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Synthesis of (±)-8,9:13,14-Diseco-18-norestradiol and Related Large-Ring Hormone Analogues

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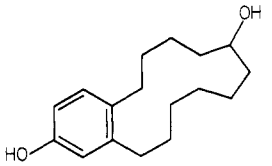
The first large-ring analogue of estradiol has been prepared by a sequence in which 6-methoxycyclodecanone is treated with sodium amide and *p*-bromoanisole. 4′,8-Dimethoxy-1,2-benzocyclododecen-3-one is separated from the mixture and converted to the title compound by expanding the ring by one carbon and then modifying the functional groups. Several other related compounds with potential fertility control properties were prepared from the title compound. The dimethyl ether derivative of the title compound showed significant uterotrophic activity.

The conformationally flexible 8,9:13,14-diseco-18-norestradiol (1) is the first analogue of the human sex steroids[1]



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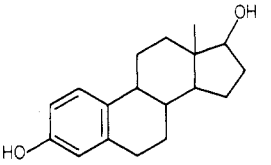


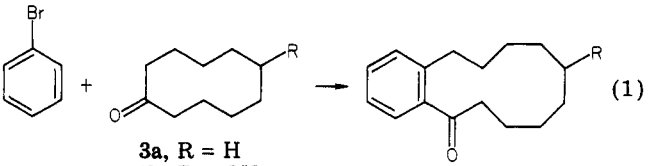
2

in which three of the steroid rings are replaced by a single large ring. Such flexible steroid analogues are of interest because of their potential biological activity at hormone receptors. According to one hypothesis of hormone action,[2] the activity of estradiol **2** depends on the shape and placement of oxygen groups to form a complex at the receptor which is then deformed to fit the rigid steroid structure. The deformation then determines the further activity of the complex. Compounds like **1** could adopt the shape and placement of oxygen groups but would lack the rigidity of the steroid. This model would predict that such compounds should not be capable of high estrogenic activity but could possibly bind to the site and act as an antiestrogen.

This work is related to a fascinating series of recent papers[3] that demonstrated that an appropriately substituted 5,10-secoprogesterone exhibits strong antiandrogenic activity. The authors pointed out that the long-accepted postulate that an unmodified steroid nucleus is required for hormonal activity "needs modification" to take account of their compounds. Surprisingly high activity had also been noted earlier for a 15,16-seco-17-isoprogesterone, which is conformationally mobile in the D ring.[4] System **1** and compounds related to it are much more flexible than the earlier cases and are designed to determine whether significant hormonal or antihormonal activity is possible for such cases.

Results and Discussion

The key step in this synthetic scheme is based on the earlier work of Caubère[5] which had shown that, under appropriate conditions, benzynes could be inserted into ring ketones with a net two-carbon ring expansion. For example, bromobenzene, sodium amide, and cyclodecanone (**3a**) (eq 1) had been shown[5] to produce 1,2-benzocyclo-



(1)

3a, R = H
3b, R = OH
3c, R = OMe

4a, R = H
c, R = OMe

dodecen-3-one (**4a**). We initially reasoned that 6-methoxycyclodecanone (**3c**) could be used in a similar way to produce **4c**, which conveniently places the carbonyl in a position where it can direct aromatic substitution to the meta position and can also be used to ring-expand the lower half of the 12-membered ring by one carbon. The required ketone (**3c**) was prepared by the reported method[6]

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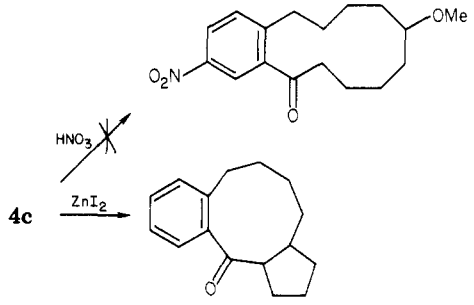
wherein Decalin is oxidized and rearranged to produce **3b**, which is converted to **3c** by extended reflux[7] with methanol and acid. The Caubère reaction then produced **4c** along with the usual byproduct of this reaction, 6-methoxy-2-phenylcyclodecanone. Medium-pressure liquid chromatographic purification[9] gave a 44% yield of **4c**.

The original plan called for selective nitration meta to the carbonyl group of **4c** so that the nitro group could then be converted to a methoxy group as had been done on related systems.[8] To our dismay, nitration gave a complex product mixture that no longer exhibited any methoxy group in the NMR spectrum. Several other electrophilic reactions were tried, and it became apparent that **4c** (eq 2) was readily transformed by acid catalysts such as aluminum chloride, ferric chloride, and zinc iodide to nonmethoxy products. For example, with ZnI_2, or more efficiently with ZnI_2 and trimethylsilyl cyanide, **4c** formed a major product with NMR, IR, and a mass spectra that are consistent with structure **5**. Such a product could result from acid-catalyzed tranannular displacement of the methoxy group by the enol form of the carbonyl.



(2)

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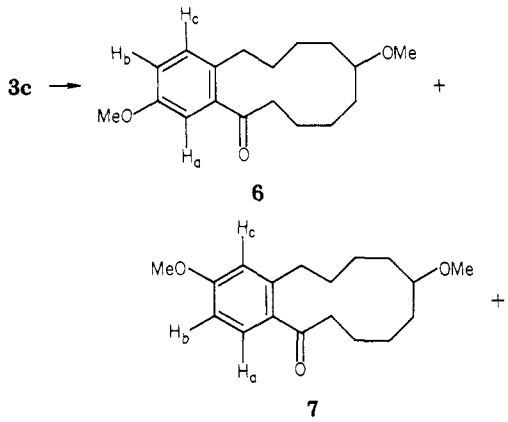
Using *p*-bromoanisole in place of bromobenzene was an intriguing alternative means to introduce the aromatic substituent although high yields could not be expected. Even the simple Caubère reaction of cyclodecanone and bromobenzene only gives a 60% yield of the ring-expanded product. Although **4c** and *p*-bromoanisole are both symmetrical, the benzyne intermediate formed from *p*-bromoanisole is not and can react in two orientations, which doubles the number of products. If the mechanism of the reaction involves an initial attack of the enolate on the benzyne there was some hope for a selective reaction based on earlier work.[10] In the fact, **3c** formed **6** and **7** in a 2:1 ratio along with the usual 2-aryl-6-methoxycyclodecanone byproducts (eq 3). This product mixture was not readily separated; however, three passes through a medium-pressure liquid chromatograph[9] gave an 11% yield of pure **6**. In spite of the low yield, the reaction is attractive because it simultaneously expands **3c** by two carbons, inserts the benzo unit with the methoxy preattached, and gives a product mixture that is separable into components that are readily assigned from their NMR spectra. Even with no added shift reagent, the coupling patterns readily identify the three aromatic protons of **7** [H_a (d, J = 8 Hz), H_b (dd, J = 2, 8 Hz), and H_c (d, J = 2 Hz)] and the downfield aromatic proton of **6** [H_c (d, J = 8 Hz)]. That the spread of aromatic chemical shifts is much greater for **7** than for **6** (δ 0.8 vs. 0.4) and that H_a of **7** is further



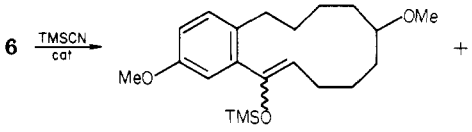
6

7

2-aryl-6-methoxycyclodecanone (3)

downfield than H_c of **6** strongly suggest that the assignments are as shown. This fits with related six-,[11] seven-,[8] and nine-membered[12] ring examples. Further confirmation was achieved by adding europium shift reagent and observing that for **6** and **7** the lanthanide-induced shift (LIS) of H_a is much greater than that for H_c or H_b, i.e., for **6** the J = 2 Hz doublet moved fastest, whereas for **7** the J = 8 Hz doublet moved fastest. The relative orders of LIS for **6** ($H_a \gg H_c > H_b$, 23:11:7) and for **7** ($H_a \gg H_c > H_b$, 15:7:5) correspond to the orders predicted by the formula LIS = $k[3(\cos^2\theta) - 1]/r^3$ for all values of the dihedral angle between the carbonyl group and the aromatic ring between 0 and 90°. The only other group to be located is the aliphatic methoxy, which is assigned on the basis that four methylene units separate the methoxy and carbonyl groups in the starting material **4c**. The assignment of structure at this stage is very critical since it is usually difficult to establish the locations of groups on large rings if they are not close together.

The carbon skeleton of **6** still requires one more methylene unit in the lower half of the large ring. Past experience[8,13] suggested that a ring expansion based on the addition of trimethylsilyl cyanide[14] (TMSCN) to the carbonyl offered the best chance of success; however, the initial tests were not encouraging. The reaction of **6** in ether or THF at room temperature with either zinc iodide or potassium cyanide/crown ether (KCN/18-crown-6) catalysts formed the enol trimethylsilyl ether **8** more efficiently than the desired cyano adduct **9** (ca. 2:1 ratio) (eq 4). Heating the KCN-catalyzed reaction did not change the product mixture appreciably, and heating the ZnI_2 catalyzed reaction produced product that had lost the



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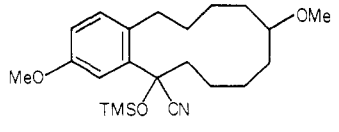

(4)

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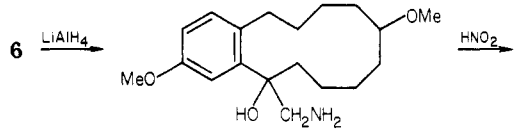
aliphatic methoxy group (see 5 above). It was noted that heating the reaction mixture before adding the catalyst increased the 8/9 ratio as did changing to more polar solvent. This suggested a nonpolar solvent at low temperature; however, pentane gave little or no reaction at low temperature. Eventually, a 1:3 ratio of 8/9 was achieved by adding TMSCN and KCN/18-crown-6 to a toluene solution of 6 at −78 °C and then allowing the mixture to stand for 1 week at −15 °C.

Because the conditions to produce 9 in reasonable yield took some time to develop, other ring-expansion methods were tested on model systems. Reactions that rely on adding anions to the carbonyl such as the Wittig,[15] dimethylsulfonium methylide,[16] or lithium dibromomethane[17] generally gave back largely, if not entirely, starting ketone. This is presumably due to preferred formation of the enolate, rather than the carbonyl adduct, in compounds like 4c or 6. Since 8 was formed so easily, carbenoid additions to 8 were tested as a possible way to expand the ring; however, neither the diiodomethane/zinc–copper[18] or bromoform/base[19] methods gave clean product mixtures in reasonable yield.

Although the TMSCN method produced enol ether 8 as a side product, this was not an unmanageable problem. The toluene was replaced by ether, and the crude mixture of 8 and 9 was reduced with lithium aluminum hydride. The desired amino alcohol 10 could be separated by extraction into acid solution while 8, or the hydrolyzed form 6, could be recovered in the ether layer. Nitrous acid treatment gave the expected Tiffeneau–Demjanov rearrangement[13] leading to ketones 11 and 12 (eq 5) in approximately equal amounts.[20] This case differs from the other ring expansions of this type that we have studied with seven–[13] or nine–[12] membered rings, which exhibit a strong preference for exclusive migration of the aryl group, which places the carbonyl β to the aromatic ring.



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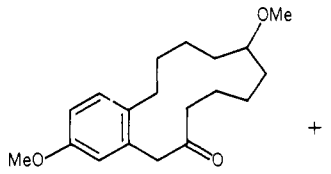
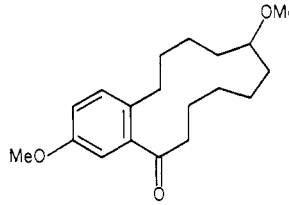


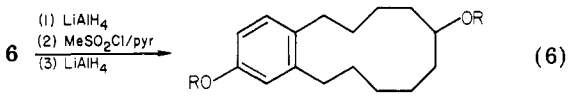
11 +



12 (5)

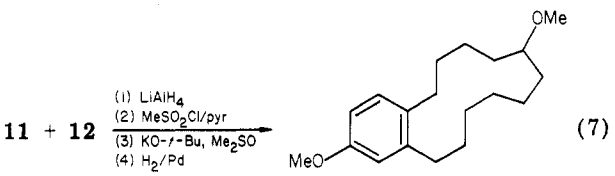
Wolf–Kishner reduction[21] of the mixture of 11 and 12 should lead to the same product. When tested, 14 was the major product of such reduction; however, only about half of the product was recovered as a crude mixture, which appeared to be quite impure. Similar reduction of 4c was quite clean, which suggests that attack at the aromatic methoxy group may be at least part of the problem. Reduction of 4c with boron trifluoride/triethylsilane[22] demonstrated again that Lewis acids can remove the aliphatic methoxy group as described above (see 5).

It seemed that a less direct method was needed for the removal of the carbonyl group in 11 and 12. Our previous work with medium-sized rings[23] suggested that the tosylhydrazones of 11 and 12 might provide an alternative means of reduction; however, under a variety of conditions, the tosylhydrazone derivatives would not form. Conversion of the ketone to the methanesulfonate of the corresponding carbinol was more successful. Thus, model system 6 was reduced with $LiAlH_4$ to the alcohol (eq 6), which readily



(6)

13a, R = Me
b, R = H



(7)

14

formed the methanesulfonate derivative which in turn was reduced to form 13a by treatment with $LiAlH_4$. This same sequence was also applied to the mixture of 11 and 12 to produce 14 (eq 7) however, a much cleaner and higher yield preparation of 14 resulted from treating the methanesulfonate mixture with t-BuOK/Me_2SO to produce a mixture of alkenes, which was catalytically reduced to 14. The four-step sequence gave an overall 51% yield from the mixture of 11 and 12.

The removal of the methyl groups on 14 posed some difficulties in that some reagents that were reported to cleave methyl ethers gave no reaction (diisobutylaluminum hydride)[24] while others (e.g., BBr_3, TMSI, BF_3/HCl/EtSH)[25] did react but gave mixtures of products that appeared to result from further side reactions with the products. Ultimately, the best results were obtained by cleaving the methyl ethers with $AlCl_3$ in ethanethiol[26] or 1,2-ethanedithiol, although there was some tendency to produce the sulfide if reaction times were too long. By careful monitoring of the reaction by TLC so as to stop at the optimum time, a reasonably clean conversion of 14 to 1 could be obtained with a yield after purification of 56%. Attempts to stop the reaction at a monodemethylated product were not successful.

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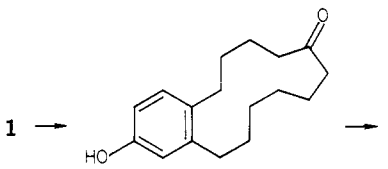
Table I. Uterotrophic Activity[a]

compd	control[b]	1 μg	10 μg	100 μg	1000 μg
1	43.7 ± 3.7	44.9 ± 1.1	46.5 ± 3.4	49.0 ± 3.1	
13b	43.4 ± 4.0	44.3 ± 3.2	46.8 ± 2.8	48.5 ± 4.9	
14	32.9 ± 1.0	46.0 ± 4.2	39.2 ± 2.4	36.7 ± 2.3	35.1 ± 2.5
15	25.9 ± 1.3		30.1 ± 2.2	30.8 ± 2.2	
16	25.9 ± 1.3		29.4 ± 2.5	31.4 ± 2.9	

[a] Uterotrophic activity was measured by an increase in wet uterine weight (mg) vs. dosage of the compound indicated, which was applied subcutaneously in sesame oil once daily for 3 days followed by sacrifice 1 day later. [b] The compounds were tested at different times with different batches of rats so that the data for each compound must be compared with the control listed on the same line.

Jones oxidation of estradiol analogue **1** produced a 74% yield of the estrone analogue **15**. The reaction of excess lithium acetylide with **15** produced the ethinylestradiol analogue **16** in 46% yield.



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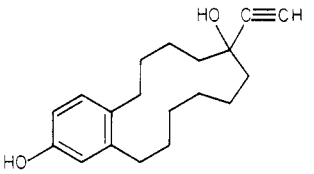

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Biological Test Results

Of the compounds prepared in this study, **1**, **13b**, and **14–16** have been tested for uterotrophic activity and postcoital activity (except for **14**) at the Contraceptive Development Branch, Center for Population, Research, National Institutes of Health (see Table I).

When compared to estradiol **2**, which approximately doubles the uterine weight at a 0.32-μg dose, all the analogues tested here except **14** are extremely weak if active at all. The only activity considered significant by the center was that for **14** at 1- and 10-μg dosages. The 40% increase in uterine weight at 1-μg dosage for **14** is clearly in the significant range and demonstrates that *estrogen analogues without the rigid steroid backbone are capable of binding to the receptor and acting as an agonist.*

Cases in which the uterine weight increase falls off substantially with increasing doses have been observed previously for such compounds as nafoxidine, which shows a 90% weight increase at 5 μg but only a 55% weight increase at 50 μg.[27] Nafoxidine has been classified as a long-acting hormone analogue with both agonist and antagonist properties.[28] Testing of **14** for antiuterotrophic properties (antagonist) showed no significant activity at 1.0-mg total dose. It is not known whether **14** is long acting since no time-dependency studies[29] have been completed on any of the compounds listed in Table I. Previous work has shown that cyclopentyl[30] or methyl[31] ether derivatives of estradiols do not bind well to the active site in vitro but are stored in the fat and released in vivo by a metabolic process that cleaves the 3- or 17-ether to a hydroxyl form. The activity of the ether derivatives is generally more prolonged and may be more or less than the hydroxyl form depending on dosage; for example, the 3,17-dimethoxy form of estradiol **2** is essentially inactive at 1 μg, where **2** shows slightly less than its maximum effect.[31] It appears that the methoxy groups of **14** allow it to be delivered to the receptor in a more active form than is the case for the diol form **1**.

Experimental Section

General Methods. Spectral measurements utilized Perkin-Elmer 727B infrared, Varian EM 360, HA 100, and FT-80 NMR, and Varian-Matt CH7 and CDC 110B mass spectrometer instruments. GC analyses were carried out on a Varian 1200 (FID) chromatograph using a 4 ft × 0.125 in. 7.4% OV 101 on a 80/100 chromosorb G column. Preparative GC used a Varian 920 chromatograph with a 2 or 5 ft × 0.25 in. 4.9% OV 101 on a 80/100 chromosorb G column. Medium-pressure liquid chromatography (MPLC) used the previously described system,[9] eluting with ethyl acetate–pentane (20:80, v/v unless otherwise specified). Melting points are uncorrected. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone dianion under nitrogen. Hexamethylphosphoramide (HMPA) was dried by storing over 13× molecular sieves (predried under nitrogen at 350 °C for 4 h).

6-Methoxycyclodecanone (3c). Oxidation of Decalin with oxygen and benzoyl peroxide followed by isomerization of the hydroperoxide with 70% H_3PO_4 in acetone by the described procedures[6] gave **3b**: mp 68.5–69.5 °C (lit.[6] 69–70 °C). Treatment of **3b** with methanol and acid as described previously[7] gave **3c**: ^{1}H NMR (CCl_4) δ 3.4–3.0 (m, 4 H, s at 3.24), 2.7–2.18 (m, 4 H), 2.04–1.06 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 214.4, 79.20, 56.37, 42.07, 29.75, 23.55, 22.64.

8-Methoxy-1,2-benzocyclododecen-3-one (4c). Sodium amide was prepared[32] from 3.2 g (0.14 mol) of sodium and 25 mL of liquid ammonia. After the ammonia had been replaced by 100 mL of dry THF, 12.4 g (0.067 mol) of **3c** in 40 mL of dry THF was added dropwise over 10 min, and the resulting mixture was stirred at 45 °C for an additional hour. Bromobenzene (5.0 g, 0.032 mol) in 30 mL of THF was added over 2 h, and the solution was allowed to stir at 45 °C for 24 h. The reaction was quenched by pouring this into a mixture of 300 mL of ice and 20 mL of concentrated HCl. The aqueous layer was extracted with three portions of chloroform, and the combined organic layers were washed with water, saturated $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$) and evaporated to yield a brown oily layer, which was transferred by Kugelröhr distillation at about 90 °C (1mmHg) to give 6.8 g of the starting cyclodecanone and 6.15 g of the crude product at about 150 °C. The crude product was purified by MPLC, and then the resultant oily layer was triturated with 7 mL of pentane to yield 3.63 g (44%) of white solid product: mp 48–49 °C; IR (CS_2) 2920, 2850, 2800, 1685, 1520, 1460, 1240, 1220, 1180, 1090, 980, 760 cm^{-1}; ^{1}H NMR (CCl_4) δ 7.5–7.0 (m, 4 H), 3.15–2.72 (m, 8 H, s at 3.18), 1.94–0.78 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 206.65, 141.83, 140.67, 130.73, 130.38, 126.07, 125.31, 79.41, 55.82, 39.59, 30.17, 28.38, 28.04, 27.83, 22.39,

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20.24, 19.80; MS, m/e 260.178 (calcd 260.178).

3,4-Benzobicyclo[7.3.0]dodec-3-en-2-one (5). Treatment of 62 mg of **4c** with excess ZnI_2 (1.2 equiv) in refluxing toluene for 15 h converted 10% to a single product. Addition of 2 equiv of trimethylsilyl cyanide followed by 78 h of reflux gave 90% conversion to this same product. The mixture was quenched with 5% H_2SO_4 and extracted with ether, which was then washed with saturated $NaHCO_3$ and dried over $MgSO_4$. Removal of solvent and MPLC (5% EtOAc–hexane) gave 47 mg (86%) of **5**: IR (Neat) 2940, 2870, 1695, 1600, 1450, 1360, 1240, 1215, 1050, 755 cm^{-1}; ^1H NMR (CCl_4) δ 7.40–6.92 (m, 4 H), 3.14–2.42 (m, 3 H), 2.42–1.04 (m, 13 H); ^{13}C NMR ($CDCl_3$)[33-35] δ 129.82, 129.59, 126.00, 125.29, 56.13, 46.79, 36.48, 35.07, 32.52, 32.24, 30.28, 26.33, 23.36; MS, m/e 228.149 (calcd for $C_{16}H_{20}O$, 228.151).

4′,8-Dimethoxy-1,2-benzocyclododecen-3-one (6) was prepared from 3.2 g (0.14 mol) of sodium, 5.0 g (0.027 mol) of *p*-bromoanisole, and 11.2 g (0.061 mol) of 6-methoxycyclodecanone in a procedure similar to that for **4c**. After the reaction in 150 mL of dry THF at 45 °C for 24 h, 6.2 g of starting 6-methoxycyclodecanone was recovered from Kugelröhr distillation at about 90 °C. At elevated temperature (ca. 150 °C) 6.0 g of crude was obtained. Purification by MPLC and trituration with a small amount of pentane gave 0.746 g (9.2%) of the desired product **6**: mp 71–74 °C; IR (mineral oil) 1680, 1615, 1570, 1295, 1260, 1210, 1180, 1100, 1040, 990, 870, 810 cm^{-1}; ^1H NMR (CCl_4) δ 7.15 (d, J = 9 Hz, 1 H), 6.75–6.90 (m, 2 H), 3.75 (s, 3 H), 3.35–2.62 (m, 8 H, s at 3.16), 1.90–0.85 (m, 12 H); ^{13}C NMR ($CDCl_3$)[33] δ 157.04, 142.34, 132.52, 131.97, 116.04, 111.59, 79.56, 55.97, 55.39, 39.65, 30.39, 28.49, 27.91, 27.40, 23.37, 20.30, 19.84; MS m/e 290.183 (calcd for $C_{18}H_{26}O_3$, 290.188). This also gave 0.334 g (4.3%) of **7**: mp 69.5–71.5 °C; IR (mineral oil) 1670, 1605, 1585, 1290, 1260, 1220, 1190, 1100, 1060, 1040, 900, 800 cm^{-1}; ^1H NMR (CCl_4) δ 7.34 (d, J = 8 Hz, 1 H), 6.74 (dd, J = 2 Hz, 1 H), 6.64 (dd, J = 8, 2 Hz, 1 H), 3.80 (s, 3 H), 3.26–2.60 (m, 8 H, s at 3.16), 1.92–0.80 (m, 12 H); ^{13}C NMR ($CDCl_3$)[33] δ 160.00, 143.79, 134.63, 129.38, 115.88, 110.38, 79.27, 55.57, 54.69, 38.03, 30.07, 28.52, 28.08, 27.60, 22.54, 20.33, 19.65; MS, m/e 290.189 (calcd for $C_{18}H_{26}O_3$, 290.188).

4′,9-Dimethoxy-1,2-benzocyclotridec-1-en-4-one (11) and -3-one (12) were prepared by ring expansion of **6** with trimethylsilyl cyanide (TMSCN). A solution of 2.53 g (8.7 mmol) of **6** in 25 mL of toluene (distilled and dried over molecular sieves) was cooled to −78 °C, whereupon, 1.5 mL of TMSCN (12.9 mmol) was introduced followed by a catalytic amount of 18-crown-6/KCN. The flask was then flushed with argon and sealed tightly with parafilm. The resulting mixture was allowed to warm up to −15 °C in a refrigerator and left at that temperature for 7 days. At the end of this period a small amount of starting material was still detected by GC. The reaction mixture was stirred at room temperature for 1 h, after which the toluene was evaporated and replaced by about 25 mL of anhydrous ether. This ether solution was cooled to 0 °C, and 0.50 g of $LiAlH_4$ was introduced in small portions. The resulting mixture was stirred at ice temperature for 15 min and then at room temperature for 3 h. At the end of the period, the reaction was cooled to 0 °C and worked up with 0.48 mL of water and 2.20 mL of 10% NaOH in the standard sequence.[32] The mixture was stirred for 5 min, the ether layer was decanted and the light brown solid residue was washed with ether (2 × 25 mL). The combined ether layers were washed four times with 20-mL portions of 5% H_2SO_4. The aqueous acidic layer was then neutralized by 10% NaOH until basic and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ and dried ($MgSO_4$) to yield 1.85 g of the amino alcohol (**10**) as a thick semisolid layer: IR (neat) 3400, 2940, 2860, 1610, 1580 cm^{-1}. The organic layer left behind from the H_2SO_4 washing yielded 0.510 g of the silyl enol ether (**8**).

A solution of the above amino alcohol **10** in 70 mL of 10% acetic acid was combined at 0 °C with 20 mL of 1.25 M $NaNO_2$ and stirred overnight. The mixture was diluted with water and extracted into ether, which was then washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Kugelröhr distillation yielded 1.46 g (55% from **6**) of **11** and **12** as a light yellow oil which appeared as one peak on GC but two spots of comparable size on TLC; IR (neat) 2940, 2860, 1715, 1690, 1615, 1580, 1500, 1460, 1260, 1100, 1020 cm^{-1}. Although it was more efficient to continue the sequence with the mixture, it was possible to crystallize out one isomer from hexane, which gave **11**: mp 90–91 °C ; IR (mineral oil) 1705, 1620, 1580, 1500, 1300, 1260, 1115, 1050, 800, 720 cm^{-1}; ^1H NMR (CCl_4) δ 7.12 (d, J = 8 Hz, 1 H), 6.9–6.6 (m, 2 H), 3.78 (s, 3 H), 3.73 (s, 2 H), 3.4–3.0 (m, 4 H, s at 3.28), 2.6–2.3 (m, 4 H), 1.9–1.1 (m, 12 H); ^{13}C NMR ($CDCl_3$) δ 209.07, 133.95, 132.77, 130.51, 117.21, 112.71, 79.06, 56.20, 55.36, 48.48, 39.65, 31.89, 29.75, 29.55 (double intensity), 22.83, 22.54, 22.40; MS, m/e 304.203 (calcd for $C_{19}H_{28}O_3$, 304.204).

4′,9-Dimethoxy-1,2-benzocyclotridecene (14). The 1.46 g of **11** and **12** was reduced with 0.18 g of $LiAlH_4$ in 35 mL of dry ether by using the standard[32] NaOH workup, which gave, after drying ($MgSO_4$), 1.33 g of the corresponding alcohols. This alcohol mixture was treated with 3 mL of methanesulfonyl chloride in 20 mL of dry pyridine at 0 °C for 5 min and then at −15 °C for 16 h. The pyridine and methanesulfonyl chloride were removed at 25 °C in vacuo, and the residue was taken up in 100 mL of CH_2Cl_2, which was washed with 5% H_2SO_4 (3 × 50 mL) and cold saturated $NaHCO_3$. The dried solution ($MgSO_4$) yielded 2.18 g of mesylates, which were reacted with 1.55 g of KO-*t*-Bu in 30 mL of dry Me_2SO at 25 °C for 8 h. The reaction mixture was diluted with water and extracted three times with pentane. The combined pentane extracts were washed twice with water and once with saturated $NaHCO_3$ and then dried over $MgSO_4$. The product mixture was filtered through a short silica gel column to yield 0.71 g of alkene products. These were hydrogenated over 45 mg of 5% Pd/C in 20 mL of 95% EtOH at 25 °C and 1 atm for 5 h. Suction filtration and removal of ethanol gave 0.71 g (51% from **11** and **12**) of **14** as a clear oil that showed only one spot on TLC and one peak on GC; IR (neat) 2950, 2870, 1620, 1580, 1505, 1470, 1260, 1215, 1160, 1100, 1055, 790 cm^{-1}; ^1H NMR (CCl_4) δ 6.93 (d, J = 9 Hz, 1 H), 6.77–6.40 (m, 2 H), 3.72 (s, 3 H), 3.40–3.00 (m, 4 H, s at 3.25), 2.95–2.50 (m, 2 H), 2.5–2.1 (m, 2 H), 1.9–1.0 (m, 16 H); ^{13}C NMR ($CDCl_3$–CCl_4)[36] δ 141.03, 130.14, 115.19, 110.98, 78.09, 55.83, 54.52, 31.71, 30.89, 30.71 (double intensity), 28.99, 27.94, 26.38, 25.18, 23.53, 21.81; MS, m/e 290.225 (calcd for $C_{19}H_{30}O_2$, 290.22).

8,9:13,14-Diseco-18-norestradiol (4′,9-Dihydroxy-1,2-benzocyclotridecene) (1). A solution of 0.71 g (2.45 mmol) of **14** in 8 mL of 1,2-ethanedithiol was chilled to 0 °C to which 1.0 g of aluminum chloride was introduced in small portions over 10 min. The reaction was then stirred at 0 °C for 5 min and at room temperature for 1.2 h. Excess ethanedithiol was evaporated at room temperature in vacuo and collected in a trap cooled to −78 °C. The catalyst was destroyed by addition of water, and the product was taken up in 75 mL of ethyl acetate. The ethyl acetate was washed with water (3 × 30 mL) and then extracted with 5% NaOH (6 × 30 mL). After further washing with saturated $NaHCO_3$ and drying over $MgSO_4$, the solvent was removed to give a semisolid product. The crude product obtained was stirred with 15 mL of pentane and filtered to yield 0.361 g (56%) of product as a white solid. Further washing (0.250 g) with a small amount of ether–hexane (1:2, v/v) yielded 0.234 g of product, mp 142–145 °C. Pure diol was obtained by washing with small amount of ether; mp 149–150 °C, IR (mineral oil) 3420, 3200, 1610, 1270, 1240, 1160, 1090, 1010, 990 cm^{-1}; ^1H NMR (Me_2SO–d_6/$CDCl_3$) δ 6.86 (d, J = 8 Hz, 1 H), 6.66–6.38 (m, 2 H), 3.82–3.54 (m, 1 H), 2.82–2.62 (m, 2 H), 2.44–2.04 (m, 2 H), 2.04–1.04 (m, 16 H); ^{13}C NMR (acetone–d_6)[36] δ 142.92, 131.88, 117.71, 114.17, 68.61, 37.71, 34.61, 32.79, 32.04, 30.39, 29.38, 27.92, 26.37, 24.84, 23.48; MS, m/e 262.192 (calcd for $C_{17}H_{26}O_2$, 262.193).

The NaOH extracts were neuralized and extracted with ether, which gave 0.335 g of yellow liquid which was purified by MPLC. The R_f value on TLC was much higher than the diol, and the NMR spectrum did not show any aromatic protons. This product was not further characterized.

4′,8-Dimethoxy-1,2-benzocyclododecene (13a). A 0.318-g portion of **6** was converted to the mesylate by essentially the same procedure as described in the preparation of **14** which gave 0.383

(33) The carbonyl carbons were outside the spectral window used.
(34) The quaternary aromatic carbons were too weak to observe clearly above the noise under the conditions used.
(35) The two peaks at δ 46.79 and 36.48 are doublets in the off-resonance decoupled spectrum.
(36) Two of the quaternary aromatic carbons were too weak to observe clearly above the noise under the conditions used.

g of product. Refluxing this mesylate for 2 days with 66 mg of $LiAlH_4$ in 20 mL of ether followed by the standard NaOH workup[32] gave 0.180 g (59%) of **13a**, which showed one spot and one peak when analyzed by TLC and GC respectively; IR (neat) 2940, 2860, 1610, 1590, 1500, 1470, 1260, 1200, 1160, 1100, 1040 cm^{-1}; ^1H NMR 6.94 (d, J = 8 Hz, 1 H) δ 6.74–6.40 (m, 2 H), 3.7 (s, 3 H), 3.36–3.00 (m, 4 H, s at 3.2), 2.9–2.2 (m, 4 H), 2.10–1.04 (m, 14 H); ^{13}C NMR ($CDCl_3$)[34] δ 130.46, 114.39, 111.52, 79.76, 56.0, 54.77, 30.51, 29.15 (greater than double intensity), 28.66, 28.57, 26.21, 21.99, 28.28; MS, m/e 276.208 (calcd for $C_{18}H_{28}O_2$, 276.209).

4′,8-Dihydroxy-1,2-benzocyclododecene (13b). A solution of 0.152 g of **13a** in 5 mL of ethanethiol was stirred 1.5 h at 25 °C with 0.3 g of $AlCl_3$. The reaction was quenched at 0 °C with 15 mL of 10% H_2SO_4, and the excess ethane thiol was allowed to evaporate overnight. The resultant mixture was taken into ether solution, which was extracted several times with 10% NaOH. The NaOH extracts were neutralized (10% H_2SO_4) and extracted with ether several times. The ether extracts were washed with saturated $NaHCO_3$ and dried ($MgSO_4$). Removal of solvent gave 73 mg of sticky solid which showed one spot on TLC. Washing with pentane or passing through MPLC gave pure **13b**: mp, 173.5–174.5 °C; IR (mineral oil) 3400, 3200, 1580, 1260, 1245, 1160, 1100, 1000, 800 cm^{-1}; ^1H NMR (acetone-d_6) δ 7.0 (d, J = 8, 1 H), 6.70–6.52 (m, 2 H) 3.9–3.6 (m, 1 H), 2.9–2.3 (m, 4 H), 2.0–1.2 (m, 14 H); ^{13}C NMR (acetone/$CDCl_3$) δ 155.02, 141.7, 131.33, 130.37, 115.63, 113.03, 69.21, 34.17, 31.30, 30.23, 29.38, 29.06, 28.32, 26.31, 21.81, 20.48; MS, m/e 248.178 (calcd for $C_{16}H_{24}O_2$, 248.178).

8,9:13,14-Diseco-18-norestrone (15). Jones reagent[32] was added dropwise at 0 °C to a solution of 0.234 g of **1** in 30 mL of acetone until the brown color persisted. Isopropanol was added to react with the excess reagent, and then the acetone was removed under reduced pressure. The green salts were washed with 50 mL of ethyl acetate, dissolved in water, and extracted with ethyl acetate. The combined ethyl acetate layers were washed with water and saturated $NaHCO_3$ and then dried over $MgSO_4$. Removal of solvent and Kugelröhr distillation yielded 0.172 g (74%) of **15**: mp 94.5–96.0 °C; IR ($CDCl_3$) 3600, 2940, 2860, 1705, 1610, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.98 (d, J = 8 Hz, 1 H), 6.74–6.44 (m, 2 H) 4.8 (s, 1 H), 2.84–2.40 (m, 8 H), 2.4–1.2 (m, 12 H); ^{13}C NMR ($CDCl_3$)[33] δ 153.9, 142.17, 132.35, 130.54, 116.29, 112.91, 42.03, 40.62, 31.77, 30.65, 29.72, 28.94, 26.46, 25.47, 23.14, 23.08; MS, m/e 260.179 (calcd for $C_{17}H_{24}O_2$, 260.178).

(±)-17-Ethynyl-8,9:13,14-diseco-18-norestradiol (16). Acetylene was passed through concentrated H_2SO_4 and bubbled through 20 mL of dry THF at −78 °C for 5 min, after which 3 mL (3.81 mmol) of 1.27 M n-BuLi in hexane was added and stirred with continuous bubbling of acetylene for 10 min. A solution of 0.150 g (0.576 mmol) of **15** in 10 mL of THF was added and stirred for 20 min at −78 °C followed by 1.5 h at 25 °C. The reaction mixture was poured into saturated NaCl and extracted into ether, which was washed with water and saturated NaCl and then dried over $MgSO_4$. Solvent was evaporated, and the resultant material was purified by chromatography on Florisil, eluting with ethyl acetate–hexane (40:60, v/v) followed by Kugelröhr distillation, which gave 76 mg (46%) of **16**: mp indefinite 45–60 °C; IR ($CDCl_3$) 3600, 3310, 3160, 2940, 2870, 2350, 1610, 1590, 1500, 1420, 1380, 1220, 1100 cm^{-1}; ^1H NMR ($CDCl_3$ δ 7.02 (d, J = 8 Hz, 1 H), 6.70–6.52 (m, 2 H) 4.7 (s, 1 H), 2.76–2.30 (m, 5 H; s at 2.43), 2.04–1.15 (m, 16 H); ^{13}C NMR ($CDCl_3$) δ 153.46, 142.23, 132.57, 130.34, 116.57, 112.87, 88.18, 71.67, 71.24, 38.48, 37.25, 32.92, 31.28, 31.06, 28.66, 26.40, 25.87, 22.47, 20.56; MS, m/e 286.194 (calcd for $C_{19}H_{26}O_2$, 286.193).

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Registry No. (±)-**1**, 76976-64-2; (±)-**3b**, 15957-40-1; (±)-**3c**, 76976-65-3; (±)-**4c**, 81423-21-4; **5**, 81423-22-5; (±)-**6**, 76976-66-4; **6** 3-deoxy-3-ol mesylate, 81423-23-6; (±)-**7**, 76987-54-7; (±)-**8**, 81423-24-7; **9**, 81423-25-8; **10**, 81423-26-9; (±)-**11**, 76987-55-8; **11** 4-deoxy-4-ol, 81423-27-0; **11** 4-deoxy-4-ol mesylate, 81423-28-1; (±)-**11** 4-deoxy-3(or 4)-ene, 81423-52-1; (±)-**12**, 76987-56-9; **12** 3-deoxy-3-ol, 81423-29-2; **12** 3-deoxy-3-ol mesylate, 81423-30-5; (±)-**12** 3-deoxy-3-ene, 81423-31-6; (±)-**13a**, 81423-32-7; (±)-**13b**, 81423-33-8; (±)-**14**, 76987-57-0; **15**, 81423-34-9; (U)-**16**, 81423-35-0; decalin, 91-17-8; bromobenzene, 108-86-1; p-bromoanisole, 104-92-7.