185. Deaminocolchinyl Methyl Ether: Synthesis from 2,3,4,4′-Tetramethoxybiphenyl-2-carbaldehyde. Comparison of Antitubulin Effects of Deaminocolchinyl Methyl Ether and Dehydro Analogs

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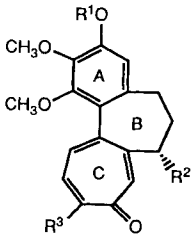
Synthesis of deaminocolchinyl methyl ether **9** was achieved from tetramethoxy-substituted biphenyl-2-carbaldehyde **12** *via* tricyclic ketone **20** and 5,6-didehydro congener **11**. Compound **9** was identical in every respect with material prepared from colchicine *via* 6,7-didehydro congener **10**. Measuring inhibition of tubulin polymerization *in vitro* showed compounds **4**, **5**, and **9**–**11** of the alloseries of colchicinoids to be particularly potent inhibitors.

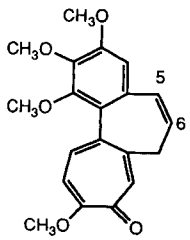
Introduction. – A large number of synthetic and natural compounds bind to the protein tubulin and, in so doing, inhibit its polymerization *in vitro* [1]. This property accounts for many of the effects observed when cells are treated with this class of agents, most notably failure of mitotic spindle formation and dissolution of the interphase microtubule network. This disruption of microtubules is probably responsible for the therapeutic properties of antimitotic agents. The majority of compounds which inhibit tubulin polymerization also, despite remarkably diverse structures, competitively inhibit the binding of radiolabeled colchicine to tubulin. This implies that, despite their structural diversity, they share features that allow them to bind at a common site on the protein. The most thoroughly studied member of this class of drugs is colchicine (= (*S*)-*N*-(5,6,7,9-tetrahydro-1,2,3,10-tetramethoxy-9-oxobenzo[*a*]heptalen-7-yl)acetamide; **1**, $R^1 = CH_3$, $R^2 = CH_3CONH$, $R^3 = CH_3O$).

Because of the antineoplastic potential of agents which inhibit microtubule assembly, a thorough understanding of the colchicine binding site is important. One approach to this problem is evaluation of antitubulin properties of analogs of active drugs. For example, virtually all colchicinoids summarized in structure **1**, as well as the dehydro analog **2** [2], inhibit tubulin polymerization and the growth of tumor cells *in vitro* and, in some cases, *in vivo*. More drastic changes in the colchicine molecule have surprisingly little apparent effect on most of these inhibitory properties. Complete elimination of ring B yields an antimitotic compound binding at the colchicine site (2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (**3**)) [3][4]. Conversion of the 7-membered 2-substituted cycloheptatrienone moiety (ring C) to a 6-membered phenyl ring yields compounds more potent than colchicine as polymerization inhibitors (allocolchicine (**4**) and *N*-acetylcolchinyl methyl ether **5**) [3][5].

In an effort to simplify further the structure of colchicine and inspired by the effectiveness of **3** as an antimitotic agent, we recently reported the synthesis of the tetramethoxy-



1 R^1 = H, CH_3, COOR
R^2 = H, AcylNH, CH_3NH
R^3 = CH_3O, CH_3S, CH_3NH



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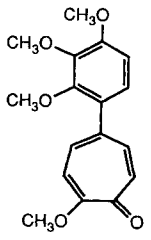

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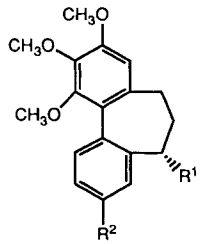
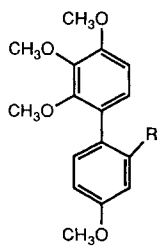
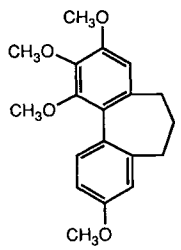


4 R^1 = CH_3CONH, R^2 = $COOCH_3$; allocolchicine
5 R^1 = CH_3CONH, R^2 = CH_3O
13 R^1 = NH_2, R^2 = OH; colchinol



6 R = H
7 R = CH_3
8 R = CH_3CH_2
12 R = CHO



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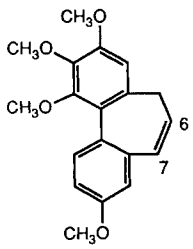

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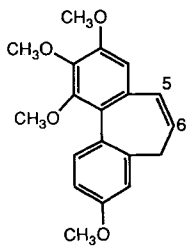


11

biphenyl **6** [6]. We were disappointed that it was only about 1/10th as inhibitory as **5** (*Powell et al.* [7] have reported similar results with a biphenyl analog of allocolchicine), but a progressive increase in inhibitory effects was obtained with **7** and **8**, methyl- and ethyl-substituted analogs of **6** [6][8].

The activity of these latter compounds, **7** and **8**, with an additional substituent in the second phenyl ring, and of deacetamidocolchicine (**1**, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3O$) and **2** and of modifications elaborated with thiocolchicine (*e.g.* **1**, $R^1 = CH_3$, $R^2 = CH_3CONH$, $R^3 = CH_3S$) [9] led us to search for simpler active derivatives of **5** which might provide insights about tubulin's colchicine site through molecular modeling studies. We, therefore, undertook the synthesis of deaminocolchinyl methyl ether **9** and of the olefins **10** and **11.**

Compound **5** is readily available from colchicine by oxidation with hydrogen peroxide [10] and has been converted by *Windaus* [11] and by *Cook* [12] into ether **9** *via* olefin **10**. The isomeric olefin **11** was obtained by *Cook* only as minor product [13] which suggested its preparation by a novel synthesis. This has now been accomplished starting from biphenyl-2-carbaldehyde **12** which is obtained by a practical route [6]. Reduction of olefin **11** afforded ether **9** identical in every respect with material prepared from **5** by the published procedures [11][12] and by *Rapoport*'s total synthesis [14].

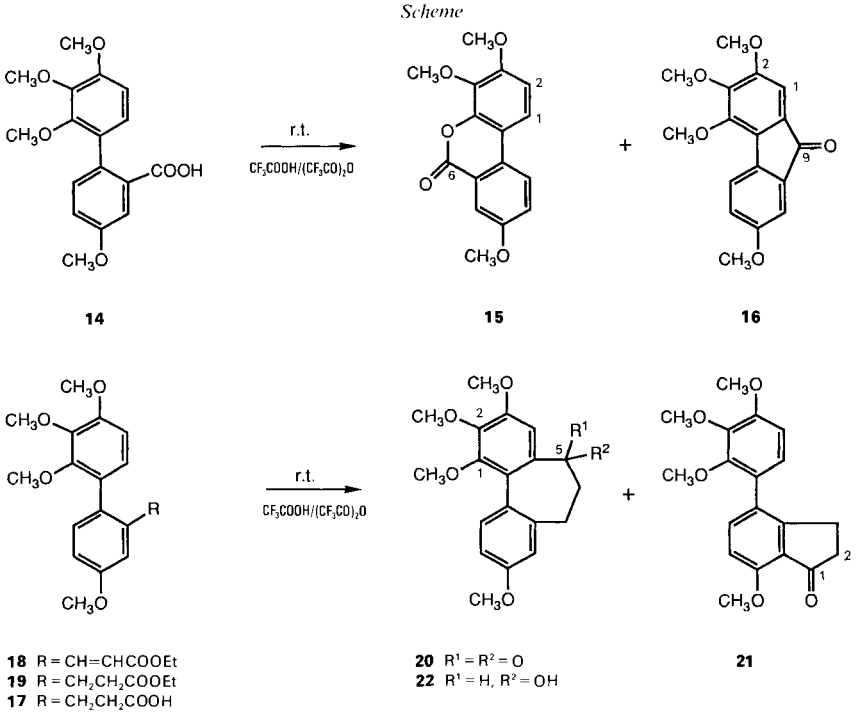
Chemistry. – Although a synthesis of dibenzocycloheptenes related to allocolchicine (**4**) and colchinol (= (*S*)-5-amino-6,7-dihydro-9,10,11-trimethoxy-5*H*-dibenzo[*a*,*c*]-cyclohepten-3-ol; **13**) was attempted from a biphenyl-5-propionic acid with negative

results [15], we thought cyclization of the isomeric propionic acid **17** more likely to succeed because of the presence of an aromatic CH_3O group in *para* position to the locus of cyclization.

Model experiments to probe cyclizations were first attempted with carboxylic acid **14** *(Scheme)*. It was found that a 1:1 mixture of trifluoroacetic anhydride and trifluoroacetic acid *(Method a)* afforded lactone **15** and fluorenone **16** in equal amounts. When only $(CF_3CO)_2O$ was used *(Method b)*, lactone **15** became the only product. We assume, at the moment, that these cyclizations are initiated by the *in situ* formed mixed anhydride.

Lactone **15** showed the carbonyl frequency in the IR spectrum at 1720 cm^{-1} and the presence of 5 aromatic H-atoms and 3 CH_3O groups in the ^{1}H-NMR at 7.93, 7.78, 7.66, 7.36, and 6.92 and 4.02, 3.96, and 3.93 ppm, respectively. The orange fluorenone **16** showed the carbonyl frequency at 1730 cm^{-1} and 4 aromatic H-atoms and 4 CH_3O groups 7.55, 7.25, 7.13, and 6.91 and 3.97, 3.94, 3.88, and 3.83 ppm, respectively.

Scheme



14 **15** **16**

18 R = CH=CHCOOEt
19 R = CH_2CH_2COOEt
17 R = CH_2CH_2COOH

20 $R^1 = R^2 = O$
22 R^1 = H, R^2 = OH

21

Cyclization of propionic acid **17**, prepared from aldehyde **12** by *Wittig* reaction with ethyl (diethoxyphosphoryl)acetate (→ **18**), catalytic reduction (→ **19**), and alkaline hydrolysis took a different course. With $(CF_3CO)_2O$ in CH_2Cl_2, ketone **20** was obtained almost exclusively (37%), whereas $CF_3COOH/(CF_3CO)_2O$ 1:1 afforded **20** (56–68%) besides indanone **21** (23.2–30%; *Scheme*). Both ketones **20** and **21** could easily be separated by chromatography on silica gel with hexane/AcOEt, affording **20** as the faster moving material.

Ketone **20** showed the carbonyl frequency in the IR spectrum at 1675 cm^{-1}, and its ^{1}H-NMR revealed 4 aromatic H-atoms (7.43, 6.91, and 2H at 6.83 ppm), 4 CH_3O groups (3.96, 3.91, 3.84, and 3.55 ppm), and 2

conformationally flexible CH_2 groups (3.17, 2.92, and 2.71 ppm). Indanone **21**, on the other hand, showed the carbonyl frequency at 1700 cm^{-1} 4 aromatic H-atoms at 7.38, 6.83, 6.78, and 6.67 ppm, 4 CH_3O groups 3.92, 3.87, 3.84, and 3.51 ppm, and 2 CH_2 groups in a sterically strained ring system at 2.86 and 2.57 ppm.

Although conversion of ketone **20** into **9** was accomplished by *Wolff-Kishner* reduction, the route *via* alcohol **22**, obtained from ketone **20** with $NaBH_4$ in MeOH and *via* dehydration of **22** to **11** at 200° under high vacuum, proved to be better. Catalytic reduction of **11** in AcOH over Pd/C gave **9**. Compound **9** was in every respect identical with material obtained by catalytic reduction of olefin **10**, obtained by *Hofmann* degradation of **5** [11].

Biological Evaluation. – The *Table* summarizes data on the inhibitory effects on tubulin polymerization of **9**, **10**, **11**, and **21** and compares them to appropriate analogs in both the biphenyl and colchicine series[1]). The methodology has been described in detail previously, and the reaction sequence includes a drug-tubulin preincubation to permit interaction of drug with protein prior to the onset of polymerization [9]. In addition, compounds **16** and **22** have been evaluated and found to be inactive (IC_{50} values > 100 μM).

The IC_{50} value of colchicine in this system was 2.4 μM. Both deacetamidocolchicine and phenylcycloheptatrienone **3** were only slightly less active (IC_{50} 2.6 μM) than col-

Table. *Inhibitory Effects of Colchicine Analogs on Tubulin Polymerization*[a])

Agent	IC_{50} (μM) [b])
Colchicine (**1**, $R^1 = CH_3$, $R^2 = CH_3CONH$, $R^3 = CH_3O$)	2.4 ± 0.08
Deacetamidocolchicine (**1**, $R^1 = CH_3$, $R^2 = H$, $R^3 = CH_3O$)	2.6 ± 0.3
2	1.6 ± 0.2
3	2.6 ± 0.3
4	1.4 ± 0.1
5	1.5 ± 0.2
6	15.5 ± 0.2
7	9.1 ± 0.2
8	7.5 ± 0.9
9	1.9 ± 0.3
10	2.2 ± 0.1
11	1.5 ± 0.3
20	10.7 ± 0.8
21	6.0 ± 0.1

a) Reaction mixtures contained 1.0M monosodium glutamate (pH 6.6 with HCl), 1.0 mM $MgCl_2$, 0.4 mM GTP, 1.0 mg/ml (10 μM) tubulin, and various drug concentrations. All components were preincubated for 15 min at 37° prior to addition of GTP.

b) IC_{50} values were determined graphically for at least three independent experiments; the reported values are average values with standard deviation.

[1]) Precise IC_{50} values vary with each tubulin preparation to a greater extent than we appreciated earlier. This, probably, is a consequence of differing percentages of active protein in each batch, for IC_{50} values rise as the amount of tubulin in the reaction mixture increases [1]. Accordingly, the IC_{50} values presented in the *Table* were all obtained with the same tubulin preparation, as opposed to our earlier reports [6] [8]. In addition, freshly prepared solutions of **5** were disproportionately more active in current experiments than in those reported previously [6], perhaps as a consequence of instability of the agent in solution. The IC_{50} value of colchicine (**1**, $R^1 = CH_3$, $R^2 = CH_3CONH$, $R^3 = CH_3O$) obtained in the present series of experiments has been reported previously [9].

chicine. Olefin **2** was distinctly more active (IC_{50} 1.6 μM) than colchicine. The IC_{50} of **2** approaches the lowest values we have observed in this tubulin polymerization system (1.2 μM, obtained with an antimitotic peptide, and 1.3 μM, obtained with thiocolchicine [9] (**1**, $R^1 = CH_3$, $R^2 = CH_3CONH$, $R^3 = CH_3S$)).

Compounds **4** and **5** in which the only modification from the structure of colchicine is replacement of the substituted cycloheptatrienone ring with a substituted phenyl ring were both significantly more inhibitory than colchicine (IC_{50} 1.4 and 1.5 μM). An additional substituent at the 2′-position enhanced activity of the biphenyls (**7** and **8** have IC_{50} values of 9.1 and 7.6 μM, resp.), although these agents were still significantly less inhibitory than **5**. The indanone **21** can be viewed as a still more extensively substituted biphenyl than **7** and **8**, and **21** (IC_{50}, 5.9 μM) was slightly more inhibitory than these simpler biphenyls.

The deacetamido analog of **5** (compound **9**, IC_{50} 1.9 μM) was slightly less inhibitory than **5**, comparable to the small reduction in activity of deacetamidocolchicine relative to colchicine. Again, introduction of a 5,6 double bond resulted in a highly inhibitory agent (compound **11**, IC_{50} 1.5 μM), although there was no enhancement relative to **5**, in contrast to the increased activity of **2** relative to colchicine. This may only represent the maximum sensitivity of this assay system, however, and an alternate assay might detect significant differences in the interactions of **5** and **11** with tubulin. Introduction of a 6,7 double bond (compound **10**, IC_{50} 2.2 μM) resulted in a further small loss in inhibitory activity relative to **5** and **9**. Finally, even an analog with a keto function at position 5 had significant activity as an inhibitor of tubulin polymerization (compound **20** IC_{50} 11 μM), but reduction of the keto group (compound **22**) yielded an inert compound. We have, at the moment, no obvious explanation for the loss in activity by going from **20** to **22**.

In summary, with the exception of the biphenyl compound **6** as compared to **3**, analogs of *N*-acetylcolchinyl methyl ether **5** and of colchicine do not differ greatly in their relative effects on tubulin polymerization when compared to the parent compounds. We are presently attempting to gain further insights into characteristics of the colchicine site of tubulin from molecular-modeling studies with both sets of active agents.

Experimental Part

General. TLC: silical-gel *GHLF* plates from *Analtech;* visualization with UV light, phosphomolybdic acid, I_2, $FeCl_3$ soln. Flash chromatography (FC): silica gel *60 (Merck)*, 230–400 mesh, 60 A. M.p.: *Fisher-Johns* melting-point apparatus. IR spectra: *Beckman IR 4230* (cm^{-1}). ^{1}H-NMR spectra: *Varian XL 300* (300 MHz). MS: *Finingan 1015 D* instrument (Cl).

2′,3′,4,4′-Tetramethoxy-1,1′-biphenyl-2-carboxylic Acid (**14**). A soln. of methyl 2′,3′,4,4′-tetramethoxy-1,1′-biphenyl-2-carboxylate (240 mg), and 4% aq. NaOH soln. (5 ml) in MeOH (20 ml) was refluxed for 2 h. The acid was precipitated with excess conc. HCl and extracted with $CHCl_3$. The org. layer was washed with brine and dried ($MgSO_4$). Evaporation gave **14** as a solid which was crystallized from $AcOH/H_2O$ (200 mg, 87%). M.p. 164°. IR ($CHCl_3$): 3500, 3400–2400, 1680, 1590, 1470, 1450, 1400. MS: 318 (M^+).

*3,4,8-Trimethoxy-6*H*-dibenzo[*b,d*]pyran-6-one* (**15**) *and 2,3,4,7-Tetramethoxy-9*H*-fluoren-9-one* (**16**). *Method a:* A suspension of **14** (50 mg) in $(CF_3CO)_2$ (2 ml) was added dropwise to CF_3COOH (2 ml). The resulting soln. was stirred at r.t. for 3 h and then evaporated. From the residue, **15** was crystallized selectively in AcOEt/hexane 3:7 (20 mg, 44.6%). M.p. 173–174°. IR ($CHCl_3$): 1720, 1610, 1480. ^{1}H-NMR ($CDCl_3$): 7.93 (*d*, $J = 8.8$, H–C(10)); 7.78 (*d*, $J = 2.5$, H–C(7)); 7.66 (*d*, $J = 9$, H–C(1)); 7.36 (*dd*, $J = 2.7$, 8.8, H–C(9)); 6.92 (*d*, $J = 9$, H–C(2)); 4.02 (*s*, CH_3O); 3.96 (*s*, CH_3O); 3.93 (*s*, CH_3O). MS: 286 (M^+).

The soluble filtrate was chromatographed. Elution with AcOEt/hexane 3:7 gave **16** as orange needles (18 mg, 38%). M.p. 110°. IR ($CHCl_3$): 1730, 1620, 1490. ^{1}H-NMR ($CDCl_3$): 7.55 (*d*, *J* = 8.3, H–C(5)); 7.25 (*s*, H–C(1)); 7.13 (*d*, *J* = 2.3, H–C(8)); 6.91 (*dd*, *J* = 2.3, 8.1, H–C(6)); 3.97 (*s*, CH_3O); 3.94 (*s*, CH_3O); 3.88 (*s*, CH_3O); 3.83 (*s*, CH_3O). MS: 300 (M^+).

Method b: A mixture of **14** (20 mg) and $(CF_3CO)_2O$ in C_6H_6/CH_2Cl_2 1:1 (2 ml) was stirred at r.t. for 3 h. Evaporation and recrystallization from AcOEt/hexane gave **15** (17 mg, 94%).

Ethyl 3-(2′,3′,4,4′-Tetramethoxy-1,1′-biphenyl-2-yl)prop-2-enoate (**18**). To a stirred suspension of NaH (140 mg, 80% in oil) in THF (20 ml) was added dropwise ethyl(diethoxyphosphoryl)acetate (0.8 ml) in THF (2 ml) at 0° under N_2. The mixture was stirred at r.t. for 20 min. A soln. of 2′,3′,4,4′-tetramethoxy-1,1′-biphenyl-2-carbaldehyde (**12**; 1.01 g) in THF (30 ml) was added dropwise at r.t. After stirring for 4 h, THF was removed and the residue dissolved in AcOEt. The org. layer was washed with a sat. $NaHCO_3$ soln. and brine and dried (Na_2SO_4). Evaporation gave an oil which was chromatographed on SiO_2. Elution with AcOEt/hexane 2:8 gave **18** (1.24 g, 99.4%). M.p. 82°. IR ($CHCl_3$): 1700, 1627, 1595. ^{1}H-NMR ($CDCl_3$): 7.57 (*d*, *J* = 15.8, CH); 7.24 (*d*, *J* = 8.6, H–C(6)); 7.21 (*d*, *J* = 2.6, H–C(3)); 6.98 (*dd*, *J* = 2.6, 8.6, H–C(5)); 6.81 (*d*, *J* = 8.5, H–C(6′)); 6.71 (*d*, *J* = 8.5, H–C(5′)); 6.35 (*d*, *J* = 15.8, CH); 4.19 (*q*, *J* = 7.2, CH_3CH_2); 3.92 (*s*, CH_3O); 3.91 (*s*, CH_3O); 3.88 (*s*, CH_3O); 3.58 (*s*, CH_3O); 1.27 (*t*, *J* = 7.2, CH_3CH_2). MS: 372 (M^+).

Ethyl 2′,3′,4,4′-Tetramethoxy-1,1′-biphenyl-2-propionate (**19**). A soln. of **18** (1.24 g) in AcOEt/MeOH 1:1 (100 ml) was hydrogenated over Pd black (150 mg) under 1 atm for 10 h. The catalyst was filtered off and washed with AcOEt. The combined filtrate and wash were evaporated to give **19** as an oil (1.14 g, 91%). IR ($CHCl_3$): 1722, 1600, 1570. ^{1}H-NMR ($CDCl_3$): 7.10 (*d*, *J* = 8.4, H–C(6)); 6.83 (*d*, *J* = 2.6, H–C(3)); 6.83 (*d*, *J* = 8.3, H–C(6′)); 6.79 (*dd*, *J* = 2.6, 8.3, H–C(5)); 6.70 (*d*, *J* = 8.4, H–C(5′)); 4.06 (*q*, *J* = 7.1, CH_3, CH_2); 3.91 (*s*, CH_3O); 3.90 (*s*, CH_3O); 3.83 (*s*, CH_3O); 3.58 (*s*, CH_3O); 2.79 (*t*, *J* = 7.9, CH_2); 2.47–2.43 (*m*, CH_2); 1.19 (*t*, *J* = 7.1, CH_3CH_2). MS: 375 ($M^+ + 1$).

2′,3′,4,4′-Tetramethoxy-1,1′-biphenyl-2-propionic Acid (**17**). A soln. of **19** (1.14 g) and 20% aq. NaOH soln. (50 ml) in MeOH (50 ml) was heated at reflux for 3 h. After cooling and acidification with conc. HCl soln. the mixture was extracted with AcOEt. The org. layer was washed with brine and dried ($MgSO_4$). Evaporation gave **17** as white crystals (1.03 g, 97%). M.p. 127°. ^{1}H-NMR ($CDCl_3$): 10.6 (br., COOH); 7.03 (*d*, *J* = 8.1, H–C(6)); 6.73 (*m*, 3 arom. H); 6.62 (*d*, *J* = 8.5, H–C(5′)); 3.82 (*s*, $2CH_3O$); 3.76 (*s*, CH_3O); 3.50 (*s*, CH_3O); 2.72 (*t*, *J* = 7.8, CH_2); 2.42 (*m*, CH_2). MS: 346 (M^+).

*6,7-Dihydro-1,2,3,9-tetramethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-one* (**20**) *and 7-Methoxy-4-(2′,3′,4′-trimethoxyphenyl)indan-1-one* (**21**). A soln. of **17** (140 mg) and $(CF_3CO)_2O$ (3 ml) in CF_3COOH (3 ml) was stirred at r.t. for 10 h. The solvent was evaporated and the residue dissolved in Et_2O. The org. layer was washed with sat. $NaHCO_3$ soln. and brine and dried ($MgSO_4$). Chromatography on SiO_2 with AcOEt/hexane 2:8 gave **20** (90 mg, 68%) which was recrystallized from $(i\text{-Pr})_2O$, white crystals. M.p. 107°. UV (EtOH): 252, 274 (sh), 320. IR ($CHCl_3$): 2990, 2930, 2830, 1675, 1605, 1575, 1480. ^{1}H-NMR ($CDCl_3$): 7.43 (*d*, *J* = 8.3, H–C(11)); 6.91 (*s*, H–C(4)); 6.85 (*m*, H–C(8), H–C(10)); 3.96 (*s*, CH_3O); 3.92 (*s*, CH_3O); 3.84 (*s*, CH_3O); 3.55 (*s*, CH_3O); 3.17 (br. *s*, CH); 2.92 (br. *m*, 2CH); 2.71 (br. *s*, CH). MS: 329 ($M^+ + 1$).

The slower-moving fraction yielded **21** (40 mg, 30.1%). Pale orange crystals from $(i\text{-Pr})_2O$. M.p. 145–146°. IR ($CHCl_3$): 3000, 2940, 2840, 1700, 1595, 1580, 1480. ^{1}H-NMR ($CDCl_3$): 7.38 (*d*, *J* = 8.3, H–C(5)); 6.83 (*d*, *J* = 8.5, H–C(6′)); 6.78 (*d*, *J* = 8.3, H–C(6)); 6.67 (*d*, *J* = 8.5, H–C(5′)); 3.92 (*s*, CH_3O); 3.87 (*s*, CH_3O); 3.84 (*s*, CH_3O); 3.51 (*s*, CH_3O); 2.86 (*t*, *J* = 6, CH_2); 2.57 (*t*, *J* = 6.1, CH_2CO). MS: 329 ($M^+ + 1$).

*6,7-Dihydro-1,2,3,9-tetramethoxy-5*H*-dibenzo[*a,c*]cyclohepten-5-ol* (**22**). To a soln. of **20** (100 mg) in MeOH (10 ml) at r.t. was added $NaBH_4$ (240 mg) in 2 portions. The mixture was stirred at r.t. for 2 h. The solvent was evaporated, and after addition of sat. NH_4Cl soln., the aq. layer was extracted with Et_2O. The org. phase was washed with brine and dried ($MgSO_4$). Evaporation of solvent gave **22** as pale yellow crystals which were recrystallized in $(i\text{-Pr})_2O$ (85 mg, 84.5%). M.p. 158°. IR ($CHCl_3$): 3600, 2995, 2920, 2820, 1600, 1565, 1475. ^{1}H-NMR ($CDCl_3$): 7.32 (*d*, *J* = 8.35, H–C(11)); 6.99 (*s*, H–C(8)); 6.76 (*m*, H–C(10), H–C(4)); 4.41 (*dd*, *J* = 6.3, 5.4, *CH*OH); 3.87 (*s*, CH_3O); 3.85 (*s*, CH_3O); 3.78 (*s*, CH_3O); 3.52 (*s*, CH_3O); 2.44 (*m*, CH_2CH_2). MS: 331 ($M^+ + 1$).

*1,2,3,9-Tetramethoxy-5*H*-dibenzo[*a,c*]cycloheptene* (**10**). For 50 min, **22** (85 mg) was heated at 190–200° *in vacuo* in a 'Kugelrohr' apparatus. The residue was dissolved in Et_2O and filtered through *Celite*. Evaporation of the filtrate gave a yellow oil which was chromatographed. Elution with $CHCl_3$ gave **10** which was crystallized from MeOH (65 mg, 80.9%). M.p. 102–103° ([13]: 101°). UV (EtOH): 249, 274 (sh). IR ($CHCl_3$): 3000, 2930, 2840, 1600, 1480, 1455. ^{1}H-NMR ($CDCl_3$): 7.51 (*d*, *J* = 8.4, H–C(11)); 6.72 (*dd*, *J* = 2.7, 8.5, H–C(10)); 6.68 (*d*, *J* = 2.7, H–C(8)); 6.53 (*s*, H–C(4)); 6.38 (*d*, *J* = 10.1, H–C(5)); 6.11 (*ddd*, *J* = 5.6, 8.1, 10.0, H–C(6)); 3.89 (*s*, CH_3O); 3.84

(*s*, CH_3O); 3.77 (*s*, CH_3O); 3.5 (*s*, CH_3O); 3.05 (*dd*, J = 8.1, 12.8, CH); 2.74 (*ddd*, J = 2.1, 5.6, 12.8, CH). MS: 313 ($M^+ + 1$).

*6,7-Dihydro-1,2,3,9-tetramethoxy-5*H*-dibenzo[*a,c*]cycloheptene* (**9**). A mixture of **10** (10 mg) and Pd black (20 mg) in AcOH (10 ml) was hydrogenated under 1 atm at r.t. for 12 h. After evaporation, the residue was triturated with Et_2O and filtered through *Celite* to remove the catalyst. The org. layer was washed with brine and dried (Na_2SO_4). Evaporation gave a colorless oil which was chromatographed. Elution with $CHCl_3$ gave **9** which was crystallized from MeOH (8 mg, 80%). M.p. 97° ([13]: 96–98°). UV (EtOH): 261. IR ($CHCl_3$): 2995, 2930, 2850, 1600, 1570, 1480, 1450. ^{1}H-NMR ($CDCl_3$): 7.33 (*d*, J = 8.4, H–C(11)); 6.77 (*dd*, J = 2.7, 8.4, H–C(10)); 6.72 (*d*, J = 2.7, H–C(8)); 6.5 (*s*, H–C(4)); 3.84 (*s*, CH_3O); 3.83 (*s*, CH_3O); 3.78 (*s*, CH_3O); 3.5 (*s*, CH_3O); 2.5–2.15 (*m*, 4 aliph. H); 2.12–1.97 (*m*, 2 aliph. H). MS: 315 ($M^+ + 1$).

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