Biomimetic Polyene Cyclizations.[1] Total Synthesis of *dl*-19-Nor-4-pregnen-20-one. Asymmetric Induction by the Initiating Center

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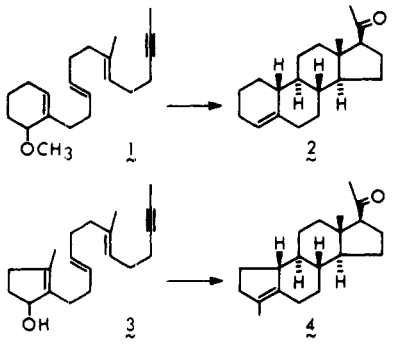
dl-19-Nor-4-pregnen-20-one (**2**) was prepared by cationic cyclization of racemic methoxy trienyne **1**. The mechanism of this reaction is discussed on the basis of byproduct analysis, deuterium labeling experiments, and the cyclization of optically active substrate **1**, which proceeded with extensive racemization.

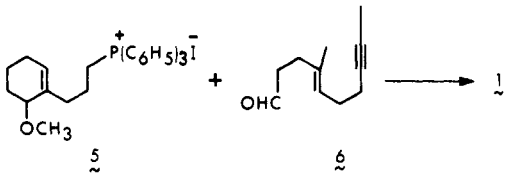
In the biomimetic total synthesis of estrone,[2] mechanistic studies[3,4] of the cyclization step, **25** → **26**, strongly point toward a synchronous process, suggesting the possibility of asymmetric induction by the chiral center of the secondary allylic alcohol function of the substrate. Consequently, optically active estrone might be obtained via cyclization of the resolved form of the substrate.[2] While generalization of this probable mechanistic pathway to other polyene cyclizations still awaits experimental verification, we report in the present paper the biomimetic cyclization of both the racemic and the resolved form of methoxy trienyne **1**. This substrate was expected[5] to give



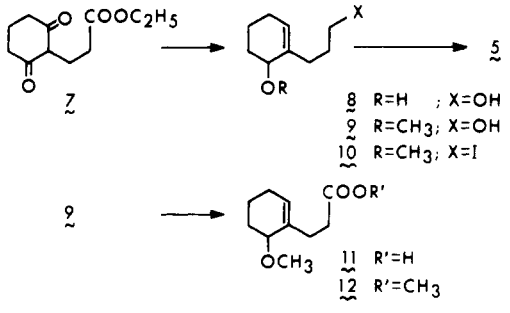
19-nor-4-pregnen-20-one (**2**) on the basis of analogy with the reported[1,4] cyclization of trienynol **3** to the 19-norprogesterone derivative **4**. The aim of the present cyclization study was to determine (a) its potential for the synthesis of the 19-norprogesterone derivative **2** and (b) the degree of asymmetric induction (if any) by the chiral center of the allylic ether function.

Synthesis of the Substrate. The *dl* and *d* forms of the cyclization substrate **1** were prepared by a convergent synthesis, the key step being a stereoselective Wittig–Schlosser condensation[6] of the phosphoranes produced from the phosphonium salts *dl*-**5** and *d*-**5** with the known[7] aldehyde **6** (see Scheme I). For the synthesis of the

Scheme I



Scheme II



phosphonium iodides *dl*-**5** and *d*-**5** (see Scheme II), ethyl 3-(1,3-dioxo-2-cyclohexyl)propanoate (**7**)[8] was reduced[9] with lithium aluminum hydride to the diol **8**, which was selectively methylated to give the allylic methyl ether **9** by prolonged treatment with methanol and hydrochloric acid at room temperature, thus protecting the chiral center. The methyl ether **9** was isolated by chromatography in 41% overall yield from the ester **7**. Oxidation with chromium trioxide in a pyridine–water system[10] gave the carboxylic acid **11** in 58% yield, characterized as the methyl ester **12** prepared with diazomethane. The carboxylic acid **11** could be resolved by repeated recrystallization of the salt formed with *d*-dehydroabietylamine. Regeneration of the free acid gave *d*-**11** with $[\alpha]^{20}_D$ +52.5°. After hydrolysis of the *l*-enriched mother liquor salt to the free acid, the *l* enantiomer was obtained by conversion to and repeated recrystallization of the *d*-1-phenylethylamine salt. Hydrolysis afforded *l*-**11** with $[\alpha]^{20}_D$ −49.0°. The enantiomeric purity of acid *d*-**11** was determined after conversion to the methyl ester *d*-**12** by using a chiral NMR shift reagent.[11] None of the enantiomeric ester *l*-**12** could be detected in the ^{1}H NMR spectrum corresponding, in this case, with

(1) For a recent paper in this series, see W. S. Johnson, W. F. Huffman, and S. G. Boots, *Recl. Trav. Chim. Pays-Bas*, **98**, 125 (1979).
(2) P. A. Bartlett and W. S. Johnson, *J. Am. Chem. Soc.*, **95**, 7501 (1973).
(3) P. A. Bartlett, J. I. Brauman, W. S. Johnson, and R. A. Volkmann, *J. Am. Chem. Soc.*, **95**, 7502 (1973).
(4) W. S. Johnson, *Bioorg. Chem.*, **5**, 51 (1976).
(5) In previous cyclization studies where a free allylic alcohol could be compared as initiator with the corresponding methyl ether hardly any difference was found in the course of the cyclization. W. S. Johnson, unpublished results.
(6) M. Schlosser and K. F. Christmann, *Angew. Chem., Int. Ed. Engl.*, **5**, 126 (1966).
(7) M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry, and B. E. Ratcliffe, *J. Am. Chem. Soc.*, **100**, 4274 (1978).
(8) H. Stetter and M. Coenen, *Chem. Ber.*, **87**, 869 (1954).
(9) W. S. Johnson, W. H. Lunn, and K. Fitzi, *J. Am. Chem. Soc.*, **86**, 1972 (1964).
(10) R. H. Cornforth, J. W. Cornforth, and G. Popják, *Tetrahedron*, **18**, 1351 (1962).
(11) M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974).

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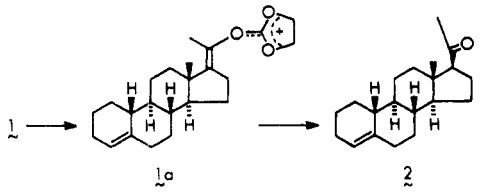
over 88% enantiomeric excess (ee).

Lithium aluminum hydride reduction of the resolved acid *d*-**11** produced the alcohol *d*-**9** in 96% yield. Both the racemic and the resolved forms of this alcohol were transformed via the crude methanesulfonates into the iodides *dl*-**10** and *d*-**10**, respectively. Attempts to determine the enantiomeric purity of *d*-**10** by using different chiral NMR shift reagents failed, insufficient enantiomeric shift differences being obtained. Treatment of *dl*-**10** and *d*-**10** with triphenylphosphine produced the phosphonium iodides *dl*-**5** and *d*-**5** in 73% overall yield from the alcohols *dl*-**9** and *d*-**9**. In the convergent step the phosphoranes derived from *dl*-**5** and *d*-**5** were condensed with aldehyde **6** under Wittig–Schlosser conditions,[6] giving the methoxy trienynes *dl*-**1** and *d*-**1** in 72% yield. Analysis by VPC showed that the reaction proceeded with 98% trans stereoselectivity. The ^{1}H NMR spectrum of *d*-**1** in the presence of a chiral shift reagent indicated over 90% ee, so no perceptible racemization had occurred during its preparation from carboxylic acid *d*-**11**.

Cyclization Studies. The racemic form of methoxy trienyne **1** was cyclized in 1,2-dichloroethane–ethylene carbonate with trifluoroacetic acid[7] (62 molar equiv, 16 h, −25 °C) or with boron trifluoride etherate (2 molar equiv, 4 h, −10 °C). Ethylene carbonate is assumed to terminate the cyclization process by forming the stabilized cation **1a**, which upon hydrolysis gives methyl ketone **2**.[7] Workup



1 **1a** **2**

with an excess of potassium carbonate in aqueous methanol and chromatography of the crude reaction product gave in both cases a tetracyclic fraction characterized by high-field, angular methyl singlets in the ^{1}H NMR spectrum. From the trifluoroacetic acid cyclization, 43% of tetracyclic material was isolated, consisting of four major components A, B, C, and D in a ratio of 51:8:15:17 as estimated from their relative VPC peak areas. Analogous results were obtained with the boron trifluoride etherate cyclization. Chromatography of the tetracyclic fraction on 20% silver nitrate impregnated silica gel gave component A as a crystalline solid in 15–18% yield. Components B, C, and D could hardly be separated due to very slight differences in polarity. Thus C was isolated as a semicrystalline solid, 90% pure by VPC, in a yield as low as 1.7%. B and D were obtained less pure as enriched fractions (ca. 55% and ca. 66% pure, respectively).

Component A showed in high-resolution mass spectroscopy a parent peak for $C_{20}H_{30}O$ as expected for **2**. The IR absorptions at 1701 and 1356 cm^{-1} indicated the presence of an acetyl side chain. The ^{1}H NMR spectrum showed two three-proton singlets at δ 0.74 and 2.09 indicative of angular methyl and acetyl, respectively, and two one-proton triplets centered at δ 2.55 and 5.50 indicative of CH—C=O and an olefinic proton, respectively. The ^{13}C NMR spectrum (see Table I, Experimental Section), however, indicated that A was isomeric with **2**. It showed one quaternary and one secondary carbon atom more and two tertiary carbon atoms less than required by **2**, indicating a rearranged skeleton. The mass spectrum exhibited a strong analogy to that of spiro[5.5]undec-1-ene[12] (Figure 1). On the basis of these facts, A was tentatively assigned the tetracyclic constitution **13** with carbon atom 10 (steroid numbering) forming a spiro union of rings A and C (steroid ring lettering), in analogy to the spiro product formed on cyclization of a trienic acetal with stannic chloride in nitromethane.[13] The signals of the ^{13}C NMR spectrum could

(12) G. D. Christiansen and D. A. Lightner, *J. Org. Chem.*, **36**, 948 (1971).

Table I. ^{13}C NMR Chemical Shifts[a] and Assignments for Compounds *d*-**2**, **13** and *d*-**15**[b]

C position	*d*-2	13	*d*-15
1	28.9, t	33.0, t	29.2, t
2	22.1, t	20.9, t	22.3, t
3	25.5, t	25.6, t	25.6, t
4	120.1, d	123.1, d	120.5, d
5	140.1, s	143.1, s	140.5, s
6	35.6, t	30.1, t	30.6, t
7	32.2, t	27.5, t	29.7, t
8	41.1, d	28.6, t	35.6, d
9	50.2, d	40.9, d	43.7, d
10	42.0, d	41.7, s	33.6, d
11	26.5, t	21.0, t	23.6, t
12	39.1, t	34.7, t	34.3, t
13	44.3, s	44.5, s	44.9, s
14	55.8, d	48.3, d	46.4, d
15	24.3, t	25.0, t	24.1, t
16	22.9, t	21.4, t	22.3, t
17	64.0, d	66.0, d	64.4, d
18	13.5, q	16.0, q	12.9, q
20	209.2, s	185.0, s	210.0, s
21	31.4, q	31.5, q	31.5, q

[a] In δ units. [b] s, d, t, and q denote SFORD multiplicities (s = singlet, d = doublet, t = triplet, q = quartet).

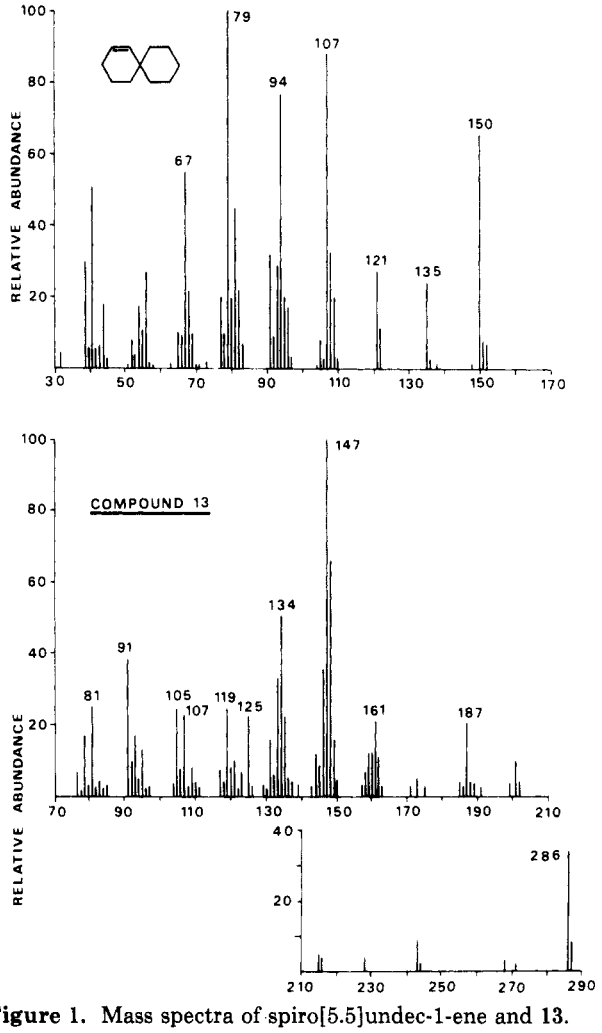
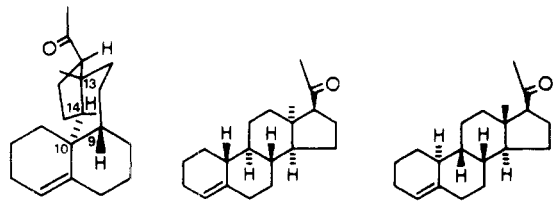


Figure 1. Mass spectra of spiro[5.5]undec-1-ene and **13**.



13 14 15

then be assigned (see Table I) by using a recent survey of ^{13}C NMR data of steroids.[14] Those assigned to C-13, C-17, and C-18 (δ 44.5, 66.0, and 16.0, respectively) and the ^1H NMR signals of the C-17 and C-21 protons (δ 2.55 and 2.09, respectively) indicate that the configurations at C-13, C-14, and C-17 are identical with those of progesterone.[15]

The fraction most enriched in component B (ca. 55% pure) showed in the ^1H NMR spectrum a characteristic singlet at δ 1.27. This value compares well with reported data for the C-18 methyl group of 13α(C/D cis),17β-pregnanes[16] consistently found in cyclizations involving methylacetylenic and phenylacetylenic terminators.[17] This suggests constitution **14** for component B.

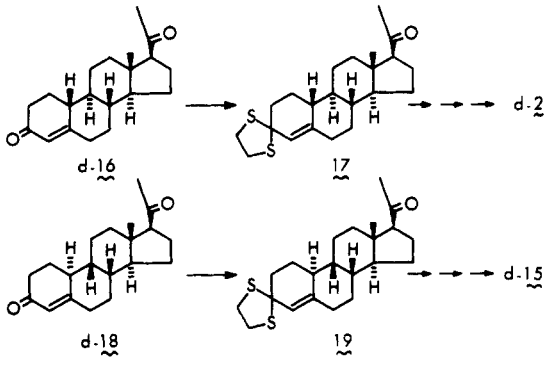
Component C was found to be identical both spectroscopically (IR and ^1H NMR) and chromatographically (TLC and VPC) with authentic naturally derived 19-nor-4-pregnen-20-one (*d*-**2**) prepared as described below.

The ^1H NMR spectrum of the fraction most enriched in component D (2:1 with C) was almost identical with that of *d*-**2**, indicating that D was a stereoisomer of **2**. Authentic *d*-19-nor-9β,10α-pregn-4-en-20-one (*d*-**15**) was prepared (see below) and found to be identical with D both spectroscopically (^1H and ^{13}C NMR) and chromatographically (VPC). The ^{13}C NMR spectrum of this fraction was superimposable with that of a 2:1 mixture of authentic *d*-**15** and *d*-**2** (see Table I), providing an unambiguous proof of the constitution of D.

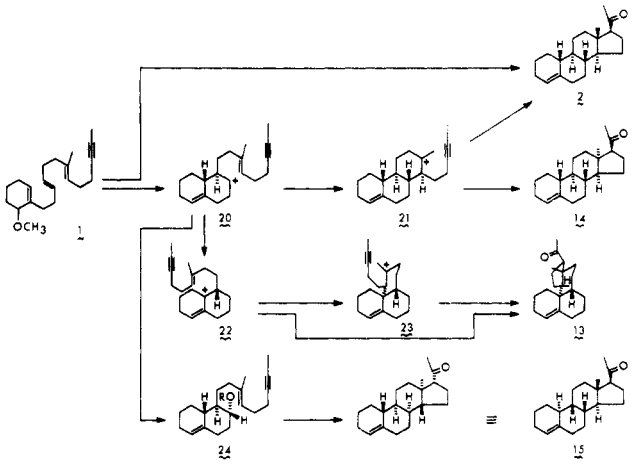
The results of the cyclization can be summarized as follows: the expected compound **2** is formed in poor yield (~6% as estimated by VPC), along with the 13α (C/D cis) isomer **14** (4–6%) and the retro isomer **15** (~7%), whereas the major product is the spiro compound **13** (~22%). It follows from these results that the secondary allylic cyclohexenol,[5] present as the methyl ether in **1**, is a poor initiator for the polyene cyclization, in contrast with methyl-substituted allylic cyclohexenols.[33]

Synthesis of Comparison Compounds. Authentic naturally derived 19-nor-4-pregnen-20-one (*d*-**2**) was synthesized by the route shown in Scheme III. Treatment of 19-nor-4-pregnene-3,20-dione (*d*-**16**)[18] with 1,2-ethanedithiol and boron trifluoride etherate produced the dithioacetal **17**, which was submitted successively to sodium borohydride reduction, reduction with lithium and liquid ammonia, and oxidation with chromic acid to give *d*-**2**.[19] Authentic *d*-19-nor-9β,10α-pregn-4-en-20-one (*d*-**15**) was

Scheme III



Scheme IV



prepared in an analogous manner from *d*-19-nor-9β,10α-pregn-4-ene-3,20-dione (*d*-**18**).[20]

Mechanistic Considerations. The formation of the compounds **2**, **13**, **14**, and **15** in the trifluoroacetic acid and boron trifluoride etherate induced cyclizations of methoxy trienyne **1** may be rationalized by assuming the mechanism outlined in Scheme IV. 19-Nor-4-pregnen-20-one (**2**) may be formed from **1** in both a concerted way and a stepwise way via bicyclic cation **20** and tricyclic cation **21**. The 13α (C/D cis) isomer **14** cannot be formed in a stereospecific process according to the Stork–Eschenmoser[22] hypothesis. A tricyclic cationic intermediate similar to **21** has previously been demonstrated[21] to give rise to a 13α (C/D cis) compound via a deprotonation–reprotonation mechanism. In another case[17c] a different mechanism seems to be involved in the formation of this byproduct from a tricyclic cation. The spiro compound **13** may be considered as arising from the bicyclic cation **20** by two consecutive suprafacial 1,2 hydride shifts to give the allylically stabilized tertiary bicyclic cation **22**. Subsequent intramolecular attack of the internal double bond and the triple bond (stepwise via **23** or concerted) then produces **13**. A similar mechanism has been postulated for the formation via biomimetic cyclization of a tricyclic spiro compound, the constitution of which was established by X-ray diffraction analysis of a derivative.[13] Finally, trapping of the bicyclic cation **20** with ethylene carbonate or trifluoroacetate ion to give the complex **24** followed by an S_N2 reaction pro-

(13) G. D. Abrams, W. R. Bartlett, V. A. Fung, and W. S. Johnson, *Bioorg. Chem.*, **1**, 243 (1971).
(14) J. W. Blunt and J. B. Stothers, *Org. Magn. Reson.*, **9**, 439 (1977).
(15) Corresponding values for progesterone: δ 43.7, 63.3, and 13.2[14] and δ 2.53 and 2.11, respectively.
(16) (a) T. Nambara and J. Goto, *Chem. Pharm. Bull.*, **19**, 1937 (1971); (b) J. Goto, K. Sudo, and T. Nambara, *ibid.*, **22**, 1140 (1974). The value δ 1.21–1.33 for 13α,17β-pregnan-20-ones is in contrast with δ 0.80–0.86 for the thermodynamically more stable 13α,17α-pregnan-20-ones.
(17) (a) W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, and T. M. Yarnell, *J. Am. Chem. Soc.*, **99**, 8341 (1977); (b) W. S. Johnson, L. R. Hughes, J. A. Kloek, T. Niem, and A. Shenvi, *ibid.*, **101**, 1279 (1979); (c) W. S. Johnson, L. R. Hughes, and J. L. Carlson, *ibid.*, **101**, 1281 (1979).
(18) J. S. Mills, H. J. Ringold, and C. Djerassi, *J. Am. Chem. Soc.*, **80**, 6118 (1958).
(19) Organon Laboratories Ltd., British Patent 875 549 (1959); *Chem. Abstr.*, **56**, 8805*b* (1962).
(20) A. Bowers, P. Crabbé, and J. Edwards, Syntex Corp., U.S. Patent 3 375 260 (1968); *Chem. Abstr.*, **69**, 87372 (1968).
(21) K. E. Harding, E. J. Leopold, A. M. Hudrlik, and W. S. Johnson, *J. Am. Chem. Soc.*, **96**, 2540 (1974).
(22) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, **77**, 5068 (1955); A. Eschenmoser, L. Ruzicka, O. Jeger, and D. Arigoni, *Helv. Chim. Acta*, **38**, 1890 (1955); P. A. Stadler, A. Eschenmoser, H. Schinz, and G. Stork, *ibid.*, **40**, 2191 (1957).

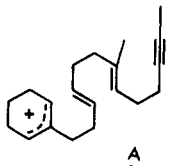
duces **15**.[23] The proposed mechanism implies that along with *d*-**2** (with natural configuration) *l*-**15** should be formed, a fact to be considered when optically active cyclization products are isolated (see below).

The mechanism of Scheme IV was supported by an experiment where cyclization of **1** was carried out with deuteriotrifluoroacetic acid. Mass spectroscopy of the isolated spiro compound **13** (91% pure by VPC) and retro compound **15** (about 70% pure by VPC) indicated that here C-17 was virtually the only position labeled. This rules out their formation via a mechanism involving deprotonation–reprotonation. The absence of deuterium labeling in the A ring illustrates that the cyclization of **1** proceeds directly and not via a cyclohexadiene intermediate, in contrast with those of tertiary allylic cyclopentenols[24] found to undergo elimination prior to cyclization.

The cyclization of optically active methoxy trienyne *d*-**1** (>90% ee; $[\alpha]^{20}_D$ +25.0°) with trifluoroacetic acid gave optically active spiro compound **13** with $[\alpha]^{20}_D$ −7.9°, 93% pure by VPC. 19-Nor-4-pregnen-20-one (**2**) was obtained 63% pure by VPC, contaminated with 9% of **14** and 18% of **15**. The specific rotation of this product ($[\alpha]^{20}_D$ +8.4°) compared with that of naturally derived *d*-**2** ($[\alpha]^{20}_D$ +146°) and with that of *l*-**15** ($[\alpha]^{20}_D$ −41°) indicated a high degree of racemization in the cyclization process.[25] Similar results were obtained when the cyclization was carried out with boron trifluoride etherate.

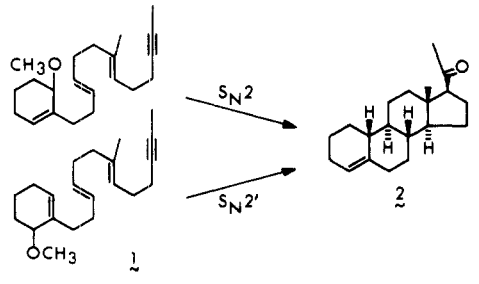
An experiment with deuteriotrifluoroacetic acid was worked up at one-fourth of the normal reaction time to establish whether racemization of *d*-**1** occurred prior to cyclization. The specific rotation of the recovered starting material ($[\alpha]^{20}_D$ +20.1°) corresponded to ca. 20% racemization, insufficient to explain the virtually complete racemization of the cyclized products. In the mass spectrum no detectable incorporation of deuterium was found, in accordance with the above conclusion that cyclization of **1** does not involve a cyclohexadiene intermediate.

These results suggest that cyclization proceeds via the allylic cation A. They do not rule out completely the less



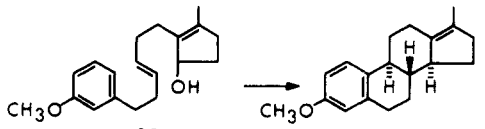
A

likely alternative that two mechanisms occur at the same time, an S_N2 reaction with inversion of configuration and an S_N2' reaction with trans stereochemistry.[26,27] However



1 2

Johnson, Brinkmeyer, and Dubas[28] also noted extensive racemization in the cyclization of partially resolved **25** where no product of an S_N2' reaction was found.



25 26

The poor cyclization results obtained with **1** can be explained by the fact that A is a reactive secondary allylic cation. It will show little selectivity and thus react with all types of double bonds. The tertiary allylic cations derived from methyl-substituted cyclohexenols,[33] however, are less reactive and more selective. They seem to prefer a pathway involving electrophilic attack on an olefinic bond with anchimeric participation of the next olefinic bond and, to a lesser extent, the acetylenic bond. This leads to cleaner cyclizations. The extensive racemization found in the cyclization of optically active **1** and **25** leads us to expect that in the cyclization of a substrate with two chiral centers, one of which is formed by a secondary allylic alcohol, the other chiral center will determine the chirality of the end product. Recent investigations in our laboratories[29] and by others[30] have shown that this is indeed the case.

Experimental Section[31]

The prefix "*dl*" has been omitted from the names of most of the racemic compounds described in this section. Melting points, determined in capillary tubes, are uncorrected. Rotations were determined at 20 °C in chloroform solution (~1%) on a Perkin-Elmer 141 polarimeter. Microanalyses were performed by Dr. W. McMeekin, Analytical Department, Organon Laboratories. Vapor-phase chromatographic (VPC) analyses were performed on a Packard Model 417 Becker gas chromatograph equipped with a flame-ionization detector with nitrogen as the carrier gas (at 10 cm s^{-1}) and using a glass capillary column (24 m × 0.25 mm i.d.) coated with OV-101 according to Schomburg[32] (column temperature 210 °C, injector and detector temperature 235 °C).

Infrared spectra were recorded on a Perkin-Elmer 357 grating spectrometer.

^{1}H NMR spectra were recorded in deuteriochloroform solution on a Varian A 60 D or a Bruker HX-90E instrument. ^{13}C NMR spectra were recorded by using the same solvent on a Bruker HX-90E instrument, operating at 22.625 MHz and equipped with a Nicolet B-NC12 data system, or on a Bruker WH 270 instrument operating at 67.88 MHz. ^{1}H and ^{13}C chemical shifts are reported

(23) In accordance with this mechanism it was recently found that an increase in the ethylene carbonate concentration led to a higher proportion of **15** in the reaction product (E. J. Leopold).

(24) W. S. Johnson and G. E. DuBois, *J. Am. Chem. Soc.*, **98**, 1038 (1976).

(25) The estimated $[\alpha]^{20}_D$ of compound **14** is about +65°, calculated by using a fragment contribution from $[M]^{20}_D$ −162° of 3β-acetoxy-13α-pregn-5-en-20-one (see ref 16a).

(26) S. Godtfredsen, J. P. Obrecht, and D. Arigoni, *Chimia*, **31**, 62 (1977).

(27) E. Toromanoff, *Tetrahedron*, **34**, 1665 (1978).

(28) W. S. Johnson, R. S. Brinkmeyer, and L. F. Dubas, unpublished observations. See the Ph.D. Thesis of L.F.D., Stanford University, 1978.

(29) M. B. Groen and F. J. Zeelen, *J. Org. Chem.*, **43**, 1961 (1978); M. B. Groen and F. J. Zeelen, *Recl. Trav. Chim. Pays-Bas*, **97**, 301 (1978); **98**, 32, 239 (1979).

(30) A. A. Macco, R. J. de Brouwer, and H. M. Buck, *J. Org. Chem.*, **42**, 3196 (1977); A. A. Macco, R. J. de Brouwer, P. M. M. Nossin, E. F. Godefroi, and H. M. Buck, *ibid.*, **43**, 1591 (1978).

(31) In cases where products were isolated by solvent extraction, the procedure generally followed was to extract the aqueous layer with several portions of the indicated solvent; the organic layers were then combined and washed with water followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate or magnesium sulfate and filtered, and the solvent was evaporated under reduced pressure (water aspirator) by using a rotary evaporator. The use of the term "wash" indicates washing the combined organic layers with saturated aqueous sodium bicarbonate solution ("base wash"), with dilute aqueous hydrochloric acid ("acid wash"), or with the indicated solution prior to the aforementioned washing with water.

(32) G. Schomberg, H. Husmann, and F. Weeke, *J. Chromatogr.*, **99**, 63 (1974).

(33) See, inter alia, W. S. Johnson, N. P. Jensen, J. Hooz, and E. J. Leopold, *J. Am. Chem. Soc.*, **90**, 5872 (1968); B. E. McCarry, R. L. Markezich, and W. S. Johnson, *ibid.*, **95**, 4416 (1973); W. R. Bartlett and W. S. Johnson, *Bioorg. Chem.*, **4**, 342 (1975).

as δ values relative to tetramethylsilane = 0. The chiral NMR shift reagent tris[3-[(heptafluoropropyl)hydroxymethylene]-*d*-camphorato]europium(III), Eu(hfc)$_3$ (Aldrich), was used in the determination of the percentage enantiomeric excess (ee) of optically active compounds. Both induced shifts $\Delta\delta$ and enantiomeric shift differences $\Delta\Delta\delta$ were determined in deuteriochloroform.

Mass spectra were obtained by using a Varian MAT 311 A instrument at 70 eV. Exact molecular weights were obtained by peak matching on the parent ion in the mass spectrum.

Column chromatography was performed on Woelm silica gel (70–230 mesh), and high-performance LC on Merck silica gel 60 (230–400 mesh). Precoated plates (silica gel 60 F 254, Merck) were used in TLC and preparative TLC. *d*-Dehydroabietylamine (90%) and *d*-1-phenylethylamine (98%) (Aldrich) were used in the optical resolution.

3-(1-Methoxy-2-cyclohexen-2-yl)propanol (9). To a stirred suspension of 29.2 g (0.77 mol) of $LiAlH_4$ in 1400 mL of anhydrous ether was added under nitrogen 31.0 g (0.15 mol) of ethyl 3-(1,3-dioxo-2-cyclohexyl)propanoate (**7**)[8] over a period of 15 min. The mixture was heated under reflux for 7.5 h and then cooled to 0 °C while 68 mL of water was added, followed by 60 mL of 10% aqueous NaOH. Filtration, washing of the inorganic salts with ether, and evaporation of the combined filtrates gave a residue of 22.8 g. Chromatography on 460 g of silica gel gave 2.2 g of apolar products (eluent, 8:2 methylene chloride–ether) followed by 16.8 g (74%) of diol **8** (eluent, 4:6 methylene chloride–ether) as a colorless liquid, pure by TLC, R_f 0.4 (6:4 hexane–acetone): IR (CCl_4) 3613 and 3325 (OH), 3036 (C=CH), 1059 cm^{-1} (OH); ^{1}H NMR 1.2–2.4 (m, 10 H), 3.66 (t, J = 6 Hz, 2 H, CH_2OH), 4.09 (m, 1 H, CHOH), 5.60 (m, 1 H, olefinic proton). The diol was dissolved in 245 mL of methanol (100%) and a 17.0-mL portion of a 3:100 mixture of concentrated HCl and methanol (100%) was added. After being allowed to stand at 20 °C for 5 days, the mixture was neutralized with saturated aqueous sodium bicarbonate solution, concentrated under reduced pressure, and, after addition of water (190 mL), extracted with ethyl acetate.[31] The residue (16.2 g) was chromatographed on silica gel (490 g), giving 2.2 g of apolar products (eluent, methylene chloride) followed by 10.0 g (55%) of methyl ether **9** (eluent, 9:1 methylene chloride–ether) as a colorless liquid: IR (CCl_4) 3640 and 3426 (OH), 2820 and 1091 (OCH_3), 1072 cm^{-1} (OCH_3 and OH); ^{1}H NMR 1.4–2.4 (m, 10 H), 3.39 (s, 3 H, OCH_3), 3.67 (t, J = 6 Hz, 2 H, CH_2OH), 3.6–3.8 (m, 1 H, $CHOCH_3$), 5.68 (m, 1 H, olefinic proton).

Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66; O, 18.80. Found: C, 70.6; H, 10.9; O, 18.9.

3-(1-Methoxy-2-cyclohexen-2-yl)propanoic Acid (11). A modification of the Cornforth procedure[10] was used. A solution of methyl ether **9** (5.7 g, 33 mmol) in pyridine (20 mL) was added at 10 °C over a period of 10 min to a stirred mixture prepared by adding successively chromium trioxide (26.6 g, 0.27 mol) and water (5.3 mL) to 300 mL of pyridine at 10 °C. Stirring was continued at 20 °C for 48 h. The usual workup with water and ethyl acetate extraction[31] gave 4.8 g of crude **11** as a brown liquid. The product was purified by redissolution in ethyl acetate (25 mL), extraction with saturated aqueous sodium bicarbonate solution (3×), acidification of the combined aqueous layers at 0 °C with concentrated HCl, and extraction with ethyl acetate[31] to give 3.6 g (58%) of carboxylic acid **11** as a colorless oil which slowly solidified at 5 °C: IR (CCl_4) 3600–2300 (carboxylic OH), 2820 (OCH_3), 1711 (carboxylic CO), 1093 and 1076 cm^{-1} (OCH_3); ^{1}H NMR 1.4–2.3 (m, 6 H), 2.45 (br s, 4 H, $=CCH_2CH_2CO$), 3.36 (s, 3 H, OCH_3), 3.65 (m, 1 H, $CHOCH_3$), 5.68 (m, 1 H, olefinic proton). The liquid methyl ester **12** was prepared with diazomethane in the usual manner. An analytical sample was obtained by chromatography on 60 parts by weight of silica gel with 8:2 hexane–ethyl acetate as eluent: IR (CH_2Cl_2) 2821 (OCH_3), 1729 (ester C=O), 1091 and 1074 cm^{-1} (OCH_3); ^{1}H NMR 1.4–2.2 (m, 6 H), 2.45 (br s, 4 H, $=CCH_2CH_2CO$), 3.35 (s, 3 H, $CHOCH_3$), 3.61 (m, 1 H, $CHOCH_3$), 3.67 (s, 3 H, $COOCH_3$), 5.60 (m, 1 H, olefinic proton); high-resolution mass spectrum, calcd for $C_{11}H_{18}O_3$, m/e 198.1256 (M^+); found, 198.1242.

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15; O, 24.21. Found: C, 66.8; H, 9.2; O, 24.5.

Resolution of 3-(1-Methoxy-2-cyclohexen-2-yl)propanoic Acid (11). *d*-Dehydroabietylamine (10.9 g, 38 mmol) was added to a solution of 7.1 g (38 mmol) of acid *dl*-**11** in methanol (85 mL). The stirred solution was heated, slowly diluted with hot water (42 mL), decanted from resinous material, again diluted with hot water (14 mL), and stored at 5 °C for 16 h. The crystalline salt was collected, washed with 10:7 methanol–water, and dried to give 8.9 g of product: mp 133–136 °C; $[\alpha]^{20}_D$ +43.7°.

Recrystallization by dissolving in hot ethyl acetate (120 mL) and adding hexane (120 mL) followed by storage at 25 °C for 1 h and then at 5 °C for 2 h gave 6.5 g of product with the following: mp 141–142 °C; $[\alpha]^{20}_D$ +45.6°. Repeating this procedure with 100 mL of ethyl acetate and 100 mL of hexane gave 5.8 g of product with the following: mp 141.5–142 °C; $[\alpha]^{20}_D$ +47.0°. This salt was suspended in ether (50 mL) and shaken with saturated aqueous sodium carbonate (3 × 15 mL). The combined aqueous layers were washed with ether (2 × 10 mL), cooled to 0 °C, and acidified with concentrated HCl. Extraction with ether and washing with brine (2×) gave 2.0 g of acid *d*-**11** as a colorless oil not solidifying at 5 °C; $[\alpha]^{20}_D$ +52.5°.

The liquid methyl ester *d*-**12** was prepared with diazomethane in the usual manner: $[\alpha]^{20}_D$ +27.9°; >88% ee determined in $CDCl_3$, [*d*-**12**] ≈ 0.2 M, [Eu(hfc)$_3$] ≈ 0.3 M; downfield $\Delta\delta \approx 1.95$ ppm; $\Delta\Delta\delta$ = 0.03 ppm for the $CHOCH_3$ resonances of *dl*-**12**. The salt recovered by evaporation of the mother liquor from the first crystallization was converted in the same manner to free acid **11** (2.9 g, 16 mmol) with $[\alpha]^{20}_D$ −27.6°. This was dissolved in ether (18 mL), *d*-1-phenylethylamine (1.9 g, 16 mmol) in 5 mL of ether was added, and the mixture was stored at 5 °C for 22 h. The precipitate was collected and washed with cold ether to give 3.6 g of salt: mp 96–97 °C; $[\alpha]^{20}_D$ −10.9°. Three successive recrystallizations from ethyl acetate (22.5, 18, and 18 mL, respectively) and storage at 5 °C for 2 h gave 2.4 g of product: mp 100.5–101.5 °C, $[\alpha]^{20}_D$ −16.3°. Final recrystallization from ethyl acetate (18 mL) gave 2.2 g of the salt (mp 101.5–102 °C, $[\alpha]^{20}_D$ −17.5°), converted in the manner described to the acid *l*-**11** (1.3 g), a colorless oil not solidifying at 5 °C; $[\alpha]^{20}_D$ −49.0°.

***d*-3-(1-Methoxy-2-cyclohexen-2-yl)propanol (*d*-9).** A solution of 1.8 g (11 mmol) of acid *d*-**11** in 20 mL of anhydrous ether was added over a period of 10 min to a suspension of 0.9 g (24 mmol) of $LiAlH_4$ in 70 mL of anhydrous ether stirred at 0 °C under nitrogen. Stirring was continued at 20 °C for 1.5 h. Water was then added cautiously, and the mixture was acidified with 6 N HCl. Extraction with ether[31] gave 1.6 g (96%) of the pure alcohol *d*-**9**, as a colorless liquid, $[\alpha]^{20}_D$ +33.3°.

[3-(1-Methoxy-2-cyclohexen-2-yl)propyl]triphenylphosphonium Iodide (5). At 0 °C a solution of methanesulfonyl chloride (3.5 mL, 45 mmol) in 15 mL of dry methylene chloride was added over a period of 5 min to a solution of alcohol **9** (3.2 g, 19 mmol) in dry methylene chloride (30 mL) and dry pyridine (11 mL). The mixture was stirred at 0 °C for 1 h, water (70 mL) was then added, and stirring was continued at 20 °C for 1.5 h. Extraction with methylene chloride[31] gave an oily product (4.5 g) that was taken up in a solution of sodium iodide (20 g, 0.13 mol) in 145 mL of dry acetone and heated under reflux for 2 h in an atmosphere of nitrogen. Workup by pouring the mixture into ice–water and extracting the resulting mixture with methylene chloride using a sodium bisulfite wash[31] gave 4.8 g (91%) of crude iodide **10** as a yellow oil: IR (CCl_4) 3057 (C=CH), 2820, 1092 and 1076 cm^{-1} (OCH_3); ^{1}H NMR 1.4–2.3 (m, 10 H), 3.19 (t, J = 6 Hz, 2 H, CH_2I), 3.35 (s, 3 H, OCH_3), 3.58 (m, 1 H, $CHOCH_3$), 5.65 (m, 1 H, olefinic proton). This product was dissolved with triphenylphosphine (7.4 g, 28 mmol) in 50 mL of benzene, and the stirred solution was heated under reflux for 48 h in an atmosphere of nitrogen. At 20 °C 65 mL of ether was added, and the precipitate was collected, washed twice, and dried to give 7.4 g (80%) of pure phosphonium iodide **5**: mp 162–163 °C; IR (CH_2Cl_2) 2822 (OCH_3), 1590 and 1489 (aromatic ring), 1440 (P-phenyl), 1116 and 1091 (OCH_3), 530, 510 cm^{-1}; ^{1}H NMR 1.3–2.7 (m, 10 H, aliphatic), 3.19 (s, 3 H, OCH_3), 3.3–3.8 (m, 3 H, CH_2–P and $CHOCH_3$), 5.68 (m, 1 H, olefinic proton), 7.6–8.0 (m, 15 H, aromatic); high-resolution mass spectrum, calcd for $C_{28}H_{32}OP^+$, m/e 415.2190; found, m/e 415.2243.

Anal. Calcd for $C_{28}H_{32}OPI$: C, 62.00; H, 5.95; I, 23.40. Found: C, 62.0; H, 6.0; I, 23.1.

***d*-[3-(1-Methoxy-2-cyclohexen-2-yl)propyl]triphenylphosphonium Iodide (*d*-5).** The phosphonium iodide *d*-**5** was prepared from alcohol *d*-**9** by the same procedure as that used

for *dl*-**5** from *dl*-**9**. The intermediate iodide *d*-**10** was obtained as a yellow oil, $[\alpha]^{20}_D$ +19.0°, and was then converted into the phosphonium iodide *d*-**5**: mp 162–163 °C; $[\alpha]^{20}_D$ +15.8°.

1-(1-Methoxy-2-cyclohexen-2-yl)-7-methyl-(3*E*,7*E*)-3,7-tridecadien-11-yne (1). To a stirred suspension of phosphonium iodide **5** (6.8 g, 12 mmol) in 27.5 mL of dry THF under nitrogen was added dropwise at 0–5 °C 1.1 M phenyllithium in ether until a permanent yellow color resulted (ca. 2 mL), and this was followed by another 10.7 mL (12 mmol). The resulting red mixture was stirred at 5 °C for 15 min and then cooled to −75 °C. A solution of 1.8 g (11 mmol) of aldehyde **6** in 10 mL of dry THF was added dropwise over a period of 10 min. After 1.5 h[34] another 33.3 mL of 1.1 M phenyllithium (37 mmol) in ether was added (−75 °C). Stirring was continued for 15 min, the mixture was warmed to −30 °C, and after 5 min the reaction was quenched with 5 mL of methanol. After being stirred at 20 °C for an additional 15 h, the mixture was poured into water and extracted with methylene chloride.[31] The residue was chromatographed on 325 g of silica gel with 95:5 hexane–ethyl acetate to give 2.4 g (72%) of **1** as a colorless oil, 95% pure and in a 98:2 trans–cis ratio of isomers of the disubstituted olefinic bond by VPC. An analytical sample was obtained by preparative TLC (95:5 hexane–ethyl acetate): IR (CCl_4) 2819 (OCH_3), 1663 (C=C), 1091 and 1075 (OCH_3), 968 cm^{-1} (trans RCH=CHR); ^1H NMR 1.62 (br s, 3 H, CH_3C=C), 1.78 (t, $J \approx 2.5$ Hz, 3 H, CH_3C≡C), 3.37 (s, 3 H, OCH_3), 3.6 (m, 1 H, C**H**OCH_3), 5.1–5.7 (m, 4 H, olefinic protons); high-resolution mass spectrum, calcd for $C_{21}H_{32}O$, *m/e* 300.2453 (M^+); found, *m/e* 300.2478.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73; O, 5.32. Found: C, 84.0; H, 10.9; O, 5.7.

***d*-1-(1-Methoxy-2-cyclohexen-2-yl)-7-methyl-(3*E*,7*E*)-3,7-tridecadien-11-yne (*d*-1).** The methoxy trienyne *d*-**1** was prepared from phosphonium iodide *d*-**5** and aldehyde **6** by the same procedure as that used for *dl*-**1** from *dl*-**5** and **6**. The chromatographed product, $[\alpha]^{20}_D$ +25.0°, was 96% pure and a 98:2 trans–cis ratio of isomers by VPC: >90% ee determined in $CDCl_3$, [*d*-**1**] ≈ 0.3 M, [Eu(hfc)$_3$] ≈ 0.1 M; downfield $\Delta\delta \approx 1.6$ ppm; $\Delta\Delta\delta$ = 0.05 ppm for the OCH_3 resonances of *dl*-**1**.

Cyclization of Methoxy Trienyne *dl*-1. *dl*-19-Nor-14(8 → 10)*abeo*-4-pregnen-20-one (13), *dl*-19-Nor-4-pregnen-20-one (2) and *dl*-19-Nor-9β,10α-pregn-4-en-20-one (15). A. With Trifluoroacetic Acid. To a stirred solution of 0.15 g (0.5 mmol) of methoxy trienyne *dl*-**1** and 3.0 g (34 mmol) of ethylene carbonate in 37.5 mL of dry 1,2-dichloroethane maintained at −25 °C was added under nitrogen 2.4 mL (3.6 g, 31 mmol) of anhydrous trifluoroacetic acid over a 5-min period. The mixture, which turned red, was stirred at −25 °C for 16 h. Then an excess of a 10% solution of potassium carbonate in 1:1 methanol–water was added. After being stirred at room temperature for 1 h, the mixture was poured into water and extracted with methylene chloride.[31] The residue was chromatographed on 12.5 g of silica gel with 95:5 hexane–ethyl acetate to give 62 mg (43% yield) of a tetracyclic fraction as a colorless oil, essentially a single spot on TLC (R_f 0.48, 9:1 hexane–ethyl acetate), and two spots on a silver nitrate impregnated plate (R_f 0.45 and 0.52, 9:1 hexane–ethyl acetate). The ^1H NMR spectrum showed high-field angular methyl singlets for tetracyclic material (see below). VPC showed four major peaks with retention times of 22.0 min (51% of total area), 24.2 min (8%), 25.1 min (15%), and 25.9 min (17%). Chromatography on 3.0 g of 20% silver nitrate impregnated silica gel with 95:5 hexane–ethyl acetate gave 22 mg (15% yield) of the spiro compound **13** as colorless crystals: mp 104–106 °C; essentially a single spot on TLC (silver nitrate impregnated plate, R_f 0.52, 9:1 hexane–ethyl acetate); 94% one peak by VPC (retention time 22.0 min); IR (CCl_4) 2660, 1701 (C=O), 1662 and 1651 (C=C), 1356 ($COCH_3$), 1211, 1170, 884, and 599 cm^{-1}; ^1H NMR 0.74 (s, 3 H, C-18 CH_3), 2.09 (s, 3 H, $COCH_3$), 2.55 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.50 (t, $J \approx 4$ Hz, 1 H, C-4 vinyl proton); ^{13}C NMR, see Table I; mass spectrum, see Figure 1; high-resolution mass spectrum, calcd for $C_{20}H_{30}O$, *m/e* 286.2297 (M^+); found, *m/e* 286.2318. Further elution with 95:5 hexane–ethyl acetate gave fractions showing three major peaks on VPC with retention times of 24.2, 25.1, and 25.9 min. The fraction most enriched in the 25.1-min component (10 mg) showed the peaks in a ratio of 3:13:4; one spot on TLC (silver nitrate impregnated plate, R_f 0.45, 9:1 hexane–ethyl acetate) was found by coinjection VPC with authentic *d*-**2** and *d*-**15** (retention times 25.1 and 25.9 min, respectively) and by ^1H NMR analysis to consist mainly of **2** with **15** as the major contaminant: ^1H NMR 0.66 (s, ca. 2.5 H, C-18 CH_3), 1.27 (s, ca. 0.5 H, C-18 CH_3), 2.11 (s, ca. 3 H, $COCH_3$), 2.44–2.83 (superimposed triplets, ca. 1 H, C-17 proton), 5.40 (m, ca. 1 H, C-4 vinyl proton).

B. With Deuteriotrifluoroacetic Acid. A solution of 0.15 g of methoxy trienyne *dl*-**1** and 3.0 g of ethylene carbonate in 37.5 mL of dry methylene chloride was treated with 2.4 mL of anhydrous deuteriotrifluoroacetic acid (99 atom % deuterated) as described in part A. After the mixture was stirred at −25 °C for 16 h, an excess of 30% potassium hydroxide was added, and stirring was continued at room temperature for 1 h. Workup and chromatography as described in part A gave 20 mg of the spiro compound **13**, 91% one peak by VPC (retention time 22.0 min). The mass spectrum indicated ca. 38% incorporation of one deuterium atom and <1% incorporation of two deuterium atoms, calculated from the relative intensitites of the peaks *m/e* 286 (M^+), 287, and 288 after correction for the natural isotopic abundances. In the same way ca. 38% incorporation of one deuterium atom was found for the fragment M − CH_3CO (peaks *m/e* 243 and 244) and <5% deuterium incorporation for the fragments M − $CH_3CO(CH_2)_2$ (peaks *m/e* 215 and 216) and M − $CH_3CO(CH_2)_3$ (peaks *m/e* 201 and 202).

Further elution gave a fraction (10 mg) showing three major peaks on VPC with retention times 24.2, 25.1, and 25.9 min in a ratio of 1.5:1.5:7, the second and third peaks corresponding **2** and **15** (see part A). Mass spectral analysis in the manner described above showed ca. 37% incorporation of one deuterium atom and <1% incorporation of two deuterium atoms in M^+ and the fragment M − CH_3CO and <5% deuterium incorporation in the fragments M − $CH_3CO(CH_2)_2$ and M − $CH_3CO(CH_2)_3$: ^1H NMR 0.66 (s, ca. 2.5 H, C-18 CH_3), 1.27 (s, ca. 0.5 H, C-18 CH_3), 2.11 (s, ca. 3 H, $COCH_3$), 2.44–2.83 (superimposed triplets, ca. 0.6 H, C-17 proton), 5.40 (m, ca. 1 H, C-4 vinyl proton).

C. With Boron Trifluoride Etherate. To a stirred solution of 0.60 g (2.0 mmol) of methoxy trienyne *dl*-**1** and 6.0 g (68 mmol) of ethylene carbonate in 120 mL of dry 1,2-dichloroethane maintained under nitrogen at −10 °C was added over a 10-min period 0.49 mL (4.0 mmol) of boron trifluoride etherate in 10 mL of dry 1,2-dichloroethane. The mixture, which turned red, was stirred at −10 °C for 4 h. Workup and chromatography of the residue on silica gel as in cyclization A gave 0.26 g (45% yield) of a tetracyclic fraction as a colorless oil. VPC showed four major peaks with retention times of 22.0 min (49% of total area), 24.2 min (13%), 25.1 min (14%), and 25.9 min (16%). The TLC behavior was as in cyclization A. This material was separated into three fractions by high-performance LC over a column (26 cm × 2.3 cm i.d.) packed with 20% silver nitrate impregnated silica gel with 99:1 hexane–ethyl acetate (10 mL/min; p = 100 kPa) as eluent. The first fraction (105 mg, 18% yield) consisted of the crystalline spiro compound **13**, mp 104–106 °C, 95% one peak by VPC (retention time 22.0 min).

The second fraction (95 mg, 17% yield; a colorless oil) showed mainly three components on VPC with retention times 24.2, 25.1, and 25.9 min and was essentially one spot on TLC (silver nitrate impregnated plate, R_f 0.45, 9:1 hexane–ethyl acetate). This material was rechromatographed (see below).

The third fraction (10 mg, 1.7% yield) of colorless, semicrystalline material was enriched in the 25.1-min component (90% one peak of this retention time by VPC) and showed one spot on TLC (silver nitrate impregnated plate, R_f 0.45, 9:1 hexane–ethyl acetate): IR (CCl_4) 3040 (C=CH), 2660, 1702 (C=O), 1663 (C=C), 1359 ($COCH_3$), 1207, 1167, 1123, 686, 597 cm^{-1}; ^1H NMR 0.66 (s, 3 H, C-18 CH_3), 2.11 (s, 3 H, $COCH_3$), 2.54 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.40 (m, 1 H, C-4 vinyl proton). This fraction was identical with authentic *d*-**2** by IR, ^1H NMR, VPC, and TLC.

(34) In one run an aliquot was removed here and worked up under normal Wittig conditions (addition of water at room temperature and extraction with methylene chloride[31]) known to give in addition to the trans olefin a substantial amount of the cis isomer. VPC of this product, including coinjection with **1**, allowed identification of the isomers: retention times of the cis and trans forms were 19.5 and 20.0 min, respectively (base-line separation). The Wittig product was a ratio of 29:71 trans–cis isomers.

The second fraction was rechromatographed (high-performance LC, identical column, 99:1 methylene chloride–ethyl acetate, 10 mL/min, p = 100 kPa) and separated into a series of fractions, all of them oils, showing a single spot on TLC (silver nitrate impregnated plate, R_f 0.45, 9:1 hexane–ethyl acetate). The second of these fractions (10 mg, 1.7% yield), showing two major peaks on VPC with retention times 25.1 and 25.9 min (ratio 1:2), was demonstrated by coinjection VPC with authentic *d*-**2** and *d*-**15** (retention times 25.1 and 25.9 min, respectively) and by ^{1}H and ^{13}C NMR analyses to be mainly a 1:2 mixture of **2** and **15**: ^{1}H NMR 0.66 (s, ca. 3 H, C-18 CH_3), 2.11 (s, ca. 3 H, $COCH_3$), 2.44–2.71 (superimposed triplets, ca. 1 H, C-17 proton), 5.40 (m, ca. 1 H, C-4 vinyl proton); ^{13}C NMR, superimposed spectra of authentic *d*-**2** and *d*-**15** (see Table I).

The last fraction of the second chromatography (11 mg, 1.8% yield) showed three major peaks on VPC with retention times 24.2, 25.1, and 25.9 min in a ratio of 6:3:2, the second and the third peak corresponding with the ketones **2** and **15** as demonstrated above: ^{1}H NMR 0.66 (s, ca. 1.4 H, C-18 CH_3), 1.27 (s, ca. 1.6 H, C-18 CH_3), 2.11 (s, ca. 1.4 H, $COCH_3$), 2.14 (s, ca. 1.6 H, $COCH_3$), 2.44–2.83 (superimposed triplets, ca. 1 H, C-17 proton), 5.40 (m, ca. 1 H, C-4 vinyl proton).

Cyclization of Methoxy Trienyne *d*-1. Optically Active 19-Nor-14(8 → 10)*abeo*-4-pregnen-20-one (13) and 19-Nor-4-pregnen-20-one (2). D. With Trifluoroacetic Acid. By use of the procedure described in part A, cyclization of methoxy trienyne *d*-**1** with $[\alpha]^{20}_D$ +25.0° gave the spiro compound **13** as a semicrystalline solid: $[\alpha]^{20}_D$ −7.9°; 93% one peak by VPC (retention time 22.0 min); ^{1}H NMR 0.74 (s, 3 H, C-18 CH_3), 2.09 (s, 3 H, $COCH_3$), 2.55 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.50 (t, $J \approx 4$ Hz, 1 H, C-4 vinyl proton). In addition, an oily fraction was isolated, $[\alpha]^{20}_D$ +8.4°, showing three peaks on VPC with retention times 24.2, 25.1, and 25.9 min in a ratio of 1:7:2, accounting for 90% of the total peak area. This corresponds with 9% of **14**, 63% of **2**, and 18% of **15**: ^{1}H NMR 0.66 (s, ca. 2.5 H, C-18 CH_3), 1.27 (s, ca. 0.5 H, C-18 CH_3), 2.11 (s, ca. 3 H, $COCH_3$), 2.44–2.83 (superimposed triplets, ca. 1 H, C-17 proton), 5.40 (m, ca. 1 H, C-4 vinyl proton).

E. With Boron Trifluoride Etherate. By use of the procedure described in part C, cyclization of methoxy trienyne *d*-**1** with $[\alpha]^{20}_D$ +25.0° gave the spiro compound **13** as a semicrystalline solid: $[\alpha]^{20}_D$ −9.0°; 90% one peak by VPC (retention time 22.0 min); ^{1}H NMR 0.74 (s, 3 H, C-18 CH_3), 2.09 (s, 3 H, $COCH_3$), 2.55 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.50 (t, $J \approx 4$ Hz, 1 H, C-4 vinyl proton). In addition, ketone **2** was isolated as a colorless oil: $[\alpha]^{20}_D$ +2.4°; 90% one peak by VPC (retention time 25.1 min); ^{1}H NMR 0.66 (s, 3 H, C-18 CH_3), 2.11 (s, 3 H, $COCH_3$), 2.54 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.40 (m, 1 H, C-4 vinyl proton).

F. Stability of *d*-1 with Deuteriotrifluoroacetic Acid. The treatment of methoxy trienyne *d*-**1**, $[\alpha]^{20}_D$ +25.0°, with deuteriotrifluoroacetic acid was identical with part B with the exception of the reaction time (4 h). Chromatography of the crude product (0.15 g) on 15 g of silica gel with 95:5 hexane–ethyl acetate gave 36 mg of recovered **1**: $[\alpha]^{20}_D$ +20.1°; 95% pure by VPC. In the mass spectrum the relative intensities of the peaks m/e 300 (M^+) and 301 (M + 1) were identical within experimental error with those of the starting material.

***d*-19-Nor-9β,10α-pregn-4-en-20-one (*d*-15).** To a stirred solution of 0.50 g (1.7 mmol) of 19-nor-9β,10α-pregn-4-ene-3,20-dione (*d*-**18**)[20] in 30 mL of methanol were added 0.40 mL (4.8 mmol) of 1,2-ethanedithiol and 0.25 mL (2.0 mmol) of boron trifluoride etherate. After the mixture was stirred for 45 min at room temperature, water was added. Extraction with ethyl acetate including a base wash[31] followed by recrystallization of the residue from methanol gave 0.41 g of dithioacetal **19**, mp 172–176 °C, and a second crop of 0.19 g with a melting point of 164–169 °C. This material was combined (95% yield) and used directly in the next step: IR (KBr) 3026 (C=CH), 1691 (C=O), 1641 (C=C), 1352 ($COCH_3$), 1275 cm^{-1}; ^{1}H NMR 0.66 (s, 3 H, C-18 CH_3), 2.12 (s, 3 H, $COCH_3$), 2.60 (t, $J \approx 8.5$ Hz, 1 H, C-17 proton), 3.1–3.5 (m, 4 H, SCH_2CH_2S), 5.60 (br s, 1 H, C-4 vinyl proton).

A solution of 0.30 g (7.9 mmol) of sodium borohydride in 1 mL of water was added to 0.60 g (1.6 mmol) of crude dithioacetal **19** in 2 mL of tetrahydrofuran and 15 mL of methanol. The mixture was boiled under reflux for 2 h and after addition of water extracted with methylene chloride.[31] The residue (0.63 g) was dissolved in 12 mL of tetrahydrofuran and added to 60 mL of liquid ammonia. Lithium (0.6 g, 86.5 mmol) in small pieces was added at −40 °C to the stirred mixture. Stirring at this temperature was continued for 45 min, 10 mL of ethanol was added dropwise, and the ammonia was allowed to evaporate. Addition of water and extraction with ether[31] gave a residue (0.51 g) that was dissolved in 15 mL of acetone. With stirring, 1 mL of 4 N chromic acid was added dropwise at 0 °C. Stirring at this temperature was continued for 30 min. Addition of water and extraction with ether including a base wash[31] gave 0.34 g of crude *d*-**15**. Chromatography on 10 g of silica gel with 9:1 hexane–ethyl acetate gave 0.27 g (59% yield) of *d*-**15** as colorless crystals, mp 109–113 °C. Recrystallization from hexane gave an analytical sample: mp 114–116 °C; $[\alpha]^{20}_D$ +41°; IR (CCl_4) 3040 (C=CH), 2666, 1701 (C=O), 1661 (C=C), 1355 ($COCH_3$), 1219, 1198, 1166, 1160, 909, 876, 838, 682, 643, 635, 549 cm^{-1}; ^{1}H NMR 0.66 (s, 3 H, C-18 CH_3), 2.11 (s, 3 H, $COCH_3$), 2.60 (t, $J \approx 8.5$ Hz, 1 H, C-17 proton), 5.40 (m, 1 H, C-4 vinyl proton); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.9; H, 10.5.

***d*-19-Nor-4-pregnen-20-one (*d*-2).** By use of the procedure described above for the synthesis of *d*-**15**, 19-nor-4-pregnene-3,20-dione (*d*-**16**)[18] was converted to the ketone *d*-**2**. Crystallization from hexane gave an analytical sample: mp 113–114 °C; $[\alpha]^{20}_D$ +146°; IR (CCl_4) 3040 (C=CH), 2660, 1702 (C=O), 1663 (C=C), 1359 ($COCH_3$), 1207, 1167, 1123, 686, 597 cm^{-1}; ^{1}H NMR 0.66 (s, 3 H, C-18 CH_3), 2.11 (s, 3 H, $COCH_3$), 2.54 (t, $J \approx 8$ Hz, 1 H, C-17 proton), 5.40 (m, 1 H, C-4 vinyl proton); ^{13}C NMR, see Table I.

Anal. Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.8; H, 10.7.

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Registry No. *dl*-**1**, 73194-05-5; *d*-**1**, 73194-05-5; *dl*-**2**, 73194-18-0; *d*-**2**, 73194-06-6; *dl*-**5**, 73194-07-7; *d*-**5**, 73194-07-7; **6**, 41143-17-3; *dl*-**7**, 73194-08-8; *dl*-**8**, 73194-09-9; *dl*-**9**, 73194-10-2; *d*-**9**, 73194-10-2; *dl*-**10**, 73194-11-3; *d*-**10**, 73194-11-3; *dl*-**11**, 73194-12-4; *d*-**11**, 73194-13-5; *l*-**11**, 73194-14-6; *dl*-**12**, 73194-15-7; *d*-**12**, 73194-15-7; *dl*-**13**, 73194-16-8; **13**, 73194-19-1; *d*-**14**, 73245-06-4; *dl*-**15**, 73245-07-5; *d*-**15**, 73245-08-6; *d*-**16**, 472-54-8; *d*-**17**, 73245-09-7; *d*-**18**, 4265-88-7; *d*-**19**, 73194-17-9.