 Hz), 2.71-2.50 (m, 4H), 1.74 (dddd, 1H, J = 14.7, 8.7, 10.2, 1.8 Hz), 1.49-1.25 (m, 1H); RMN ¹³C (CDCl₃, 75 MHz) δ 155.8, 151.7, 146.3, 139.8, 135.3, 134.0, 133.3, 130.7, 130.6, 124.6, 123.2, 121.2, 115.7, 111.7, 66.4, 56.3, 38.7, 34.7, 32.9, 27.7; HRMS (DCI, CH₄) m/z 310.1569 [M]⁺ (calcd for C₂₀H₂₂O₃, 310.1561).

(6*Z*,8*E*)-*I*⁶-Methoxy-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-diene (**22a**) and (6*E*,8*E*)-*I*⁶-Methoxy-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-diene (**22b**). To a solution of alcohol **21** (227 mg; 0.731 mmol) in CH₂Cl₂ (10 mL) at 0 °C were added dropwise NEt₃ (306 μL, 2.19 mmol) and CH₃SO₂Cl (68 μL, 0.878 mmol). After stirring at 0 °C for 90 min and at rt for 3 h, the reaction mixture was quenched with satd aq NH₄Cl solution. The aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with satd aq NH₄Cl solution, H₂O and brine then dried over Na₂SO₄ and concentrated under vacuum. Column chromatography on silica gel (CH₂Cl₂/pentane = 3/7) of the residue to yielded a 60/40 mixture of isomers **22a** and **22b** (161 mg, 75%). Preparative HPLC (Eluent: heptane /CH₂Cl₂ = 95/5. Flowrate: 15 mL/min) allowed isolation of pure isomer **22a** (94 mg, 44%) and **22b** (38 mg, 13%) as colorless crystals. R_f = 0.31 (CH₂Cl₂/pentane = 2:8). For **22a** : colorless block (CH₂Cl₂); mp > 200°C; UV (MeOH) λ_{max} (log ε) 277 (3.26) nm, 247 (3.98) nm; IR (neat) ν_{max} 2960 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz, 25 °C) δ 7.23-6.88 (broad coalescent signals, 4H), 6.75 (d, 1H, J = 8.1 Hz), 6.64 (dd, 1H, J = 8.1, 2.1 Hz), 5.97 (dd, 1H, J = 11.1, 10.8 Hz), 5.71 (ddd, 1H, J = 15, 10.8, 0.6 Hz), 5.53 (dt, 1H, J = 15.3, 7.8 Hz), 5.45 (d, 1H, J = 2.4 Hz), 5.31 (dt, 1H, J = 11.1, 8.6 Hz), 3.94 (s, 3H), 3.01 (d, 2H, J = 7.8 Hz), 2.40 (brs, 2H) ; ¹³C NMR (CDCl₃, 75 MHz, 25°C) δ (four C not detectable because of a coalescence at rt) 155.1, 151.6,

146.5, 139.5, 132.6, 131.6, 130.7, 128.7, 128.4, 120.4, 116.8, 111.3, 56.3, 36.2, 35.2, 32.1; HRMS (DCI, CH₄) : m/z 293.1553 [M+H]⁺ (calcd for C₂₀H₂₁O₂, 293.1542).

For **22b** : colorless needles (CH₂Cl₂); mp > 200°C; UV (MeOH) λ_{\max} (log ϵ) 275 (2.87) nm, 237 (3.98) nm; IR (neat) ν_{\max} 2920, 1580 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.08 (d, 2H, J = 8.4 Hz), 6.97 (d, 2H, J = 8.4 Hz), 6.81 (d, 1H, J = 8.1 Hz), 6.70 (dd, 1H, J = 8.1, 2.1 Hz), 5.74 (d, 1H, J = 2.1 Hz), 5.71-5.58 (m, 2H), 5.21 (dt, 1H, J = 14.7, 7.5 Hz), 5.14 (dt, 1H, J = 14.4, 7.2 Hz), 3.95 (s, 3H), 3.13 (d, 2H, J = 7.5 Hz), 2.89 (t, 2H, J = 6.6 Hz), 2.46 (q, 2H, J = 6.9 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 153.8, 150.6, 146.5, 138.8, 134.0, 133.1, 133.0, 130.9, 130.8, 129.8, 123.5, 120.9, 116.4, 111.6, 56.3, 36.3, 34.3, 33.9. HRMS (DCI, CH₄): m/z 293.1554 [M+H]⁺ (calcd for C₂₀H₂₁O₂, 293.1542).

Demethylation of Macrocycles 22a-b. To a solution of a 60/40 mixture of **22a-22b** (96 mg, 0.33 mmol) in DMF (5 mL) was added EtSNa (70 mg, 0.82 mmol). The reaction mixture was refluxed for 1.5 h. After cooling to 0 °C, 5% aq HCl solution was added, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with 5% aq HCl solution, H₂O and brine. The solution was dried over Na₂SO₄ and concentrated under vacuum. Column chromatography on silica gel (EtOAc/PE = 1:9) provided a mixture of phenols **1**, **23** and **24** (77 mg, 84%). Flash chromatography (CH₂Cl₂/pentane = 10/90 to 40/60) allowed the isolation of derivative **24** (22 mg, 24%) as a light yellow solid.

For (7*E*,9*Z*)-2-oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-7,9-dien-16-ol (**24**). R_f = 0.23 (CH₂Cl₂/pentane = 1:1); IR (neat) ν_{\max} 3406, 1651 cm⁻¹; ¹H NMR (CD₃OD, 300 MHz) δ 7.37 (d, 2H, J = 8.5 Hz), 7.08 (d, 2H, J = 8.5 Hz), 6.75 (d, 1H, J = 8.1 Hz), 6.56 (dd, 1H, J = 8.1, 2.0 Hz), 6.07 (d, 1H, J = 2.0 Hz), 6.00 (d, 1H, J = 11.3 Hz), 5.81 (dd, 1H, J = 11.3, 8.8 Hz), 5.60 (dd, 1H, J = 15.2, 8.8 Hz), 5.56 (m, 1H), 2.68 (t, 2H, J = 6.3 Hz), 2.10 (q, 2H, J = 6.1 Hz), 1.67 (brs, 2H); ¹³C NMR (CD₃OD, 125 MHz) δ 156.4, 150.5, 146.0, 140.9, 137.5, 132.6, 130.7, 128.4, 128.2 (2C), 124.7, 123.6, 118.7, 116.9, 36.4, 31.6, 29.6; HRMS (DCI, CH₄) : m/z 278.1314 [M]⁺: (calcd for C₁₉H₁₈O₂, 278.1307).

(*Z*)-2-Oxa-1(1,3),3(1,4)-dibenzenacyclodecaphan-6-ene-16,8-diol (**13**). To a solution of alcohol **21** (141 mg, 0.45 mmol) in DMF (7 mL) was added EtSNa (143 mg, 1.6 mmol). The reaction mixture was refluxed for 3.5 h. After cooling to 0 °C, 5% aq HCl solution was added, the aqueous layer was extracted with EtOAc and the combined organic layers were washed with 5% aq HCl solution, H₂O and brine. The solution was dried over Na₂SO₄ and concentrated under vacuum. The residue was purified by column chromatography on silica gel (0.2% of

MeOH in CH₂Cl₂) yielded phenol **13** (106 mg, 79%) as a white solid. $R_f = 0.22$ (CH₂Cl₂/MeOH = 99:1); IR (neat) ν_{\max} 3432, 1590 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.30 (dd, 1H, $J = 8.4$, 2.1 Hz), 7.09-7.05 (m, 1H), 7.02-6.96 (m, 2H), 6.81 (d, 1H, $J = 8.1$ Hz), 6.58 (dd, 1H, $J = 8.1$, 2.1 Hz), 5.53 (dddd, 1H, $J = 12.1$, 11.0, 4.7, 1.0 Hz), 5.43 (ddd, 1H, $J = 11.0$, 6.6, 1.4 Hz), 5.37 (d, 1H, $J = 2.1$ Hz), 3.54 (ddd, 1H, $J = 9.6$, 6.6, 3 Hz), 3.05 (ddd, 1H, $J = 12.8$, 5.7, 2.4 Hz), 2.65 (dd, 1H, $J = 16.2$, 9.6 Hz), 2.52-2.29 (m, 4H), 1.72 (dddd, 1H, $J = 14.7$, 9.7, 8.4, 2.1 Hz), 1.46 (dddd, 1H, $J = 14.7$, 9.6, 3.3, 2.1 Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 155.8, 149.6, 142.7, 140.2, 134.4, 134.0, 133.6, 131.0, 130.6, 124.4, 123.1, 122.1, 115.4, 115.0, 66.0, 38.6, 34.8, 33.0, 27.8; HRMS (DCI, CH₄) : m/z 297.1480 [M+H]⁺ (calcd for C₁₉H₂₁O₃, 297.1491).

(6*Z*,8*E*)-2-Oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-dien-16-yl methanesulfonate (**25a**) and (6*E*,8*E*)-2-Oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-dien-16-yl methanesulfonate (**25b**). To an ice cooled solution of **13** (59 mg, 2 × 10⁻⁴ mol) in CH₂Cl₂ (3 mL) were added NEt₃ (167 μ L, 1.2 mmol) and CH₃SO₂Cl (46 μ L, 6 × 10⁻⁴ mol). The reaction mixture was stirred at 0 °C for 2 h and at rt for 1 h, then quenched with satd aq NH₄Cl solution; The aqueous layer was extracted with CH₂Cl₂ and the combined organic layers were washed with satd aq NH₄Cl solution, H₂O and brine, dried over Na₂SO₄ and concentrated under vacuum. The crude residue was purified by column chromatography on silica gel (CH₂Cl₂) to provide a 60/40 mixture of isomers **25a** and **25b** (57 mg, 80%). $R_f = 0.24$ (CH₂Cl₂/PE = 1:1). IR (neat) ν_{\max} 1500, 1361, 1173 cm⁻¹; For **25a** (from a mixture): ¹H NMR (CDCl₃, 300 MHz) δ 7.15 (d, 1H, $J = 8.1$ Hz), 6.69 (dd, 1H, $J = 8.1$, 2.1 Hz), 5.98 (dd, 1H, $J = 10.9$, 10.9 Hz), 5.58 (d, 1H, $J = 2.0$ Hz), 5.70 (dd, 1H, $J = 15.0$, 10.6 Hz), 5.54 (dt, 1H, $J = 15.2$, 7.7 Hz), 5.33 (dt, 1H, $J = 10.9$, 8.6 Hz), 3.34 (s, 3H), 3.05 (d, 2H, $J = 7.7$ Hz), 2.40 (brs, 2H); ¹³C NMR (CDCl₃, 75 MHz) δ (four C not detectable because of a coalescence at rt) 154.2, 152.8, 140.0, 139.4, 135.3, 131.7, 131.1, 129.2, 128.6, 123.9, 121.0, 118.0, 38.5, 36.1, 35.0, 31.9. HRMS (DCI, CH₄): m/z 357.1156 [M+H]⁺ (calcd for C₂₀H₂₁O₄S, 357.1161). For **25b** (from a mixture): ¹H NMR (CDCl₃, 300 MHz) δ 7.19 (d, 1H, $J = 8.2$ Hz), 7.10 (d, 2H, $J = 8.5$ Hz), 6.93 (d, 2H, $J = 8.5$ Hz), 6.77 (dd, 1H, $J = 8.2$, 2.1 Hz), 5.85 (d, 1H, $J = 2.1$ Hz), 5.75-5.66 (m, 2H), 5.29-5.10 (m, 2H), 3.32 (s, 3H), 3.17 (d, 2H, $J = 7.9$ Hz), 2.91 (t, 2H, $J = 6.7$ Hz), 2.46 (q, 2H, $J = 6.9$ Hz); ¹³C NMR (CDCl₃, 75 MHz) δ 153.4, 152.5, 140.1, 139.4, 135.4, 134.4, 132.7, 131.01, 130.4, 128.8, 124.0, 122.9, 121.5, 117.5, 38.5, 36.2, 34.0, 33.7.

(6*E*,8*E*)-2-Oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-dien-16-ol (**23**) and (6*Z*,8*E*)-2-Oxa-1(1,3),3(1,4)-dibenzenacyclodecaphane-6,8-dien-16-ol or Tedarene A (**1**). To a solution

of **25a-b** (42 mg, 1.18×10^{-4} mol) in dioxane (3.5 mL) were added successively MeOH (3.5 mL) and aq 20% NaOH solution (9 mL). The reaction mixture was stirred at 60 °C for 3 h then cooled to 0 °C. Aqueous 3M HCl solution was added and the aqueous layer was extracted with CH₂Cl₂. The combined organic layers were washed with aq 3M HCl solution, H₂O and brine, dried over Na₂SO₄ and concentrated under vacuum. Column chromatography on silica gel (CH₂Cl₂) of the residue yielded a 60/40 mixture of isomers **1** and **23** (22 mg, 67%). Preparative HPLC (Eluent: heptane /iPrOH = 99:1; Flowrate: 20 mL/min) allowed isolation of pure isomer **1** (12.7 mg, 38.5 %) and **23** (7.6 mg, 23%) as colorless solids. $R_f = 0.23$ (CH₂Cl₂/pentane = 1:1). For **23**: colorless block crystals (CH₂Cl₂); mp 156-157 °C; UV (MeOH) λ_{\max} (log ϵ) 271 (3.60) nm, 241 (4.42) nm; IR (neat) ν_{\max} 3512, 1593 cm⁻¹; ¹H NMR (CD₃OD, 300 MHz) δ 7.13 (d, 2H, $J = 8.4$ Hz), 6.92 (d, 2H, $J = 8.4$ Hz), 6.70 (d, 1H, $J = 8.0$ Hz), 6.57 (dd, 1H, $J = 8.0, 2.1$ Hz), 5.70 (d, 1H, $J = 2.1$ Hz), 5.66-5.57 (m, 2H), 5.20-5.10 (m, 2H), 3.05 (d, 2H, $J = 7.5$ Hz), 2.91 (t, 2H, $J = 6.8$ Hz), 2.46 (q, 2H, $J = 7$ Hz); ¹³C NMR (CD₃OD, 125 MHz) δ 155.2, 150.6, 144.6, 140.1, 134.8, 134.2, 133.0, 132.0, 131.6, 131.0, 124.3, 122.1, 117.5, 116.6, 37.0, 35.0, 34.7; HRMS (DCI, CH₄): m/z 279.1396 [M+H]⁺ (calcd for C₁₉H₁₉O₂, 279.1385).

For tedarene A¹¹ (**1**): colorless block crystals (CH₂Cl₂); mp 122-123 °C; IR (neat) ν_{\max} 3451, 1605 cm⁻¹; ¹H NMR (CD₃OD, 300 MHz, 25 °C) δ 7.34-6.83 (broad coalescent signals, 4H), 6.65 (d, 1H, $J = 7.9$ Hz), 6.50 (dd, 1H, $J = 7.9, 2.1$ Hz), 5.94 (dd, 1H, $J = 11.4, 10.4$ Hz), 5.72 (dd, 1H, $J = 15.1, 11.1$ Hz), 5.45 (dt, 1H, $J = 15.6, 7.6$ Hz), 5.42 (d, 1H, $J = 2.1$ Hz), 5.31 (dt, 1H, $J = 11.0, 8.3$ Hz), 2.94 (d, 2H, $J = 7.9$ Hz), 2.40 (brs, 2H); ¹H NMR (CD₃OD, 300 MHz, -40 °C) δ 7.38 (dd, 1H, $J = 8.3, 2.2$ Hz), 7.04 (dd, 1H, $J = 8.0, 2.1$ Hz), 7.03 (dd, 1H, $J = 8.2, 2.1$ Hz), 6.79 (dd, 1H, $J = 8.2, 2.4$ Hz), 6.63 (d, 1H, $J = 7.8$ Hz), 6.52 (dd, 1H, $J = 7.9, 2.1$ Hz), 5.95 (t, 1H, $J = 11.0$ Hz), 5.72 (dd, 1H, $J = 15.0, 10.9$ Hz), 5.47 (m, 1H), 5.40-5.28 (m, 1H), 5.35 (d, 1H, $J = 2$ Hz), 3.08-2.99 (m, 1H), 2.97-2.91 (m, 2H), 2.51 (td, 1H, $J = 12.0, 2.5$ Hz), 2e².45-2.35 (m, 2H); ¹³C NMR (CD₃OD, 75 MHz, 25 °C) δ (four C not detectable because of a coalescence at rt) 156.6, 151.7, 144.5, 140.9, 133.8, 131.8, 131.6, 129.6, 129.2, 121.6, 118.0, 116.4, 36.9, 36.0, 33.0; ¹³C NMR (CD₃OD, 75 MHz, -40 °C) δ 156.2, 151.5, 144.4, 141.0, 133.8, 133.3, 131.7, 131.5, 131.2, 129.6, 129.3, 125.5, 123.7, 121.6, 117.6, 116.0, 36.9, 35.9, 33.0; HRMS (DCI, CH₄): m/z 278.1298 [M]⁺ (calcd for C₁₉H₁₈O₂, 278.1307).

ASSOCIATED CONTENTS

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

^1H and ^{13}C NMR spectra of all new compounds. ^1H spectra of known compounds, X-ray crystallographic data of **1**, **22a**, **22b** and **23** (PDF).

X-ray data for **1** (CIF).

X-ray data for **22a** (CIF).

X-ray data for **22b** (CIF).

X-ray data for **23** (CIF).

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Notes

The authors declare no competing financial interest.

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