von Hand eingestellt werden. Die gleiche Temperaturprogrammiereinheit steht hiebei im Temperaturintervall von 25 bis 60° in Stufen von 1° Abstand zur Verfügung. Ein selbstentwickelter Temperaturregler mit Differentialeingang sorgt dafür, dass die Temperaturüberhöhung des Luftthermostaten gegenüber dem Ultrathermostaten bei allen Stufen konstant bleibt. Der Wert der Überhöhung ist zwischen 0° und 5° auf 0,02° genau wählbar.

Die gesamte Apparatur, die Abb. 2 zeigt, wurde in der Werkstätte des *Theodor-Kocher*-Instituts (Direktor Prof. *P. v. Tavel*) gebaut. Besonderen Dank schulden die Autoren dem Mechanikermeister *M. Oetliker* für die präzise Konstruktion aller mechanischen Teile.

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269. Steroid Total Synthesis, Part VIII[1]); (+)-Estr-4-ene-3,17-dione

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(24. VII. 72)

Summary. A novel synthesis of the title compound, involving the resolution of a *Mannich* base derived from racemic 11,11-*o*-phenylenedioxy-7-hydroxy-1-dodecen-3-one is described. In an alternate approach 2(*S*)-acetamido-6,6-*o*-phenylenedioxy-heptanoic acid was used as the optically active starting material. This scheme features the preparation of a chiral 1,2-epoxide and its regiospecific alkylation with lithio-1,1-diethoxy-2-propyne.

In the preceding publication [1] we reported on the synthesis of racemic estr-4-ene-3,17-dione and its 13β-ethyl analog, in which the use of a pyrocatechol derived protecting group was a novel feature. This paper[2]) describes the preparation of optically active (+)-estr-4-ene-3,17-dione (**19**), based on the previously reported results [1] [3]. As outlined in Scheme 1, the ketal lactone **1** [4] was first converted to the vinyl ketone **2** [1] by reaction [3] with vinylmagnesium chloride in the cold. Reaction of crude **2** with (*S*)-(−)-α-methylbenzyl-amine gave rise to a mixture of two diastereomeric *Mannich* bases **3** + **5**[3]). As before [2] [5], the desired diastereomer **3** was readily obtained in crystalline form as its oxalate salt ($[\alpha]_D^{25} = -23.3°$; 58% overall yield from lactone **1**). From the mother liquor, the diastereomer **5** ($[\alpha]_D^{25} = -37°$) could be isolated by crystallization from hexane. The use of (*R*)-(+)-α-methylbenzylamine resulted in a mixture of the bases **4** + **6**. The base **6** ($[\alpha]_D^{25} = +37°$) was obtained by direct crystallization of the mixture **4** + **6** and the diastereomer **4** was again isolated as its oxalate salt, $[\alpha]_D^{25} = +22.7°$. An additional amount of the desired intermediate **3** could be obtained from the isomer **5** by the following inversion cycle. The *Mannich* base **5** was treated with methanesulfonyl chloride in pyridine to afford the mesylate **7** which on solvolysis with methanol and triethylamine yielded the inverted product **8**, possibly by the mechanism shown. Acid hydrolysis of the crude methoxy compound **8** afforded the base **3**, which was purified as the oxalate salt (54% overall from **5**).

Previously we had shown in two related cases [2] [5] that compounds such as **3**, **6** and **9**, with the absolute stereochemistry at C(6) as shown, would predominantly

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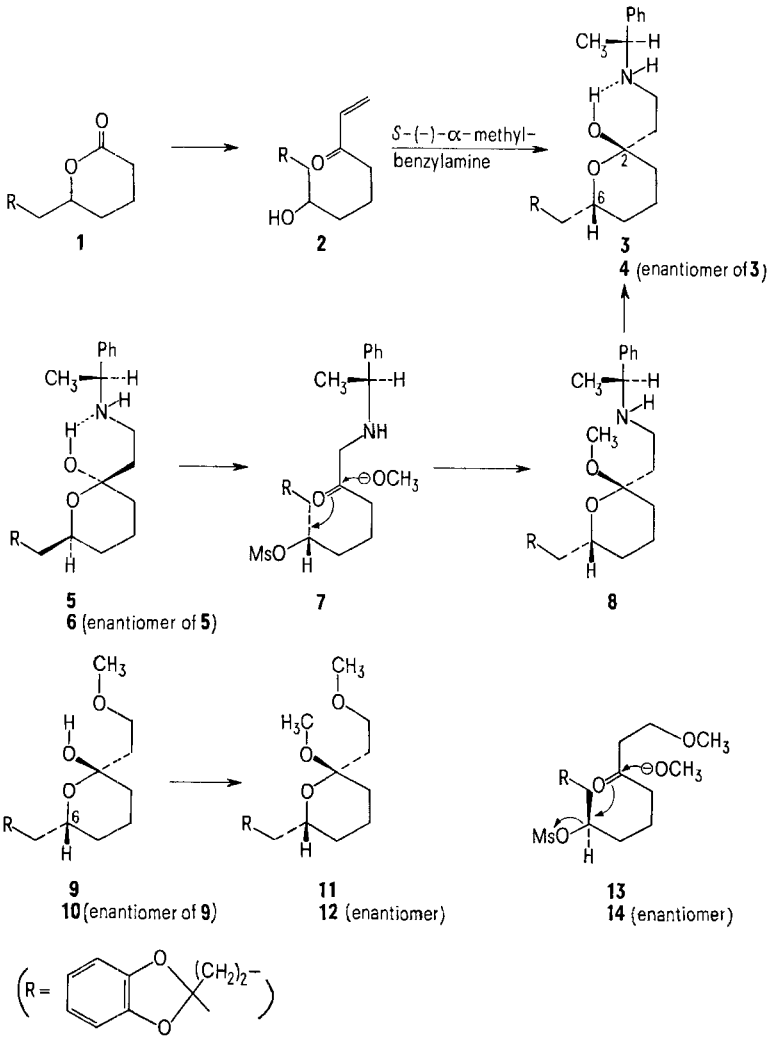
[1]) Part VII, see [1].

[2]) See [2] for a related synthesis of **19** (use of the isoxazole moiety).

[3]) See [2] regarding the conformation of such bases.

furnish the desired 13β-methyl product **15** on condensation with 2-methyl-cyclopentane-1,3-dione (see Scheme 2). When the base **3** was directly condensed with the β-diketone (acetic acid/pyridine/toluene, reflux) the major isomer was indeed the *trans* product **15**, isolated in 46% yield. The *cis*-isomer **16** was never obtained in pure form. As expected, the base **6** upon condensation with the methylcyclopentanedione also gave **15**. In order to both improve the transformation **3** → **15** and facilitate the recovery of the resolving agent, the *Mannich* base **3** was first converted to the methoxy derivative **9**[4]) by treatment [5] with benzaldehyde/methanol in the presence of sodium hydrogencarbonate. The crude product **9** was then condensed (acetic acid/

Scheme 1



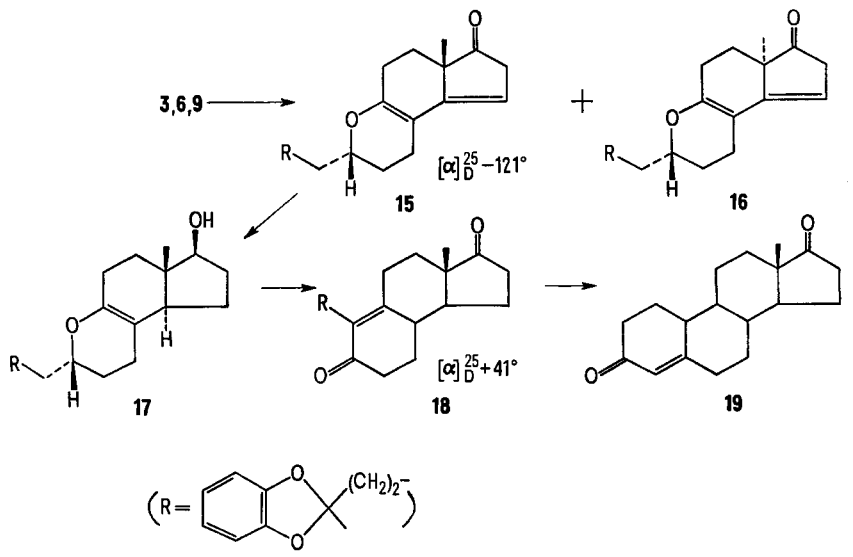
[4]) This exists as a mixture of cyclic acetal and the open hydroxy ketone.

toluene, reflux) with 2-methylcyclopentane-1,3-dione to give the mixture of **15** and **16**, from which the desired isomer **15** ($[\alpha]_D^{25} = -121°$) was obtained by crystallization (55% from **3**). The finding that the diene **15** is readily separated from its isomer **16** is of obvious practical importance.

An inversion cycle similar to the one described above **5** → **3** was also performed with the methanol adduct **9**. Thus, the enantiomer **10** could be obtained from **9** *via* the mesylate **13** and the mixed acetal **12**. Based on this model, it should be possible to obtain **9** from both the bases **4** and **5** *via* intermediates **14** and **11**.

The *conversion of* **15** *to the final product* **19** followed the procedures developed in the racemic series [1]. The keto-diene **15** was reduced with lithium aluminum hydride[5]), followed by regiospecific and highly stereoselective catalytic hydrogenation to afford the CD-*trans* intermediate **17** as the major product. Hydration of the crude enol ether **17**, followed by oxidation and base cyclization of the generated triketone, gave the tricyclic product **18**. This enone **18** was conveniently purified by crystallization (40% from **15**). In addition to optically pure **18** a small amount of racemic material [1] was also isolated[6]). In order to complete the synthesis, the enone **18** was hydrogenated to the saturated ketone, followed by acid hydrolysis-cyclization to yield (+)-estr-4-ene-3,17-dione (**19**). Again, the product was purified by direct crystallization of the crude. Pure **19** was thus obtained in 68% from **18** (6% overall from lactone **1**) and was identified by comparison with a previous preparation [2].

Scheme 2



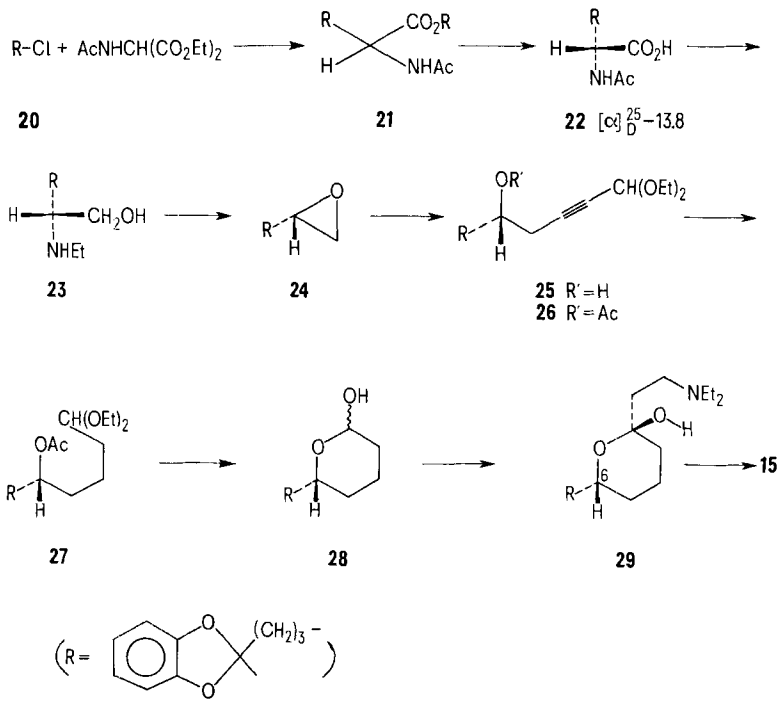
In an alternate approach (see Scheme 3) the key intermediate **15** was produced from the amino acid derivative **22**. The racemic ester **21** (R′ = Me) was formed directly

5) Later work showed Dibal-H (diisobutylaluminum hydride) and Red Al (sodium bis-(2-methoxyethoxy)-aluminum hydride) to be equally useful.

6) This is probably an indication that the precursor **15** was contaminated with its 13α-isomer **16**. Alternately, **15** may not have been optically pure.

in the condensation of diethyl acetamidomalonate with the chloroacetal **20** [4] in dimethylformamide in the presence of sodium iodide. Resolution of the corresponding free acid was achieved *via* the (*S*)-α-methylbenzylamine salt. The enantiomer was readily racemized [8] *via* the corresponding azlactone and could be reintroduced into the resolution cycle. Reduction of the resolved acid **22** with lithium aluminum hydride yielded the ethylamino alcohol **23** without apparent racemization. Reaction of this secondary amine with methyl iodide afforded the corresponding quaternary salt which, with sodium hydride in dimethylformamide, produced the optically active epoxide **24**, $[\alpha]_D^{25} = -4°$[7]). Alkylation of **24** with the lithio derivative of propargyl aldehyde diethylacetal [7] in dimethyl sulfoxide[8]) afforded the desired secondary alcohol **25** in a highly regiospecific fashion. Somewhat surprisingly, the catalytic hydrogenation (Pd on calcium carbonate in benzene) of the triple bond in compound **25** was not straightforward, presumably due to interaction of the free hydroxyl group [10]. In contrast, the corresponding acetate **26** was easily hydrogenated and gave the expected product **27**. Upon base and subsequent acid hydrolysis, **27** was transformed to the hemiacetal **28** which, when subjected to a previously reported [3] sequence (vinyl-*Grignard*, manganese dioxide oxidation in the presence of diethylamine),

Scheme 3



[7]) The sequence **22** → **24** appears to be novel, although the last step has, in principle, been known for many years [9].

[8]) The choice of this solvent resulted from a successful model experiment with (±)-1,2-epoxybutane. In the same model, the use of ether gave rise to both possible ring-opened products.

produced the base **29** (*R*-configuration at C(6)). As before, the *Mannich* base **29** was directly condensed with 2-methylcyclopentane-1,3-dione to give the dienol ether **15** ($[\alpha]_D = -116°$)[9]) as the major product.

Experimental Part

General. Melting points (m.p.) are uncorrected. Thin-layer chromatography (TLC.) was carried out on *Brinkman* F 254 silica gel plates, using a 1:1 mixture of ethyl acetate and benzene for developing. The spots were made visible under UV. light and by spraying with 50% aqueous *p*-toluenesulfonic acid and heating to 120° for 1–3 min, followed by exposure to iodine vapor. Ultraviolet spectra (UV.) were measured in ethanol and were recorded with a *Carey* Model 14 spectrometer, while infrared spectra (IR.) were determined with *Beckman* IR 8 and IR 9 spectrophotometers. Nuclear magnetic resonance (NMR.) spectra were recorded with *Varian* HA-60 and HA-100 spectrometers with tetramethylsilane as an internal standard.

Removal of solvents *in vacuo* refers to removal at 20 Torr and 45° on a *Büchi* rotavapor and finally at 0.5 Torr.

2(S)-[2-((S)-α-Methylbenzylamino)-ethyl]-6(R)-(4,4-o-phenylenedioxypentyl)-tetrahydropyran-2-ol (**3**) *and oxalate of* **3** *from* **1**. A solution of the lactone **1** (118 g) in tetrahydrofuran (1 liter) was cooled to −70° and treated over 6 min with a solution of vinylmagnesium chloride (315 ml; 2.28 M) while the temperature was maintained between −50° and −70° (dry ice/acetone bath). After complete addition the mixture was stirred for a further 14 min at −50°, cooled to −65° and treated with methanol (50 ml). At this point the cooling bath was removed and an aqueous solution of ammonium chloride (500 ml; 10%) was added (the temperature rose to −5°). The organic materials were extracted into ether (5 × 500 ml), the solution of crude **2** dried over anhydrous magnesium sulfate, filtered free of solids and then concentrated to ~200 ml *in vacuo*. Benzene (250 ml) was then added, followed by a solution of (*S*)-(−)-α-methylbenzylamine (51 g) dissolved in benzene (150 ml), and the mixture was kept at room temperature for 4 h. The solvents were removed *in vacuo* and the residue was extracted with boiling hexane (1 × 500 ml; 3 × 250 ml); the combined hexane extracts were then concentrated to yield the mixture of bases **3** and **5** as a pale yellow colored oil (157.2 g). This oil was dissolved in acetone (400 ml) and added, at room temperature, to a solution of anhydrous oxalic acid (49 g) dissolved in acetone (400 ml). The clear solution was seeded with the desired oxalate salt and left at room temperature for 8 h and then at 5° for a further 8 h. The solids were filtered off, washed with acetone (2 × 100 ml) and dried over P_2O_5 to give the crude oxalate (84.2 g): m.p. 78–82°, $[\alpha]_D^{25} = -21°$ ($c = 6.45$, methanol). Recrystallization from methyl ethyl ketone (1.1 l) yielded the pure *oxalate salt of* **3** (51.2 g): m.p. 81–83°, $[\alpha]_D^{25} = -23.3°$ ($c = 3.95$, methanol).

$C_{26}H_{35}NO_4(CO_2H)_2$ (515.6) Calc. C 65.23 H 7.23 N 2.7% Found C 64.91 H 7.09 N 2.49%

Liberation of the *free base* with aqueous sodium carbonate solution gave **3** as an oil. NMR. ($CDCl_3$): δ 7.25 (*s*, 5H, phenyl), 6.8 (*s*, 4H, phenyl), 3.9 (*m*, 1H, C(6) proton), 3.62 (*q*, 1H, J = 6.5 Hz, >C*H*—CH_3), 1.55 (*s*, 3H, >C—CH_3) and 1.29 ppm (*d*, 3H, J = 6.5 Hz, >CH—CH_3).

2(R)-[2-((S)-α-Methylbenzylamino)-ethyl]-6(S)-(4,4-o-phenylenedioxypentyl)-tetrahydropyran-2-ol (**5**). The mother liquors resulting from the crystallization of the oxalate of **3** were partitioned between hexane (400 ml) and water (800 ml) and the aqueous phase was extracted with more hexane (400 ml). The hexane extracts were then washed with aqueous acetic acid (200 ml; 10%) and the combined aqueous fractions made basic with sodium carbonate solution (20%). Extraction with hexane gave a semi-solid (75 g) which after several crystallizations from hexane yielded the pure base **5** (40 g): m.p. 78–80°, $[\alpha]_D^{25} = -37°$ ($c = 1.55$, benzene).

The rotation is a function of solvent and time, probably due to an equilibrium set up between the open and closed forms of the *Mannich* base. IR. ($CDCl_3$): 3200 (broad; hydrogen-bonded OH and NH), 1480 and 1240 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 7.2 (*s*, 5H, phenyl), 6.62 (*s*, 4H, phenyl), 3.78 (*m*, 1H, C(6) proton), 3.68 (*q*, 1H, J = 7 Hz, >C*H*—CH_3), 1.51 (*s*, 3H, >C—CH_3) and 1.31 ppm (*d*, 3H, J = 7 Hz, >CH—CH_3). MS.: M^+ *m/e* 425, *m/e* 135[10]).

$C_{26}H_{35}NO_4$ (425.6) Calc. C 73.38 H 8.29 N 3.29% Found C 73.68 H 8.40 N 3.47%

[9]) This result indicates that the epoxide **21** was of high optical purity.

When the hexane mother liquors were treated with oxalic acid in acetone, a further crop of the oxalate salt of **3** was formed (12.9 g; $[\alpha]_D^{25} = -23.6°$).

2(R)-[*2*-((R)-α-*Methylbenzylamino*)-*ethyl*]-*6*(S)-(*4,4*-o-*phenylenedioxypentyl*)-*tetrahydropyran-2-ol* (**4**) (as the oxalate) *and* *2*(S)-[*2*-((R)-α-*methylbenzylamino*)-*ethyl*]-*6*(R)-(*4,4*-o-*phenylenedioxypentyl*)-*tetrahydropyran-2-ol* (**6**) *from* **2**. Reaction of the crude vinyl ketone **2** with *R*(+)-α-methylbenzylamine, as described above for the (*S*)-(−)-isomer, gave a mixture of the bases **4**+**6** from which **6** was obtained by direct crystallization from hexane: m.p. 75–77°, $[\alpha]_D^{25} = +37°$ ($c = 1.053$; benzene). IR. ($CHCl_3$): 3250 (broad; hydrogen-bonded —OH and —NH), 1490 and 1250 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 7.19 (*s*, 5H, phenyl protons), 6.62 (*s*, 4H, phenyl protons), 3.75 (*m*, 1H, C(6) proton), 3.6 (*q*, 1H, $J = 6.5$ Hz, >CH—C*H*$_3$). MS.: M^+ *m/e* 425, *m/e* 135[10]).

$C_{26}H_{35}NO_4$ (425.6) Calc. C 73.38 H 8.29 N 3.29% Found C 73.62 H 8.41 N 3.26%

From the mother liquors, **4** was isolated as the crystalline *oxalate salt:* m.p. 81–83°, $[\alpha]_D^{25} = +22.7°$ ($c = 3.96$, methanol).

$C_{26}H_{35}NO_4(CO_2H)_2$ (515.6) Calc. C 65.23 H 7.23 N 2.72% Found C 65.31 H 7.31 N 2.70%

Oxalate of base **3** *from diastereomer* **5** (*inversion cycle*). A solution of the *Mannich* base **5** (4.25 g) in pyridine (100 ml) was cooled to 5° and treated over 20 min with methanesulfonyl chloride (8 ml) dissolved in pyridine (50 ml). The mixture was then warmed to room temperature and stirred for a further $1^1/_2$ h. Saturated sodium hydrogencarbonate solution (150 ml) was added and the products were isolated by ether extraction. Removal of the solvents *in vacuo* yielded the crude *mesylate* **7** (6.4 g) as an oil. This material was dissolved in methanol (110 ml) containing triethylamine (11 ml) and heated at reflux for 1 h. Sodium carbonate solution (10%; 100 ml) was then added, followed by brine (250 ml), and the mixture was extracted with ether. Removal of the ether yielded the crude *methanol adduct* **8**[11]) (4.8 g) as an oil.

A solution of this oil (**8**) in acetone (50 ml) was exposed to sulfuric acid (1N; 75 ml) and left at room temperature for 2 h. After quenching the mixture with an aqueous sodium carbonate solution (10%; 200 ml) the product was isolated with ether. Removal of the solvents *in vacuo* gave the base **3** as an oil (4.29 g). For purification, this crude product was dissolved in acetone (5 ml), then treated with oxalic acid (1 g) dissolved in acetone (5 ml). After 1 h at room temperature the solids were filtered off and dried over P_2O_5 at 0.1 Torr to give the *oxalate salt of* **3** (2.8 g; $[\alpha]_D^{25} = -21.5°$) ($c = 1.0$, methanol).

Oxalate of base **3** *from lactone* **1** *with inversion cycle.* The lactone **1** (41.4 g) was converted to the vinyl ketone **2** as above, and the ethereal extracts were treated directly with (*S*)-(−)-α-methylbenzylamine (18 g) and left at room temperature for 90 min. The solvents were then removed and the residue (66.5 g) was dissolved in acetone (160 ml), reacted with oxalic acid (20 g) in acetone (150 ml) and kept at 5° for 48 h after seeding. The solids were filtered off, washed with acetone and dried over P_2O_5 at 1 Torr to give the salt of **3** (31.5 g).

The mother liquors were added to water (500 ml)and extracted with hexane to remove any neutral impurities. From the aqueous layer the free base was liberated with aqueous sodium hydrogen-carbonate solution and extracted into ether. Removal of the solvents *in vacuo* gave an oil (mostly **5**; 32.9 g). This material was dissolved in tetrahydrofuran and treated at 10° with methanesulfonic acid (5.5 ml) followed by pyridine (78 ml). Methanesulfonyl chloride (36 ml) was then added with ice cooling and the mixture was stirred for 5 h at room temperature. Aqueous sodium carbonate solution (600 ml; 10%) was added and the mixture extracted with toluene. The organic extracts were washed with brine and taken to dryness *in vacuo* to yield crude *mesylate* **7** as an oil (36 g). IR. (film): 3200 (very broad; bonded NH), 1705 (>C=O), 1480, 1240, 900 (phenylenedioxy), 1175 and 1350 cm^{-1} (methanesulfonate). The mesylate was dissolved in methanol (770 ml) containing triethylamine (80 ml) and heated at reflux for 3 h. Aqueous sodium carbonate solution (1 l, 5%) was then added and the mixture extracted with ether. Removal of the solvents *in vacuo* gave the *methanol adduct* **8** which was dissolved in acetone (300 ml), treated with aqueous

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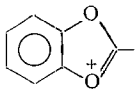
[10]) Base peak,  .

[11]) This material had the same TLC. characteristics as an authentic sample prepared from **3** with methanol and methanesulfonic acid.

sulfuric acid (1 N; 450 ml) and left to stand at room temperature for 3 h. The resulting mixture was extracted with hexane and the aqueous phase then made basic with aqueous sodium hydroxide solution (2 N). Extraction with hexane finally gave the base **3** (22.3 g; oil) which was dissolved in acetone (45 ml) and treated with a solution of oxalic acid (5.2 g) in acetone (45 ml) to afford the *oxalate salt* (13 g) *of* **3**. This was combined with the material obtained above (total 44.5 g) and recrystallized from methyl ethyl ketone to give pure material (35.5 g; oxalate of **3**).

2(S)-(*2-Methoxyethyl*)-*6*(R)-(*4,4*-o-*phenylenedioxypentyl*)-*tetrahydropyran-2-ol* (**9**) *from* **3**. The oxalate salt of **3** (15.45 g) was dissolved in methanol (360 ml) containing benzaldehyde (4.5 ml) and sodium hydrogencarbonate (6 g; anhydrous) and heated at reflux for 16 h. At this point most of the methanol was removed *in vacuo* and the residue was partitioned between dilute aqueous hydrochloric acid (2 N) and ether. The ether layer was washed with a sodium hydrogensulfite solution (3 × 200 ml; 20%), brine, and dried over anhydrous sodium sulfate. Removal of the solvents *in vacuo* gave the methanol adduct **9** (9.9 g) as an oil. Material from another experiment was chromatographed on silica gel (50:1) to yield pure **9** as an oil on elution with ether: $[\alpha]_D^{25} = +8.9°$ (c = 1.6328, benzene). IR. (film): 3475 (hydroxyl), 1710 (>C=O of the open form), 1490, 1245 and 750 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.74 (*s*, 4H, phenyl protons), 3.8 (*m*, 3H, >C*H*—O type), 3.3 and 3.27 (two *s*, total of 3H, 1:1 ratio; —OCH_3 of the cyclic and open forms) and 1.60 ppm (*s*, 3H, >C—CH_3). MS.: M^+ *m/e* 336, *m/e* 135[10]).

$C_{19}H_{28}O_5$ (336) Calc. C 67.83 H 8.39% Found C 67.96 H 8.11%

2(S)-(*2-Methoxyethyl*)-*2-methoxy-6*(R)-(*4,4*-o-*phenylenedioxypentyl*)-*tetrahydropyran* (**11**) *from* **9**. The methanol adduct **9**[4]) (444 mg) was dissolved in methanol (10 ml), treated with methanesulfonic acid (0.1 ml) and left at room temperature for 3 h. After quenching with water and extraction with ether the crude mixture of products (main impurity was unreacted **9**) was chromatographed on silica gel (12 g). Elution with an ethyl acetate/benzene mixture (5:95) yielded pure **11**. (91.4 mg) as an oil: $[\alpha]_D^{25} = -56°$ (c = 4.56, benzene). IR. (film): no hydroxyl bands, while NMR. ($CDCl_3$) only showed the presence of two methoxyls per molecule.

2(R)-(*2-Methoxyethyl*)-*2-methoxy-6*(S)-(*4,4*-o-*phenylenedioxypentyl*)-*tetrahydropyran* (**12**) *from* **9** (*inversion, model experiment*). The pure adduct **5** (3.6 g) was dissolved in pyridine (40 ml), treated with methanesulfonyl chloride (2 ml), dissolved in pyridine (20 ml) at 5° and then left at room temperature for 16 h. Ether was added (500 ml) to the mixture and the solution washed with water, aqueous sulfuric acid (1 N), sodium hydrogen-carbonate solution (5%) and dried over magnesium sulfate. Removal of the solvents *in vacuo* gave *12-methoxy-10-oxo-2,2*-o-*phenylenedioxy-dodecyl-6*(R)-*methane-sulfonate* (**13**) as an unstable oil (4.5 g). IR. (film): 1710 (>C=O), 1480, 1240, 740 (phenylenedioxy), 1360 and 1175 cm^{-1} (sulfonate). NMR. ($CDCl_3$): δ 6.81 (*s*, 4H, phenyl protons), 4.67 (*m*, 1H, >C*H*—O), 3.65 (*t*, 2H, J = 6 Hz, —CH_2—OCH_3), 3.37 (*s*, 3H, —O—CH_3), 2.99 (*s*, 3H, OSO$_2$CH_3), 2.65 (*t*, 2H, J = 6 Hz, —CO—CH_2—), and 1.67 ppm (*s*, 3H, >C—CH_3).

A solution of the mesylate **13** (130 mg) in methanol (2 ml) containing triethylamine (0.1 ml) was heated at reflux for 2 h and then quenched with ether. The organic phase was then washed with water and taken to dryness *in vacuo*. Chromatography of the material on silica gel (6 g) yielded chemically *pure* **12** (76.5 mg) on elution with ethylacetate/benzene mixture 5:95; $[\alpha]_D^{25} = +47°$ (c = 3.82, benzene). The spectra of **12** were identical to those obtained with the enantiomer **11**.

3(S)-(*4,4*-o-*Phenylenedioxypentyl*)-*6a*(S)*β-methyl-1,2,3,5,6,6a-hexahydro-cyclopenta*[*f*]*chromen-7*(*8*H)-*one* (**15**) *from* **3**. A solution of the amine **3** (850 mg) in toluene (30 ml), aqueous acetic acid (12 ml; 90%) and pyridine (6 ml) containing 2-methylcyclopentane-1,3-dione (330 mg) was heated at reflux for 16 h and then 35 min in conjunction with a *Dean-Stark* water trap. The reaction mixture was worked up as described below. The crude dienol ether (red oil) was filtered through a column of alumina (Alox III; 50 ml) in a benzene/hexane mixture 1:1 to yield the dienol-ether mixture **15** and **16** (575 mg) as a pale yellow solid. Crystallization from isopropyl alcohol gave the desired isomer **15** (397 mg): $[\alpha]_D^{25} = -119°$ (c = 1.0, chloroform). Recrystallization raised the rotation to −121° (further data see below).

Diene **15** *from* **9**. The crude adduct **9** (9.9 g; see preparation of **9** from **3**) was dissolved in a mixture of toluene (200 ml) and acetic acid (100 ml) containing 2-methylcyclopentane-1,3-dione (3.5 g) and heated at reflux for 8 h. A *Dean-Stark* water trap was then inserted into the system and the solution was heated at reflux for a further 90 min. After cooling to room temperature more

toluene (350 ml) was added and the mixture was washed with water, followed by an aqueous sodium carbonate (10%) solution. Removal of the solvents *in vacuo* yielded an orange colored oil which was crystallized twice from isopropyl alcohol to yield pure **15** (5.5 g): m.p. 111–113°, $[\alpha]_D^{25} = -121°$ ($c = 1.0$, chloroform). UV. max (ethanol) 253 nm ($\varepsilon = 18770$). IR. ($CHCl_3$): 1740 (cyclopentanone), 1640 (dienol ether), 1485 and 1240 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.74 (*s*, 4H, phenyl protons), 5.4 (*t*, 1H, $J = \sim 2$ Hz, =CH—CH_2—), 3.8 (*m*, 1H, O—C*H*), 3.06 (*d* of *d*, 2H, $J = 22$ Hz, =CH—CH_2—C=O), 1.6 (*s*, 3H, CH_3—C<) and 1.11 ppm (*s*, 3H, CH_3—C<).

$C_{24}H_{28}O_4$ (380.5) Calc. C 75.76 H 7.42% Found C 75.99 H 7.63%

Diene **15** *from* **6** via **9**. The base **6** (15.02 g) was first converted to the methanol adduct **9** as described for the transformation **3** → **9**. Crude **9** was subsequently reacted (see above) with 2-methylcyclopentane-1,3-dione to afford **15** (7.3 g): m.p. 112–113°, $[\alpha]_D^{25} = -122°$ ($c = 1.15$, chloroform).

(+)-*6-(3,3-o-Phenylenedioxybutyl)-3aβ-methyl-2,3,3a,4,5,7,8,9,9a,9b-decahydro-1*H*-cyclopenta[a]naphthalene-3,7-dione* (**18**) *from* **15**. – *Reduction.* The dienol ether **15** (14 g) was dissolved in dry tetrahydrofuran (100 ml) and added to a slurry of lithium aluminum hydride (5 g) in tetrahydrofuran (100 ml) at 5°. After complete addition the mixture was warmed to room temperature and stirred for a further 2 h. Wet ether (200 ml) was then added, followed by a saturated solution of sodium sulfate (30 ml), and the solids were filtered off and washed well with ether. Removal of the solvents *in vacuo* yielded the 17β-alcohol (15.4 g) as a glass (IR. showed absence of the cyclopentanone carbonyl).

Hydrogenation. This material was dissolved in tetrahydrofuran (100 ml) containing a palladium catalyst (5% on carbon; 1.5 g) and hydrogenated at room temperature and pressure until the hydrogen uptake ceased. The solids were filtered off, washed with more solvent, and the filtrate was taken to dryness *in vacuo* to yield **17** (*3-(4,4-o-phenylenedioxypentyl)-6aβ-methyl-1,2,3,5,6-6a,7,8,9,9a-decahydro-cyclopenta[f]chromen-7β-ol*) (15 g) as an oil: IR. (film): 3375 (hydroxyl), 1660 (enol ether), 1480, 1230 and 730 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.72 (*s*, 4H, phenyl protons), 3.7 (*m*, 2H, >C*H*—O), 1.59 (*s*, 3H, >C—CH_3), 0.96 and 0.78 ppm (*s*, total 3H, *cis*-6aβ-CH_3 and *trans*-6aβ-CH_3; ~1:9).

Hydrolysis/oxydation. The crude enol ether **17** (15 g) was dissolved in acetone (150 ml), treated with aqueous sulfuric acid (50 ml; 5 N) and left at room temperature for 2 h (disappearance of the enol ether by TLC. and IR.). Brine (500 ml) was then added and the products were isolated with ether. The crude hydration product was dissolved in acetone (300 ml), cooled to 0° and treated over 20 min with a fresh solution of *Jones'* chromic acid mixture (45 ml). The reaction mixture was stirred for an additional $2^1/_2$ h at room temperature and then treated with brine (250 ml) followed by an aqueous solution and sodium hydrogen-sulfite (100 ml; 10%). The mixture was extracted with benzene, the benzene extracts were then washed with a sodium carbonate solution (5%; 100 ml) and taken to dryness *in vacuo* to give the crude *triketone* (cf. [1]) (13.3 g) as a pale orange colored oil (IR. ($CHCl_3$): showed weak hydroxyl and strong carbonyl bands at 1735 and 1710 cm^{-1}).

Cyclization. Treatment of this triketone with a methanolic solution of potassium hydroxide (2 g in 150 ml) at reflux for 90 min effected ring closure to **18**. Acetic acid (3 ml) was added to the reaction mixture and the bulk of the methanol was removed *in vacuo*. The residue was partitioned between benzene and aqueous sodium carbonate solution (5%) and yielded the crude tricyclic diketone **18** on removal of the solvents (11.1 g; ~80% enone content by UV. assay). Crystallization from a dichloromethane/isopropyl ether mixture and then absolute ethanol yielded *pure* **18** (5.56 g): m.p. 117–119°, $[\alpha]_D^{25} = +41°$ ($c = 1.7267$, chloroform). UV. max (ethanol): 240 nm (ε 13850). IR. ($CHCl_3$): 1735 (cyclopentanone), 1660 and 1600 (cyclohexenone), 1480 and 1240 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.73 (*s*, 4H, phenyl protons), 1.61 (*s*, 3H, >C—CH_3) and 0.97 ppm (*s*, 3H, 3aβ—CH_3).

$C_{24}H_{28}O_4$ (380) Calc. C 75.76 H 7.42% Found C 75.96 H 7.31%

(+)-*Estr-4-ene-3,17-dione* (**19**). – *Hydrogenation.* A solution of the tricyclic material **18** (3.8 g) in tetrahydrofuran (35 ml) containing triethylamine (0.7 ml) and a palladium catalyst (5% on carbon; 400 mg) was hydrogenated at room temperature and pressure until one equivalent

of hydrogen had been consumed. The catalyst was then filtered off and the solvents were removed *in vacuo* to yield the saturated ketone (IR. showed the absence of the 1660 and 1600 cm^{-1} bands).

Hydrolysis/cyclization. The hydrogenation product was dissolved in ethanol (30 ml) containing aqueous hydrochlorid acid (20 ml; 2N) and heated at reflux for 4 h. The bulk of the solvent was removed *in vacuo* and the residue partitioned between benzene and aqueous sodium hydroxide solution (1N). Removal of the benzene *in vacuo* yielded crude **19** (2.8 g) as a white solid: $[\alpha]_D^{25} = +125°$ ($c = 2.2$, chloroform). Crystallization from a dichloromethane/isopropyl ether mixture and then from aqueous methanol furnished pure **19** (1.86 g): m.p. 172–174° (*Kofler* hot stage); $[\alpha]_D^{25} = +141.9°$ ($c = 2.6823$, chloroform)[12]. UV. max (ethanol): 239 nm (ε 16200). IR. ($CDCl_3$): 1730 (cyclopentanone), 1660 and 1620 cm^{-1} (cyclohexenone).

The IR., NMR.- and UV. solution spectra were indistinguishable from those obtained with material prepared previously [1].

(±)-*6,6*-o-*Phenylenedioxy-2-acetamido-heptanoic acid methylester* (**21**, $R' = CH_3$). Sodium metal (14 g) was dissolved in methanol (600 ml), treated with diethyl acetamidomalonate (135 g) and taken to dryness *in vacuo*. The last traces of alcohol were removed at 0.1 Torr and 50° and a slurry of the salt in dimethylformamide (DMF) (500 ml) was added to a mixture of 4,4-*o*-phenylenedioxy-1-pentyl chloride (63 g) and sodium iodide (45 g) in more DMF (800 ml). This heterogeneous mixture was heated at 100° with stirring for 22 h and then quenched with water. Extraction with dichloromethane yielded the crude methyl ester **21** ($R' = CH_3$) as a syrup (ester exchange having occurred during the salt formation of the substituted malonate).

A small sample of this material was distilled (bulb tube) to yield pure **21** ($R' = CH_3$), b.p. 160–180°/0.02 Torr. IR. ($CHCl_3$): 3490 (amide —NH), 1735 (methyl ester carbonyl), 1690 (amide carbonyl), 1500 and 1260 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.75 (*s*, 4H, phenyl protons), 6.2 (*m*, 1H, —N*H*—), 3.72 (*s*, 3H, —CO_2CH_3), 1.98 (*s*, 3H, —CO—CH_3) and 1.58 ppm (*s*, 3H, $\geqslant$C—CH_3). MS.: M^+ *m/e* 307, *m/e* 135[10]).

$C_{16}H_{21}NO_5$ (307.4) Calc. C 62.53 H 6.89% Found C 62.68 H 7.03%

(±)-*6,6*-o-*Phenylenedioxy-2-acetamido-heptanoic acid* (**21**, $R' = H$). The crude ester **21** ($R' = CH_3$) was treated with aqueous sodium hydroxide (1 l; 10%) at 80° for 1 h. After this time a clear solution was obtained and the mixture was cooled to room temperature and extracted with ether to remove any neutral material. The aqueous layer was acidified to pH 2 with sulfuric acid (6N) and the liberated acid isolated with dichloromethane. Removal of the solvents yielded the crude acid (90 g) as a buff colored solid. This material was dissolved in acetone (1.2 l) and purified by treatment with racemic α-methylbenzylamine (65 ml). After standing at 0° for 18 h the white crystalline material was filtered off (110.1 g) and partitioned between dichloromethane and sulfuric acid (6N). Removal of the solvents from the organic layer gave the acid as a gum (74.3 g). Crystallization from a mixture of methanol and ether gave pure **14** (65.2 g), m.p. 130–131°. IR. ($CHCl_3$): 3450 (amide —NH), 3500–2750 (carboxyl; very broad), 1720 (carboxyl-carbonyl; broad), 1680 (amide carbonyl), 1480 and 1240 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 7.3 (*m*, 1H, —CO—N*H*—), 6.7 (*s*, 4H, phenyl protons), 1.99 (*s*, 3H, —$COCH_3$) and 1.57 ppm (*s*, 3H, $\geqslant$C—CH_3). MS.: M^+ *m/e* 293.

$C_{15}H_{19}NO_5$ (293) Calc. C 61.42 H 6.53 N 4.70% Found C 61.54 H 6.30 N 4.62%

6,6-o-*Phenylenedioxy-2*(R)-*acetamido-heptanoic acid* (**22**). The free acid **21** ($R' = H$) (15.4 g) was dissolved in hot methyl ethyl ketone (2 l), mixed with (*S*)-α-methylbenzylamine (7.5 ml), seeded with the desired isomer (from previous separations) and left at room temperature for 18 h. The solids were filtered off (7.205 g; $[\alpha]_D^{25} = -21.2°$, $c = 1$, methanol) and recrystallized from methyl ethyl ketone to give the pure *salt* (6.4 g): m.p. 180–181°; $[\alpha]_D^{25} = -23°$ ($c = 1.37$, methanol).

Partitioning of this salt between dichloromethane and sulfuric acid (6N) yielded the *free acid*, crystallization from ether gave the pure **22** (*e.g.* 280 mg from 590 mg of salt): m.p. 129–130°, $[\alpha]_D^{25} = -13.8°$ ($c = 1.8493$, methanol).

$C_{15}H_{19}NO_5$ (293) Calc. C 61.42 H 6.53 N 4.78% Found C 61.38 H 6.69 N 4.70%

6,6-o-*Phenylenedioxy-2*(S)-*acetamido-heptanoic acid.* The enantiomeric acid of **22** could be isolated from the mother liquors of the salts, but was more conveniently obtained by using (*R*)-α-

[12]) Ref. [6] gives $[\alpha]_D^{25} = +139°$; m.p. 170–171° (hot stage).

methylbenzylamine in the resolution. This then yielded 6,6-*o*-phenylenedioxy-2(*S*)-acetamido-heptanoic acid: m.p. 129–130°, $[\alpha]_D^{25} = +13.43°$ ($c = 1$, methanol).

$C_{15}H_{19}NO_5$ (293) Calc. C 61.42 H 6.53 N 4.78% Found C 61.17 H 6.73 N 4.66%

6,6-o-phenylenedioxy-1,2(S)-epoxy-heptane (**24**). The (*S*)-α-methylbenzylamine salt of **22** (13 g) was converted to the acid (10 g) with dichloromethane and sulfuric acid (6 N). A solution of this crude acid (10 g) in tetrahydrofuran (THF; 300 ml) was added to a slurry of lithium aluminum hydride[13] (4.25 g) in more THF (150 ml) at room temperature. The mixture was then heated at reflux for 15 h, cooled to 10° and treated with wet ether (200 ml) followed by a saturated solution of sodium sulfate (30 ml). The solids were filtered off, washed well with more ether, and the solvents were then removed *in vacuo* to yield the crude *ethylamino alcohol* **23** (9.9 g) as an oil: $[\alpha]_D^{25} = -14°$ ($c = 1.0$, chloroform). IR. (film): 3350 (hydroxyl), 1480, 1235 and 730 cm^{-1} (phenylenedioxy).

This alcohol (9.8 g) was dissolved in a mixture of acetone (140 ml) methyl iodide (15 ml) and potassium carbonate (18 g) and stirred at room temperature for 24 h. The solids were filtered off, washed well with acetone and the combined filtrates were taken to dryness *in vacuo* to yield the crude *quaternary salt of* **23** (15 g) as a glass.

A solution of the above salt in DMF (250 ml) was cooled to 0° and treated with solid sodium hydride (4.08 g, oil-free) and stirred at room temperature for 16 h. The mixture was then cooled to 5° and quenched with ether and water. Isolation of the products by ether extraction gave the crude *epoxide* **24** (7.6 g) on removal of the solvents *in vacuo*. Two distillations furnished pure **24** (4.2 g), b.p. 90–98°/0.05 Torr, $[\alpha]_D^{25} = -3.9°$ ($c = 1.0$, dioxane). IR. ($CHCl_3$): 3050 (terminal epoxide), 1490 and 1245 (phenylenedioxy), and 1115 cm^{-1} (terminal epoxide). NMR. ($CDCl_3$): δ 6.76 (*s*, 4H, phenyl protons), 2.6 (*m*, 3H, $-CH\!\!-\!\!CH_2$) and 1.61 ppm (*s*, 3H, $\geqslant C-CH_3$). MS.: M^+ *m/e* 220, *m/e* 135[10]).

$C_{13}H_{16}O_3$ (220.3) Calc. C 70.89 H 7.32% Found C 70.82 H 7.33%

9,9-o-Phenylenedioxy-5(S)-acetoxy-dec-2-yne-1-al diethyl acetal (**26**). A solution of methyl lithium in ether (17.2 ml; 2.07 M) was added at 0° to 2-propyne-1-al diethyl acetal (4.6 g) dissolved in ether (50 ml). The solvents were then removed *in vacuo* and the residue was treated with dimethyl sulfoxide (DMSO; 75 ml). The mixture was cooled to 0° and with stirring, treated with a solution of the epoxide **24** (3.9 g) in DMSO (50 ml). After complete addition, the reaction mixture was stirred for a further 18 h at room temperature and then quenched with ice water (300 ml). Extraction with ether furnished the crude *alcohol* **25** (6.8 g) as a brown-colored oil. IR. (film): 3400 (hydroxyl), 2225 (acetylene), 1480, 1240 and 740 cm^{-1} (phenylenedioxy).

The crude alcohol was dissolved in a mixture of benzene (100 ml), pyridine (1.6 ml) and acetic anhydride (3.4 ml) and heated at reflux for 1 h. Removal of the solvents *in vacuo* and distillation of the residue from an oil jacketed flask gave the *acetate* **26** (4.53 g) as a viscous oil: b.p. 160–190/0.05 Torr; $[\alpha]_D^{25} = -11°$ ($c = 1{,}1323$, dioxane). IR. (film): 1740 (acetoxy), 2240 (acetylene), 1480, 1240 and 740 cm^{-1} (phenylenedioxy). NMR. ($CDCl_3$): δ 6.73 (*s*, 4H, phenyl protons), 5.25 (*t*, 1H, $J = 1$ Hz, $-CH(OEt)_2$), 4.25 (*t*, 1H, $J = 6$ Hz, $>CHOAc$), 3.75 (*m*, 4H, $-O-CH_2-CH_3$), 2.5 (*d* of *d*, 2H, $J = 1$ and 6 Hz, $-CH_2-C\equiv C$), 2.03 (*s*, 3H, $-COCH_3$), 1.6 (*s*, 3H, $\geqslant C-CH_3$), and 1.22 ppm (*t*, 6H, $J = 6$ Hz, $-O-CH_2-CH_3$). MS.: M^+ *m/e* 390.

$C_{22}H_{30}O_6$ (390.2) Calc. C 67.67 H 7.74% Found C 68.13 H 8.02%

6(R)-(4,4-o-Phenylenedioxypentyl)-2(S)-(2-diethylaminoethyl)-tetrahydro-pyran-2-ol (**29**). The acetate **26** (4.4 g) was dissolved in benzene (75 ml) containing palladium on calcium carbonate (1%; 500 mg) and hydrogenated at room temperature and pressure until the uptake of hydrogen ceased (~45 h). The solids were filtered off and the solvents removed *in vacuo* to give the *saturated product* **27** as an oil (4.32 g). IR. (film): 1740 (acetoxy), 1480, 1240 and 740 cm^{-1} (phenylenedioxy).

This material was used directly in the next step. A solution of **27** (4.32 g) in methanol (18 ml) was added to potassium hydroxide (1 g) dissolved in methanol (30 ml) and left at room temperature for 18 h. Ether was added and the mixture was washed well with water and then taken to dryness *in vacuo*. The residue (3.81 g) showed no acetate bands in the IR. and, after dissolving in acetone (50 ml), was reacted with sulfuric acid (16 ml; 1 N) at room temperature for 18 h (even after 100 h the reaction was incomplete and still contained the partially hydrolyzed mixed acetal). Ether was

[13]) Red-Al also proved satisfactory.

added and the mixture washed with water. Removal of the solvents yielded a mixture of products (3.03 g) which contained the *cyclohemiacetal* **28**. This mixture was dissolved in THF (40 ml) and treated with vinylmagnesium chloride in THF (13.5 ml; 2M) at 0°. After 2 h at room temperature an aqueous ammonium chloride solution (25 ml; 10%) was added and the products were isolated with ether.

Removal of the solvents *in vacuo* and chromatography of the residue (3.37 g) on silica gel (150 g) yielded pure *11,11-phenylenedioxy-7(R),3(S,R)-dihydroxy-1-dodecene* (1.9 g) on elution with ethyl acetate/benzene mixtures (25–50%). The structure was confirmed by comparison (IR., solution) and TLC. with totally racemic material prepared previously [2]. Oxidation of this material in the presence of diethylamine by the previously described procedure [2] yielded the *Mannich* base **29** (1.1 g), exhibiting the same TLC. and IR. (solution) characteristics of totally racemic material [2]. When this product was treated with 2-methylcyclopentane-1,3-dione as in the case of the methanol adduct **9**, the mixture of dienol ethers **15** and **16** was generated. Crystallization from isopropyl alcohol (3 times after chromatography on alumina) gave chemically pure **15** (170 mg), $[\alpha]_D^{25} = -116°$ ($c = 1.0$, chloroform).

BIBLIOGRAPHY

[1] *M. Rosenberger, A. J. Duggan & G. Saucy*, Helv. *55*, 1333 (1972).
[2] *J. W. Scott, R. Borer & G. Saucy*, J. org. Chemistry *37*, 1659 (1972).
[3] *G. Saucy & R. Borer*, Helv. *54*, 2121 (1971).
[4] *M. Rosenberger, D. Andrews, F. Di Maria, A. J. Duggan & G. Saucy*, Helv. *55*, 249 (1972).
[5] *G. Saucy & R. Borer*, Helv. *54*, 2517 (1971).
[6] *C. Djerassi*, J. Amer. chem. Soc. *76*, 4092 (1954).
[7] *J. C. Sauer*, Org. Syntheses, coll. vol. IV, 813 (1963); *H. Pasedach & G. Schmidt-Thomée (BASF)*, U.S. Pat. 2879305 [Chem. Abstr. *63*, 18869b (1959)].
[8] *V. du Vigneaud & C. E. Meyer*, J. biol. Chemistry *99*, 143 (1933).
[9] *J. Read & I. G. M. Campbell*, J. chem. Soc. *1930*, 2377.
[10] *A. Mondon*, Liebigs Ann. Chem., *577*, 181 (1952).

270. Electron Spin Resonance Studies of Free Radicals Arising from α-Hydrogen Abstraction from Thioethers

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(17. VI. 72)

Résumé. On rapporte les spectres de résonance paramagnétique de radicaux libres du type R–S–$\dot{C}$–R^1R^2, créés par photolyse d'un mélange de *t*-butylperoxyde et d'un thioéther. Pour les thioéthers cycliques, tétrahydrothiophène et thiopyranne, les spectres indiquent une interconversion rapide du cycle qui est empêchée dans le 4 *t*-butyl-thiopyranne, permettant ainsi l'attribution des couplages aux divers protons axiaux et équatoriaux.

Introduction. – The recent publication [1] of a study of the electron spin resonance spectra of various organic free-radicals having a sulfur atom directly bonded to the radical site prompts us to report the results of our own work on this problem which has been proceeding along similar lines. The object of this study has been to investigate the way in which the sulfur atom interacts with a π-center ('conjugation'), and the effect of the sulfur substituent on the geometry of the radical center.