Tetrahedron. Vol. 30, pp. 819 to 830. Pergamon Press 1974. Printed in Great Britain

A STEREOSELECTIVE TOTAL SYNTHESIS OF *NAT* (−) PROSTAGLANDIN E_1 AND ITS OPTICAL ANTIPODE[1]

H. L. SLATES, Z. S. ZELAWSKI, D. TAUB and N. L. WENDLER*
Merck Sharp & Dohme Research Laboratories, Merck & Co., Inc., Rahway, New Jersey 07065

(*Received in the USA* 9 *September* 1973; *Received in the UK for publication* 30 *October* 1973)

Abstract—A stereoselective total synthesis of *nat* (−) prostaglandin E_1 and its optical antipode employing the Diels–Alder adduct of *trans*-piperylene and maleic anhydride as starting material is described.

In our previous paper[2] on prostaglandin E_1 total synthesis, a route to the key olefinic keto ester **24** was described starting from 5-methoxy-indanone-1. The conversion of **24** to (±) prostaglandin E_1 was effected by cleavage oxidation of the cyclohexene ring of the derived ketal **27** followed by elaboration of the *seco* system to the PGE_1 end-functionality.

The present synthesis constitutes a more efficient route to the olefinic keto ester **24**, and at the same time permits optical resolution of the initial intermediate en route thereto. Conversion of **24** to the end product, furthermore, was effected by a new sequence to give both *nat* (−) prostaglandin E_1 as well as its optical antipode (+) *ent* PGE_1.

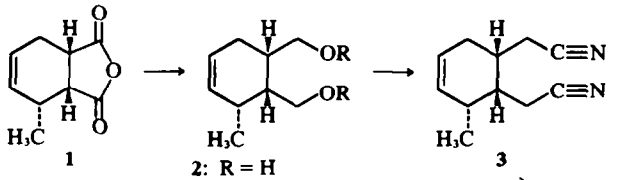
The Diels–Alder adduct of *trans*-piperylene and maleic anhydride **1**[3] was reduced with lithium aluminum hydride, and the diol **2** thus produced converted to the corresponding ditosylate **2a**. Treatment of the latter with sodium cyanide in dimethylsulfoxide (90°) afforded the dinitrile **3** in turn saponified to the crystalline (±) diacid **4**, m.p. 150–152° in 70% overall yield. In the conversion **2**→**3** a minor amount of elimination product **7** was formed in the generation of the dinitrile from its ditosylate precursor. This emphasizes the more restricted access to tosylate displacement at the C-2 substituent in virtue of adjacent Me shielding. Hydrolysis of **3**→**4** on the other hand is accompanied by small amounts of amino nitrile **8** (*cf* 21→22) arising from competitive Thorpe–Ziegler cyclization.

For the purpose of optical resolution the anhydride **1** was submitted to methanolysis with one equivalent of sodium methoxide in methanol at 0° to yield predominantly (70% direct, 90% based on mother liquor recycle to anhydride **1**) the 2-monomethyl ester **6**.* Resolution of **6** *via* its dehydroabietylammonium salt (80%), m.p. 163–165° yielded (−) **6** (natural series), m.p. 60–61, $[\alpha]_D^{Chf}$ − 69°; 2nd crop DAA salt m.p. 143–145° yielded (+) **6**, m.p. 60–63°, $[\alpha]_D^{Chf}$ + 67·7°. Conversion of (−) **6** as its dimethyl ester *via* the aforementioned sequence provided optically active diacid (−) **4**, m.p. 98·5–100°, $[\alpha]_D^{Chf}$ − 55·6°.

Treatment of the (±) diacid **4** with N-bromosuccinimide in t-butyl alcohol at 0° afforded *exclusively* the bromolactonic acid **5**, m.p. 144–146° (85%). Similarly **4** in sodium bicarbonate solution on treatment with iodine in potassium iodide solution *quantitatively* yielded the corresponding iodolactonic acid **5a**, m.p. 150–152°. This remarkable singularity in directional course of lactone formation is apparently the consequence of optimized conformational effects.[5] In this regard the alternative lactone **9** possesses an axial–axial interaction of methyl *vs* lactone–ether oxygen and methylene absent in **5**. The same specificity in the directional course of cyclization was observed in the formation of the corresponding cyclic bromoether **10** from precursor diol **2** on treatment with N-bromosuccinimide in aqueous t-butanol. The NMR spectrum of **10** was exceptionally well resolved permitting unequivocal assignment of structure **10** to the product of this reaction (*cf* Experimental and Ref 5). The conversion sequence **2**→**5**→**24** was subsequently undertaken largely on the basis of the observation made on the specific directional course of cylization **2**→**10**.

Oxymercuration of the dimethyl ester **11**, interestingly, proceeded entirely in the opposite sense to produce after reduction, the hydroxy diacid **12**, m.p. 201–203°. The latter proved likewise to be different from the hydroxy acid subsequently derived from **5b** (see later). The free diacid **4** failed to undergo oxymercuration. The hydroxy diacid **12** was further converted to the crystalline acetoxy ketone **13** and thence *via* the corresponding mesylate **13b** to a mixture of olefinic ketones **14** possessing a methyl doublet at 0·95δ (J = 7) in its NMR

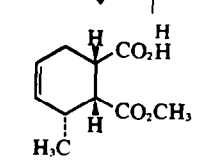
*The 1-monomethyl ester (m.p. 100–101°) was prepared *via* an unrelated route.[4]



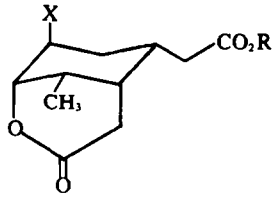
1

2: R = H
2a: R = $OSO_2C_7H_7$

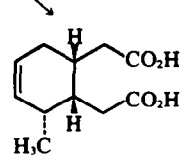
3



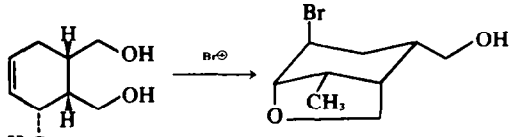
(±) 6; m.p. 110–112°
(−) 6; m.p. 60–61°
$[\alpha]_D$ − 69°



5: X = Br; R = H
5a: X = I; R = H
5b: X = I; R = CH_3
5c: X = H; R = CH_3
5d: X = H; R = H

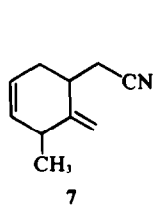


(±) 4; m.p. 150–152°
(−) 4: m.p. 98·5–100°
$[\alpha]_D$ − 55·6°

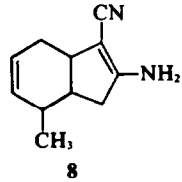


2

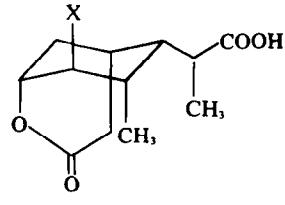
10



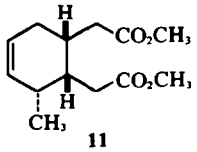
7



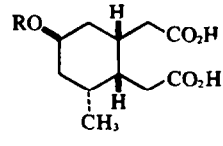
8



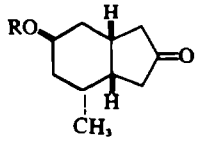
9: X = Br, I



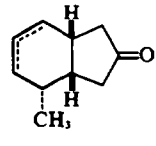
11



12: R = H
12a: R = Ac



13: R = CH_3CO
13a: R = H
13b: R = CH_3SO_2



14

spectrum. The latter observation coupled with the absence of a signal at 1·65δ associated with vinyl methyl permitted assignment of the OH function at the position indicated in **12**. Further, since **12** on acetylation gave an acetoxy diacid, m.p. 155–159° and *not* a lactone (compare **20**→**5d**) the steric orientation of the hydroxyl function was thereby established as *trans* oriented with respect to the other substituents as formulated. In this instance as well, a conformational argument can be advanced as previously cited, although less convincingly, to rationalize the course of the oxymercuration reaction, if it be assumed that the reaction proceeds by initial complexing with the ester function adjacent to the C-3 Me group.

Hydrogenation of the bromolactonic acid **5** as its methyl ester derivative over Raney–Nickel in methanol effected debromination to yield, after saponification, the free lactonic acid **5d**, m.p. 138–140°. By a superior route the iodolactonic acid **5a** in the form of its methyl ester **5b** was reductively deiodinated in essentially quantitative yield to ester **5c** by the method of Barton *et al.*[6] employing chromous acetate and ethyl mercaptan in dimethyl sulfoxide. The lactonic acid **5d** in the racemic series could, furthermore, be resolved independently into its optical antipodes by means of dehydroabietylamine.

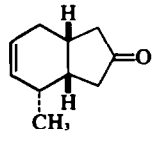
Saponification of **5d** in turn afforded a hydroxy diacid (±) **20**, m.p. 151–153°, differing from the diacid **12** prepared by oxymercuration of **4** and reconvertible to **5d** on treatment with acetic anhydride in pyridine. Conversion of **20** to its dimethyl ester **20a** followed by dehydration with methanesulfonyl chloride in pyridine–benzene at 100° and ensuing saponification quantitatively produced the olefinic diacid (±) **21a**, m.p. 121–122·5°; (−) **21a**, m.p. 102·5–104°; $[\alpha]_D^{Chf}$ −99·6°.

The sequence **4** → **21** has thus cleanly accomplished a migration of the double bond from the **4** to the **3** position. Early in our work direct double bond isomerization experiments on **15** and its derivatives by acid and transition metal catalysis failed to yield the corresponding isomer (e.g., **16**) cleanly.

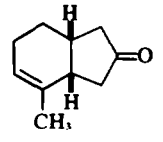
The methyl ester lactonic acid **5c** was submitted to Dieckmann ring-closure with sodium hydride in benzene to yield the tricyclic β-keto lactone **17**. Attempts to alkylate this compound at the α′-position *via* the dianion technique[7] were unrewarding. On the other hand alkylation with one mole of base and methyl iodide afforded **18**.

There are two possibilities for Dieckmann ring-closure of **21**, namely, to give either or both **19** and **22**. Steric considerations would *a priori* favor **22**; however, the fact that **22** was indeed the exclusive isomer formed as far as could be ascertained was an unpredictable as well as fortunate consequence. Since the Dieckmann reaction is reversible, an avenue for diverting any kinetically formed **19** into **22** is available, wherein the latter is the apparent thermodynamically stable isomer. The Dieckmann closure was driven to completion by distilling out the product methanol.

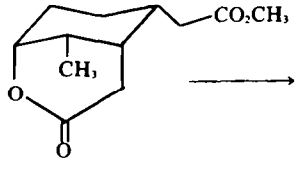
The diester **21** therefore underwent Dieckmann cyclization as mentioned *unidirectionally* to give the β-keto ester **22**. The latter without isolation could be directly alkylated with methyl 7-iodoheptanoate to yield the β-keto diester **23**. De-



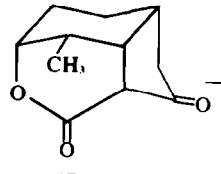
15



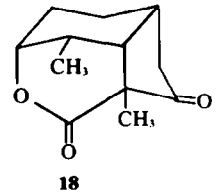
16



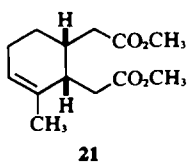
5c



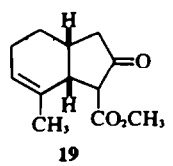
17



18

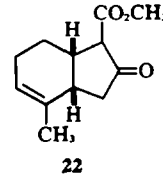


21



19

and/or



22

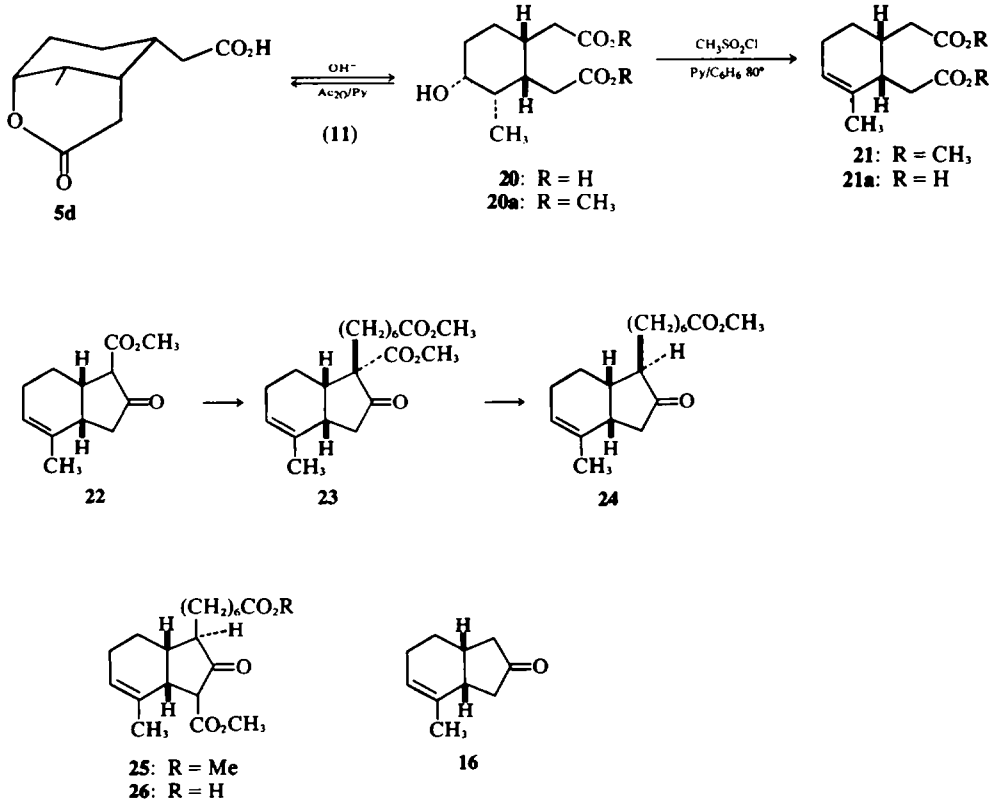
carbomethoxylation of **23** was smoothly effected by refluxing with lithium iodide in collidine[8] followed by concluding methylation (CH_2N_2) to give the ketoheptanoate **24** (6:1 *exo/endo*)[2] in 80–85% overall yield from **21**. The overall yield of (±) **24** from **1** (or resolved **24** from (−) **6**) was 40–45%. This material was identical with (±) **24** obtained from our earlier series.[2] An alternative route **23**→**24** consisted in the retro-Dieckmann transformation **23** → **25** with hot sodium methoxide–methanol followed by hydrolysis and decarboxylation of the latter and concluding methylation with diazomethane to provide **24**. Of incidental interest is the conversion of the diacid **21a** with hot acetic anhydride–sodium acetate to the hydrindenone **16**, likewise formed on decarbomethoxylation of **22**.

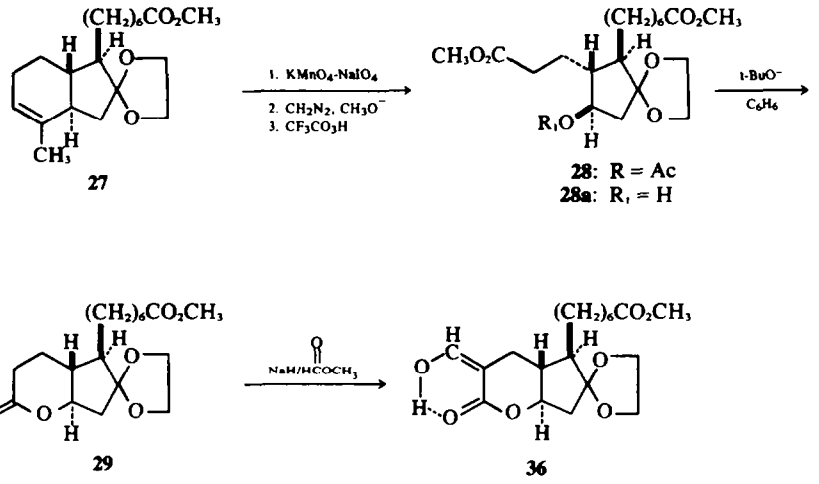
Transformation of the olefinic keto ester **24** to the *seco*-acetoxy diester **28** was effected *via* its dioxalane derivative **27** employing essentially the oxidation–isomerization sequence previously described.[2] Deacetylation of **28** with sodium methoxide–methanol afforded the corresponding hydroxy diester **28a**. Lactonization of **28a** proceeded quantitatively in benzene with a trace of potassium t-butoxide on slow distillation to give the lactone **29** (40–45% from **24**).

It had been the design of the synthetic projection to transform **29** by dehydrogenation with DDQ to the corresponding α,β-unsaturated lactone in anticipation of subsequent oxidative scission. The proposed sequence was consequently studied with the model lactone **30**.[15]* Dehydrogenation of **30** with DDQ in refluxing dioxane proceeded smoothly to yield 60% of an unsaturated lactonic product from which pure *trans* lactone **31** was isolated by chromatography (m.p. 76–77°; λ_{max} 207 nm (ϵ 10,600)). The latter was oxidatively cleaved (OsO_4-$NaIO_4$-dioxane-H_2O) to yield the corresponding aldehyde **32**, identified by conversion to the 2,4-dinitrophenylhydrazone of cyclopent-1-enaldehyde, m.p. 209–212°.[16] Application of the DDQ dehydrogenation procedure to the PG-lactone precursor **29**, however, did not give the desired product, but resulted instead in deep-seated changes in the system proper, initiated by loss of the dioxalane grouping.

Alternatively the model lactone **30** readily formed a crystalline hydroxymethylene derivative **33**, m.p. 156–160° which could be sequentially oxidized to the aldehyde **32a**. This aldehyde was further converted by standard procedure *via* **34** to the 3′-

*Lactone **30** was a 2:1 *trans/cis* mixture as determined by integration of the NMR multiplets at δ 4·18 (*trans*) and 4·75 (*cis*).





epimeric diols **35** and **35a** separable by silica gel chromatography into the respective pure isomers.

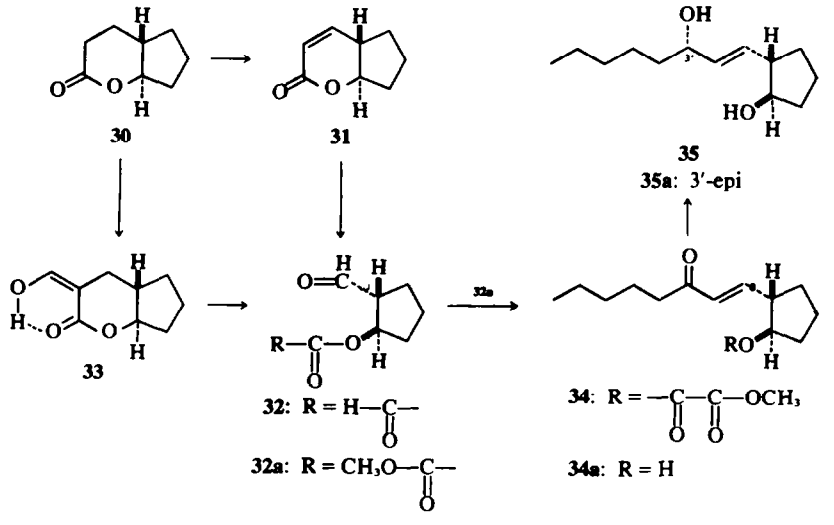
Application of this sequence to the PG-lactone precursor **29** proceeded in the desired manner. The latter was converted to the crystalline hydroxy-methylene lactone (±) **36**, m.p. 88–90° in 80% yield on treatment with sodium hydride in methyl formate at 25°; λ_{max}^{MeOH} 252 nm (ϵ 9,550); $\lambda_{max}^{MeOH/OH^-}$ 286 nm (ϵ 16,800).

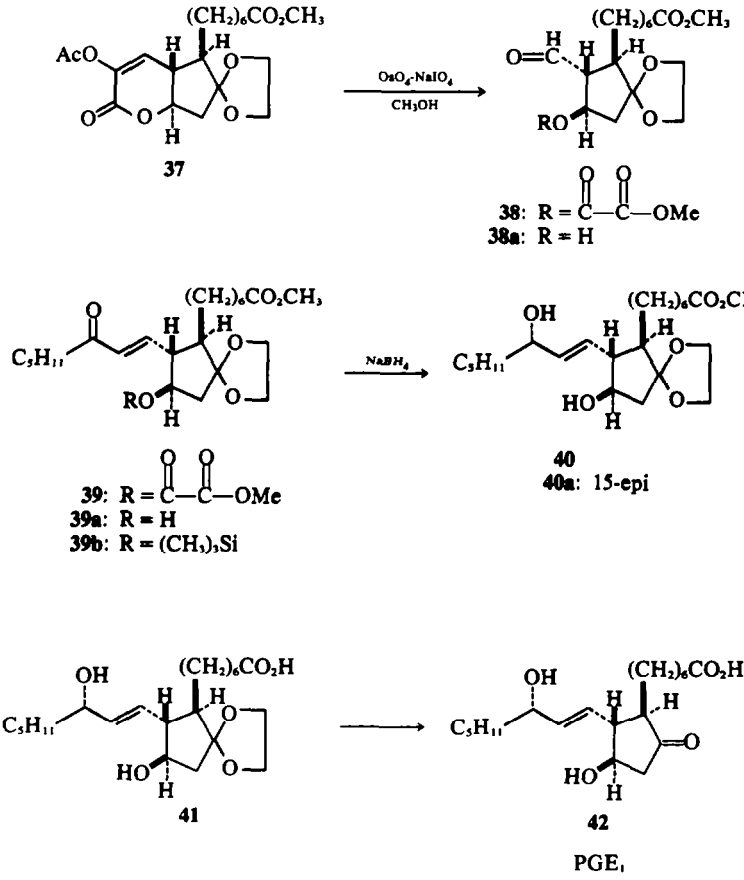
The hydroxymethylene lactone **36** was ozonized in a mixture of methylene chloride and pyridine[9] at −70° with concluding acetylation to afford the enol acetoxylactone (±) **37**, m.p. 82–84°; λ_{max}^{MeOH} 229 nm (ϵ 9,100) (40–45%). Double-bond cleavage of **37** in methanol with OsO_4–$NaIO_4$ gave an intermediate methoxalyl aldehyde **38** which was submitted directly to Wittig condensation with dimethyl 2-oxoheptylphosphonate. The Wittig product **39** thus obtained was treated with ethylenediamine in methanol to selectively remove the oxalyl function[10] and give the dioxalane derivative, **39a**, of 15-dehydroprostaglandin (55% from **37**). Reduction of **39a** in the form of its trimethylsilyl ether **39b** with sodium borohydride in methanol at 0° afforded a 2:1 mixture of **40** (15S) and its 15R epimer **40a** respectively which was readily separable by silica gel chromatography. The 15S isomer **40** on successive saponification (KOH, CH_3OH/25°) to **41** and deketalization (50% aq. HOAc/25°, 3 h) afforded (±) prostaglandin E_1 **42**, m.p. 111–113° (80–85% yield). Similarly, natural series **38** yielded *nat* (−) prostaglandin, m.p. 112–113°; $[\alpha]_D^{Thf}$ − 59° identical with the natural product.

Repetition of this sequence in the enantiomeric series provided *ent* (+) prostaglandin E_1, m.p. 112–113°; $[\alpha]_D^{Chf}$ + 58°.

EXPERIMENTAL

M.ps were taken on a microscope hot-stage apparatus and are uncorrected. UV spectra were determined in





MeOH on a Cary model 11 PMS spectrometer and IR spectra on a Perkin-Elmer Infracord instrument. NMR spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. TLC was carried out on silica gel G coated glass plates and column chromatography on silica gel H columns by the "dry column" technique. The proper elution system was determined by TLC probes, and fractions were collected automatically. VPC determinations were carried out on a Varian–Aerograph No. 200 instrument employing a 5 ft × 0·25 in 20% S.E. 30 on Chrom W Column.

3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *dicarboxylic acid* 2 - *monomethyl ester* **6**. A soln of 3α - *methyl* - 4 - *cyclohexene* - 1α, 2α - *dicarboxylic acid anhydride* **1**[3] (4·98 g; 0·0256 mol) in 30 ml anhyd MeOH was treated dropwise with stirring at 0° with ~20 ml 1·35 N NaOMe soln to a phenolphthalein end-point. The product was isolated by evaporation of the MeOH *in vacuo*, addition of conc NaH_2PO_4 aq and extraction with ether. Crystallization of the residue from ether gave 3·5 g of **6** as prisms, m.p. 104–111°. Recrystallization of the residue from ether gave 3·2 g, m.p. 110–113°. (Found: C, 60·78; H, 7·14. Calc. for $C_{10}H_{14}O_4$: C, 60·61; H, 7·07%). The mother liquors were recycled by concentration and reconversion to starting anhydride (90%) by refluxing with *p*-TSA in xylene. Correspondingly 154 g of anhydride **1** was converted to 105 g of first crop monomethyl ester.

Resolution of the half-ester **6**. A soln of **6** (19·8 g; 0·1 mol) in 100 ml warm EtOAc was treated with 31·4 g (0·1 mol + 10%) of dehydroabietylamine (90 + %). When seeded, the desired salt separated in a pure condition almost immediately. After standing 18 h there was obtained 20·2 g of the DAA salt (*nat* series), m.p. 163–164·5° (80%); $[\alpha]_D^{MeOH}$ − 16·1°. (Found: C, 74·67; H, 9·23; N, 2·75. Calc. for $C_{30}H_{45}NO_4$: C, 74·53; H, 9·31; N, 2·90%). In another run 64 g of **6** in 250 ml acetone treated with 105 g dehydroabietylamine afforded 60 g, after crystallization from $CHCl_3$-acetone, m.p. 163–164° of the desired DAA salt. The mother liquors after due processing and repeated recrystallization from acetone gave 16 g (20%) of diastereomeric salt, m.p. 141–143°; $[\alpha]_D^{MeOH.}$ + 65·32°. (Found: C, 74·83; H, 9·56; N, 2·70%).

(−) *and* (+) 3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *dicarboxylic acid* - 2 - *monomethyl ester* **6**. Regeneration of the free ester acids from their dehydroabietylammonium salts was effected by $NaHCO_3$ extraction of the respective acids from EtOAc suspensions of the corresponding salts followed by acidification, extraction with ether and crystallization from ether–pentane. (−) **6** (*nat* series), m.p. 60–61°; $[\alpha]_D^{CHf}$ − 69°. (Found: C, 60·71; H, 6·85%). (+) **6** (*ent* series), m.p. 60–63°; $[\alpha]_D^{CHf}$ + 68°. (Found: C, 60·59; H, 7·17%).

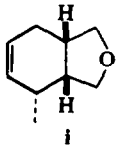
(±) 3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *dimethanol* **2**. A soln of **1** (25 g) in THF (140 ml) was added to a stirred suspension of LAH (10·5 g) in THF (140 ml) at such a rate as to maintain gentle reflux. The mixture was refluxed an additional 3 h, cooled, and the complex decomposed by careful addition of a 1:1 THF-water mixture (100 ml). Af-

ter dilution with $CHCl_3$ (150 ml), the mixture was filtered and the solid washed with 3 portions of $CHCl_3$. Concentration of the filtrate under reduced pressure yielded an oily residue which was dissolved in benzene, dried over $MgSO_4$ and reconcentrated. The viscous oil on pumping for 2 h solidified to a white waxy solid (22·45 g, 96%), m.p. 47–49·5°, (lit. 51·5–52°),[11] IR ($CHCl_3$) 3·00, 6·10μ; NMR ($CDCl_3$) δ 1·03 (3H, d), 3·63 (4H, m), 4·12 (2H, broad s exchangeable with D_2O), 5·30–5·70 (2H, m).

(−) 3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *dimethanol.* To a soln of LAH (10 g) in 150 ml anhyd THF was added dropwise a soln of 12 g diester derived from (−) **6** (CH_2N_2) in 150 ml of THF. The mixture was refluxed 3 h, allowed to stand overnight at room temp and decomposed in the cold with 75 ml of 1:1 H_2O-THF. The product was treated with 150 ml $CHCl_3$ and filtered, followed by washing the collected solid 4× with $CHCl_3$. The filtrate was concentrated *in vacuo* to dryness to give 8·8 g *nat* series **2** $[\alpha]_D^{Chf}$ − 26°. Repetition in the *ent* (+) series gave diol with $[\alpha]_D^{Chf}$ + 24°.

3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *dimethanol* di - p - *toluenesulfonate* **2a.** Using the low temp tosylation procedure,[11] the diol **2** (10 g) in pyridine (30·4 g) was treated with 10% molar excess of *p*-toluenesulfonyl chloride (26·8 g) at − 15° to give **2a** as a white solid (27·7 g, 93%), m.p. 62·5–65°; IR ($CHCl_3$) 6·25, 7·35, 8·40, 8·50μ. (Found: C, 59·20; H, 6·19; S, 13·63. Calc. for $C_{23}H_{28}O_6S_2$: C, 59·47; H, 6·08; S, 13·78%). *Nat* series **2a** had m.p. 52–54°; $[\alpha]_D^{CHCl_3}$ − 12°. (Found: C, 59·73; H, 6·08; S, 13·98%).

This method was found superior to tosylation at room temp in minimizing formation of bicyclic ether **i**, b.p. 45–46°/0·45 mm; M^+ = 138; IR ($CHCl_3$) 6·05, 9·45μ; NMR ($CDCl_3$) δ 1·01 (3H, d), 5·61 (2H, m). (Found: C, 78·06; H, 10·06. Calc. for $C_9H_{14}O$: C, 78·21; H, 10·21%).



i

3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *diacetonitrile* **3.** The Bloomfield and Fennessey procedure[12] was modified by increasing the molar ratio of sodium cyanide to substrate and extending the duration to 18 h at 90–95° in order to achieve complete conversion to **3**. Thus ditosylate **2a** (23·7 g), sodium cyanide (10 g) in DMSO (100 ml), after work up gave **3** as an orange oil (7·81 g, 87%); IR (neat) 4·43, 6·05μ.

3α - *Methyl* - 4 - *cyclohexene* - 1α, 2α - *diacetic acid* **4.** A soln of dinitrile **3** (10 g) in 95% EtOH (25 ml) was added with vigorous stirring to 33% KOH aq (100 ml). The mixture was refluxed for 24 h at which time evolution of ammonia had essentially ceased. EtOH was removed under vacuum and the mixture was extracted with ether. After acidification with 50% HCl, the separated semi-solid was extracted with EtOAc. The combined extracts were washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to dryness yielding a tacky tan solid (11·8 g). Recrystallization of the crude diacid from acetone–ether gave white crystals of (±) diacid **4** (7·9 g, 66%), m.p. 150–152°; NMR (acetone-D_6) δ 0·95 (3H, d), 5·50 (2H, m), 7·52 (2H, broad s). (Found: C, 62·54; H, 7·64. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60%).

Nat series diacid **4**, derived from the homologation of the resolved monomethyl ester **6** had m.p. 98·5–100°; $[\alpha]_D^{Chf}$ − 55·6°. (Found: C, 62·65; H, 7·52. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60%).

Bromoxide **10** *derived from* 3α - *methyl* - 4 - *cyclohexene* - 1α, 2α - *dimethanol* **2.** A soln of **2** (320 mg, 0·002 mol) in 5 ml t-BuOH plus 1 ml of water was treated at 0–5° with N-bromosuccinimide (356 mg; 0·002 mol) with stirring. After 1 h the NBS had all dissolved and the mixture was stored at 0–5° for 16 h. Excess NBS was destroyed with $NaHSO_3$ aq and the solvents were removed on the water pump at 40°. The residue was extracted with ether, dried ($MgSO_4$) and concentrated to dryness to give **10**; NMR ($CDCl_3$) δ 1·03 (J = 7, d, CH_3–CH–) 2·30 (s, OH exchanges with D_2O), 2·70 (J = 7, q, CH–C–CH_3), 3·45 (J = 6, d, $-CH_2OH$), 3·82 (J = 2, d, $-CH_2-O$), 4·0 (J = 4·5, d, –O–CH–CHBr), 4·22 (broad quartet, –CH–CHBr–CH_3).

4α - *Hydroxy* - 5β - *bromo* - 3α - *methyl* - 1α, 2α - *cyclohexanediacetic acid* δ - *lactone* **5.** A soln of **4** (2·54 g) in 40 ml t-BuOH and 8 ml of H_2O was treated with stirring at 0–5° with 2·2 g of N-bromosuccinimide for 1 h and kept at 0° for 16 h. The product **5** was isolated as in the preceding experiment and was crystallized from ether: 1st crop 2·65 g, m.p. 144–146°, 2nd crop 350 mg (86%). (Found: C, 45·37; H, 5·43; Br, 27·47. Calc. for $C_{11}H_{15}O_4Br$: C, 45·36; H, 5·15; Br, 27·49%).

Esterification of **5** in MeOH-ether with diazomethane gave 4α - *hydroxy* - 5β - *bromo* - 3α - *methyl* - 1α, 2α - *cyclohexanediacetic acid methyl ester* δ-*lactone* **5** (R = CH_3), m.p. 76–77°. (Found: C, 47·39; H, 5·72; Br, 25·90. Calc. for $C_{12}H_{17}O_4Br$: C, 47·21; H, 5·57; Br, 26·23%).

Reductive debromination of bromlactonic ester **5** (R = CH_3). A soln of **5** (R = CH_3; 5 g) in 25 ml MeOH containing 670 mg NaOAc (1 mol eq) was treated with Raney-Ni and hydrogenated to cessation of H_2-uptake. After filtration and concentration, the product crystallized from acetone–hexane to give 1·3 g of **5c**, m.p. 83–84° identical with material obtained from the iodolactone series (see below). Hydrogenolytic elimination also occurred in this reaction to give 3-methylcyclohexane diacetic acid monomethyl ester.

4α - *Hydroxy* - 5β - *iodo* - 3α - *methyl* - 1α, 2α - *cyclohexanediacetic acid* δ - *lactone* **5a.** The iodolactonization was carried out by the procedure of Ref 13 with minor modifications. To a clear soln of diacid **4** (12·8 g) in water (150 ml) containing $KHCO_3$ (36·23 g), a soln of I_2 (30·68 g) in water (180 ml) containing KI (65·21 g) was added with stirring. The dark brown soln, protected against light, was stirred for 3·5 h, decolorized with sat $NaHSO_3$ aq, acidified with 2·5N HCl, salted and extracted with EtOAc. The combined extracts were washed with sat NaCl aq containing a small amount of $NaHSO_3$, dried over Na_2SO_4 and concentrated to dryness. The light tan solid (20·04 g, 98%) had m.p. 150–152°. The analytical sample recrystallized from EtOAc–ether had the same m.p.; NMR ($CDCl_3$) δ 1·19 (3H, d), 4·61 (2H, m), 10·70 (1H, s). (Found: C, 38·99; H, 4·28. Calc. for $C_{11}H_{15}O_4I$: C, 39·05; H, 4·44%).

4α - *Hydroxy* - 5β - *iodo* - 3α - *methyl* - 1α, 2α - *cyclohexanediacetic acid* δ - *lactone methyl ester* **5b.** The *iodolactone methyl ester* **5b** was prepared from crude **5a** (49·7 g) in MeOH (250 ml) by treatment with distilled diazomethane at 0°,[14] yield 51 g (99%), m.p. 80–82° (from acetone–ether). (Found: C, 40·99; H, 4·97. Calc. for $C_{12}H_{17}O_4I$: C, 40·91; H, 4·83%).

4α - Hydroxy - 3α - methyl - 1α, 2α - cyclohexanediacetic acid δ - lactone methyl ester **5c**. To freshly prepared chromous acetate[6] (68 g) in DMSO (250 ml) and ethylmercaptan (40 ml), a soln of **5b** (20 g) in DMSO (70 ml) was added with vigorous stirring. The mixture was stirred for 1¼ h at room temp. Ice-water (600 ml) was then added followed by 2·5N HCl (250 ml) and water (250 ml). The dark blue soln was extracted with CH_2Cl_2. The organic extract was washed with water until colorless, dried over $MgSO_4$ and concentrated to dryness. The solid product (12·95 g) was recrystallized from benzene ether to give colorless crystals of **5c** (12·6 g, 98%), m.p. 80·5–82°; IR ($CHCl_3$) 5·75 μ; NMR ($CDCl_3$) δ 1·18 (3H, d), 3·70 (3H, s), 4·51 (1H, m). (Found: C, 63·59; H, 8·13. Calc. for $C_{12}H_{18}O_4$: C, 63·70; H, 8·08%).

4α - Hydroxy - 3α - methyl - 1α, 2α - cyclohexanediacetic acid δ - lactone **5d**. The dehalogenated **5c** (32 g) was selectively saponified by treatment with KOH aq (15·8 g in 280 ml H_2O) for 1 h at room temp. The resulting homogeneous aqueous soln was washed with ether, acidified with 2·5N HCl, salted and extracted with EtOAc. The combined EtOAc extracts after washing with sat NaCl, drying over $MgSO_4$, and concentration gave a solid residue, which on recrystallization from acetone–ether yielded **5d** as white crystals (27·52 g, 91%), m.p. 139–141°; IR ($CHCl_3$) 2·8–4·1, 5·77–5·83 μ. (Found: C, 62·26; H, 7·35. Calc. for $C_{11}H_{16}O_4$: C, 62·26; H, 7·55%).

Resolution of lactonic acid **5d**. To a soln of crude lactonic acid **5d** (53·9 g) in $CHCl_3$ (150 ml) was added a soln of 90 + % ($[\alpha]_D^{pyridine}$ + 56·1) dehydroabietylamine (79 g) in benzene (300 ml). The resulting clear soln yielded a crystalline ppt on standing overnight which was filtered and washed with ether. Two recrystallizations from MeOH–ether gave the DAA-salt (*ent* series) as colorless crystals (37·7 g, 60%), m.p. 169–170°; $[\alpha]_D^{MeOH}$ + 44·4°, unchanged on further crystallization. The combined mother liquors and washings were concentrated to dryness and diluted with ether to yield crystals of the second diastereomeric salt which on two recrystallizations from MeOH–ether gave large needles of the DAA-salt (*nat* series) (20·64 g, 33%), m.p. 148–150° unchanged by further recrystallization and exhibiting no measurable rotation.

Regeneration of lactonic acid. The salt, m.p. 169–170°, was suspended in EtOAc and extracted thoroughly with $KHCO_3$ aq. The combined basic extracts were washed with ether, acidified with 2·5N HCl, salted out and extracted with EtOAc. The organic extract was washed with sat NaCl aq, dried over $MgSO_4$ and concentrated to give in quantitative yield flaky crystals of *ent* **5d**, m.p. 118·5–120·5; $[\alpha]_D^{CHf}$ + 54·5°. The salt, m.p. 148–150°, was processed similarly to give lactonic acid *nat* **5d**, m.p. 118·5–120·5°; $[\alpha]_D^{CHCl_3}$ – 54·6°. The ORD curve (MeOH) of each acid was the mirror image of the other.

4α - Hydroxy - 3α - methyl - 1α, 2α - cyclohexanediacetic acid **20**. A mixture of **5c** (1 g), KOH (2 g) in water (10 ml) was heated on the steam bath, under N_2, for 1·5 h. After cooling CO_2 was bubbled through the soln to pH ~ 8 followed by careful acidification with 2·5N HCl to congo red and extraction with EtOAc to give crystalline **20**, m.p. 151–153°. (Found: C, 57·60; H, 7·63. Calc. for $C_{11}H_{18}O_4$: C, 57·40; H, 7·83%).

Esterification with CH_2N_2 produced **20a** as an oil. *Nat* series **13a** had $[\alpha]_D^{CHCl_3}$ – 6·6°.

3 - Methyl - 3 - cyclohexene - 1α, 2α - diacetic acid dimethyl ester **21**. To a stirred soln of methanesulfonyl chloride (2·05 g) in pyridine (40 ml) at 0°, a soln of **20a** (4 g) in benzene (8 ml) was added dropwise. After stirring at 0° overnight, the mixture was heated at 100–105° for 18 h. The mixture was chilled, diluted with light petroleum and acidified with 6N HCl. After separation of phases the aqueous acid phase was extracted with 1:1 light petroleum–benzene. The combined extracts were washed with $KHCO_3$ aq, sat NaCl aq, dried over $MgSO_4$ and concentrated to yield **21** as an orange oil (3·47 g, 93%); single spot on TLC and single peak on VPC; NMR ($CDCl_3$) δ 1·62 (3H, t), 3·65 (6H, s), 5·38 (1H, m).

3 - Methyl - 3 - cyclohexene - 1α, 2α - diacetic acid **21a**. A mixture of **21** (0·240 g), KOH (0·48 g) in water (2·5 ml) containing MeOH (2 ml) was stirred at room temp overnight. MeOH was removed under reduced pressure, the basic mixture extracted with ether, acidified with 2·5N HCl, salted out, and extracted with EtOAc. Concentration to dryness gave a solid residue (0·189 g, 89%) which crystallized from ether–hexane as long needles of (±) diacid **21a**, m.p. 121–122·5; IR ($CHCl_3$) 5·85 μ; NMR (acetone-D_6) δ 1·65 (3H, t), 5·39 (1H, s), 9·96 (2H, s). (Found: C, 62·36; H, 7·65. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60%).

Nat series diacid **21a** had m.p. 102·5–104°; $[\alpha]_D^{CHf}$ – 99·6°; identical IR and NMR as (±) **21a**. (Found: C, 62·45; H, 7·87. Calc. for $C_{11}H_{16}O_4$: C, 62·25; H, 7·60%).

5β - Hydroxy - 3α - methylcyclohexane - 1α, 2α - diacetic acid **12**. To a stirred mixture of 1·6 g mercuric acetate, 5 ml THF and 5 ml water was added 500 mg of the diester **11** and the mixture was stirred at room temp for 1 h. The mixture was treated with 5 ml of 3 M NaOH followed by a soln of 95 mg of $NaBH_4$ in 5 ml of 3 M NaOH. At the conclusion of the reduction the mercury was separated, the aqueous layer was saturated with NaCl, 10 ml THF added and the organic layer separated, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (480 mg) was slurried twice with ether to give **12**, 323 mg, as micro prisms, m.p. 201–203°; IR ($CHCl_3$) 2·85 and 5·83 μ. (Found: C, 57·47; H, 7·65. Calc. for $C_{11}H_{18}O_5$: C, 57·38; H, 7·78%).

Acetylation of **12** with AC_2O in pyridine provided the corresponding acetate **12a** from ether, m.p. 155–159°; IR ($CHCl_3$) 5·75; and 5·78 μ. (Found: C, 57·22; H, 7·38. Calc. for $C_{13}H_{20}O_6$: C, 57·34; H, 7·40%).

6β - Acetoxy - 4α - methyl - cis - hydrindan - 2 - one **13**. A soln of **12** (1·0 g) in 10 ml Ac_2O was refluxed for 2·5 h followed by addition of 1·0 g NaOAc and continued refluxing with stirring for 2·5 h. The mixture was concentrated *in vacuo* and the residue treated with 10 ml MeOH (exothermic) and filtered. The filtrate was concentrated to a semi-solid mass, water was added and the mixture made basic with $KHCO_3$. The product, obtained by ether extraction of the basic aqueous soln, was an oil which subsequently crystallized to give **13**, m.p. 43–47°; 835 mg; single peak VPC; IR ($CHCl_3$) 5·78 μ. (Found: C, 68·41; H, 8·57. Calc. for $C_{12}H_{18}O_3$: C, 68·54; H, 8·63%).

6β - Hydroxy - 4α - methyl - cis - hydrindan - 2 - one **13a**. The hydrindanone **13** (600 mg) was saponified at room temp with 20% aqueous methanolic KOH for 2 h to give **13a** (600 mg) which crystallized from ether, m.p. 70–72°; IR ($CHCl_3$) 2·8 and 2·9 μ; VPC single peak. (Found: C, 71·22; H, 7·67. Calc. for $C_{10}H_{16}O_2$: C, 71·39; H, 9·59%).

Dehydration of **13a** *to mixture of hydrindenones* **14**. The ketone **13a** (560 mg) in 9 ml pyridine at 0° was treated with 3 g methanesulfonyl chloride for 18 h to give an intermediate mesylate **13b** (600 mg; m.p. 73–75°; IR ($CHCl_3$) 5·75, 7·4 and 8·5 μ). A soln of **13b** (190 mg) in 2 ml dry DMSO under N_2 was heated at 100° for 5 h. The mixture was cooled, diluted with 20 ml water and extracted thoroughly with hexane. The hexane extracts were

washed with water, dried over $MgSO_4$ and concentrated *in vacuo* to afford **14** as a colorless oil, 53 mg; IR ($CHCl_3$) 5·75 and 6·05μ; VPC single peak; NMR ($CDCl_3$) δ 0·93 (3H, d, J = 7), 5·2–5·9 (2H, m), no resonance at δ 1·65 for vinylic Me.

Dieckmann cyclization of lactonic ester to tricyclic keto lactone **5c** → **17**. A mixture of 226 mg (1 mol) of **5c** and 42 mg of NaH (1 mol 57% oil dispersion) in 10 ml dry benzene under N_2 was stirred under reflux for 18 h. The mixture was cooled and treated with stirring with an excess of a sat soln of NaH_2PO_4. The benzene layer was separated, dried and concentrated *in vacuo*. There was obtained 190 mg of **17** as a colorless oil. VPC indicated **17** plus *ca* 5% starting material; NMR ($CDCl_3$) δ 1·13 (3H, d, J = 7), 4·55 (1H, m); mass spec. M^+ (Found: 194. Calc. for $C_{11}H_{14}O_3$: 194).

Alkylation of tricyclic keto lactone **17** → **18**. Cyclization of **5c** (226 mg; 1 mmol was effected as described above. Half of the benzene was removed by distillation, 3·0 g MeI was added and the slurry was refluxed with stirring overnight under N_2. The mixture was cooled, diluted with 25 ml dry benzene and filtered. The filtrate was concentrated *in vacuo* to give a semi-solid residue which was purified on silica gel to give after crystallization from ether 60 mg of **18**, m.p. 145–147°; IR ($CHCl_3$) 5·68 and 5·80μ; NMR ($CDCl_3$) δ 1·20 (3H, d, J = 6), 1·50 (3H, s), 4·60 (1H, m). (Found: C, 69·43; H, 7·81. Calc. for $C_{12}H_{16}O_3$: C, 69·21; H, 7·74%; mass spec. M^+ Found: 208. Calc. 208).

1 - *Carbomethoxy* - 2 - *oxo* - 4 - *methyl* - cis - *hydrind* - 4 - *ene* **22**. A soln of **21** (0·240 g) in benzene (25 ml) was added to a suspension of anhyd t-BuOK (0·224 g) in benzene (5 ml). The mixture was refluxed for 2 h, followed by partial concentration (10 ml) in order to remove the MeOH formed. After cooling, the mixture was acidified with 2·5N HCl, washed with water, $KHCO_3$ aq, sat NaCl aq and dried over $MgSO_4$. Removal of solvent under reduced pressure gave **22** as a colorless oil (0·187 g, 89%). TLC essentially single spot; VPC ~ 95% of **22** and ~ 5% of a compound with retention time similar to that of **16**; IR ($CHCl_3$) 5·72, 5·82, 6·08, 6·20μ; NMR ($CDCl_3$) δ 1·65 (3H, m), 3·72 (3H, 2s, possibly from α and β carbomethoxy groups), 5·50 (1H, m); + $FeCl_3$ test.

cis 3a, 6, 7, 7a - *Tetrahydro* - 1α - (*methoxycarbonyl*) - 4 - *methyl* - 2 - *oxo* - 1β - *indaneheptanoic acid methyl ester* **23**. To a suspension of t-BuOK (2·34 g) in xylene (50 ml), obtained by evaporation and drying of 0·565N t-BuOK in BuOH (36·83 ml), **21** (5·00 g) in xylene (40 ml) was added with stirring. Lower boiling components were distilled off and the mixture was further concentrated by distillation of xylene (~ 40 ml). After refluxing for 2 h methyl 7-iodoheptanoate (6·18 g) in xylene (5 ml) was added dropwise and refluxing was continued for 16 h. On cooling and dilution with benzene solid KI was removed by filtration (3·42 g – 98%). The clear organic filtrate was washed with sat NaCl aq and dried over $MgSO_4$. Concentration to dryness gave **23** as an orange–brown oil (7·5 g) of about 90% purity by VPC. A small sample was purified by dry column chromatography using 2% acetone–chloroform as eluant; IR ($CHCl_3$) 5·70–5·78, 6·15μ; NMR ($CDCl_3$) δ 1·75 (3H, m), 3·70 (3H, s), 3·78 (3H, s), 5·57 (1H m). (Found: C, 68·57; H, 8·53. Calc. for $C_{20}H_{30}O_4$: C, 68·54; H, 8·63%; mass spec. M^+ 350. Calc. 350).

cis 3a, 6, 7, 7a - *Tetrahydro* - 4 - *methyl* - 2 - *oxo* - 1β - *indaneheptanoic acid methyl ester* **24**. A mixture of crude **23** (6·8 g) and lithium iodide dihydrate (21·1 g) in collidine (120 ml) was refluxed for 11 h. The solvent was removed under vacuum and flushed with toluene. The solid residue was dissolved in $NaHCO_3$ aq and extracted twice with benzene–ether in order to remove neutral **26**, a minor by-product, formed in the Dieckmann cyclization (see previous step). The aqueous medium was chilled, acidified with 2·5N HCl, salted and extracted with 1:1 benzene–hexane (3 ×) to minimize extraction of residual 7-iodoheptanoic acid which took place on EtOAc extraction. The combined extracts were washed with sat NaCl, dried over $MgSO_4$ and concentrated to an oily residue. After esterification with CH_2N_2 **24** was obtained as an orange oil (4·15 g) ~ 96% pure VPC. This material was used as such in the subsequent steps. A small sample was freed of volatile impurities very efficiently by steam distillation to give **24** in high purity; IR ($CHCl_3$) broad 5·73–5·76μ; NMR ($CDCl_3$) δ 1·70 (3H, m), 3·68 (3H, s), 5·48 (1H, m). All spectroscopic data were identical with those of **24** prepared in our earlier synthesis.[2] (Found: C, 73·69; H, 9·59. Calc. for $C_{18}H_{28}O_3$: C, 73·93; H, 9·65%). *Nat* series **24** had $[\alpha]_D^{CHCl_3}$ + 11·5°. *Ent* series **24** had $[\alpha]_D^{CHCl_3}$ – 11·8°.

3a, 6, 7, 7a - *Tetrahydro* - 3 - (*methoxycarbonyl*) - 4 - *methyl* - 2 - *oxo* - 1β - *indane* - *heptanoic acid methyl ester* **25**. Alkylated **23** (0·272 g) in MeOH (5 ml) was refluxed for 2·5 h with 2N NaOMe (5 ml). Excess MeOH was partially distilled off, and the remaining MeOH was removed by azeotropic distillation by gradual addition of benzene (40 ml) to the refluxing mixture. The resulting gelatinous solid in benzene was heated at reflux for an additional 2 h. The mixture was chilled, quenched with AcOH (2 ml), poured into ice-water and the phases separated. After extraction with benzene, the combined extracts were washed with sat NaCl aq and dried over $MgSO_4$. On concentration to dryness a yellow oil (0·210 g) was obtained which by TLC (2% acetone–$CHCl_3$) was principally polar material. This was purified by dry column chromatography and proved to be **26** (0·123 g, 50%); positive $FeCl_3$ test; IR ($CHCl_3$) 3–4, 5·73, 5·75, 5·81μ; NMR ($CDCl_3$) δ 1·61 (3H, m), 3·78 (3H, s), 5·58 (1H, m), 10·53 (1H, s—exchangeable with D_2O). This substance was stable to decarboxylation in refluxing xylene. The partial saponification may have been caused by traces of moisture in the MeOH employed in the retro Dieckmann reaction.

Esterification of the above acid with CH_2N_2 in ether gave single spot (TLC) diester **25**; IR ($CHCl_3$) 5·72, 5·78μ; NMR ($CDCl_3$) δ 1·62 (3H, m), 3·63 (3H, s), 3·75 (3H, s), 5·50 (1H, broad s); $\lambda_{max}^{MeOH+OH}$ 289 nm (ε 10,480). (Found: C, 68·59; H, 8·45. Calc. for $C_{20}H_{30}O_5$: C, 68·54; H, 8·63%).

Diester **25** (0·128 g), KOH (0·085 g) in water (1·5 ml) were stirred overnight. The saponification mixture was cidified with 2·5N HCl, extracted with ether, washed with NaCl and dried over $MgSO_4$. Removal of solvent gave an orange–brown oil (0·111 g, 89%) which was decarboxylated on refluxing for 2·5 h in xylene. Evaporation of the solvent and esterification with CH_2N_2 gave **24** with TLC, VPC, IR and NMR identical with an authentic sample. The dinitrophenyl hydrazone had m.p. 90·5–92·5°, and the mixed m.p. with an authentic sample was 91–93°.

2β - *Hydroxycyclopentane* - 1α - cis - *prop* - 2 - *enoic acid lactone* **31**. A mixture of **30**[15] (*trans*/*cis* 2:1 4·0 g) and dichlorodicyanoquinone (8·0 g) in 50 ml of peroxide-free dioxane was stirred under reflux for 66 h. The mixture was diluted with 100 ml of hexane, cooled and filtered. The filtrate was concentrated *in vacuo* to a dark oil. The latter was dissolved in 25 ml ether and treated with stirring with 100 ml cyclohexane. The resulting sus-

pension was filtered through celite and concentrated to 3·3 g of oil ($\lambda_{max}^{isooctane}$ 207mμ, ε 449). The crude product was chromatographed on 150 g of silica gel H and eluted with ether to yield 0·6 g (23%) of the *trans*-unsaturated lactone **31**; m.p. 76–77° (from ether–hexane); $\lambda_{max}^{isooctane}$ 207mμ (ε 10,700); IR ($CHCl_3$) 5·80μ; NMR ($CDCl_3$) δ 4·16 (1H, m), 5·98 (1H, d,d, J = 9, J = 3), 7·05 (1H, d,d J = 9, J = 2). (Found: C, 69·39; H, 7·46. Calc. for $C_8H_{10}O_2$: C, 69·54; H, 7·30%).

Cyclopentene aldehyde 2,4-dinitrophenylhydrazone. A soln of 400 mg of the unsaturated **31** in 5 ml dioxane and 10 ml water was treated with 6 ml of 1% aqueous osmium tetroxide and the mixture was stirred at room temp for 1·5 h. Sodium periodate, 1·2 g, was added portionwise over a period of 1·5 h and the resulting suspension was stirred an additional 1·5 h. The mixture was filtered and the filtrate saturated with NaCl aq and thoroughly extracted with $CHCl_3$. The dried extract (Na_2SO_4) was filtered and concentrated *in vacuo* to afford *ca* 400 mg of **32** as an unstable oil. The latter in 5 ml MeOH was treated with excess methanolic 2,4-dinitrophenylhydrazine reagent and warmed on the steam bath for 5 min. There was obtained, after cooling and filtration, 300 mg of dark red hydrazone derivative. Recrystallization from EtOAc gave the 2,4-dinitrophenylhydrazone of cyclopentene aldehyde, m.p. 209–212° (lit.[16] 214–216°); $\lambda_{max}^{CHCl_3}$ 377 nm (ε 27,000) (lit.[16] 377 nm (ε 27,600).

2-Hydroxymethylene derivative of trans-β-*2-hydroxycyclopentyl propionic acid lactone* **33**.* A soln of **30** (5 g; 0·0356 mol) in 285 ml dry benzene was treated, under dry N_2, with 8·9 g of 48% sodium hydride (0·178 mol). A trace (0·05 ml) of MeOH was added to initiate the reaction, and the suspension was stirred under N_2 for 15 min, at which time 14·2 ml (0·178 mol) of ethyl formate (freshly distilled from K_2CO_3) was added at a rapid dropwise rate. The mixture was stirred at room temp for 2½ h, whereupon another 14·2 ml (0·178 mol) of ethyl formate was added, and the mixture stirred under N_2, at room temp overnight. The mixture was diluted with 500 ml of ether and extracted successively with H_2O, and 50 ml of 10% Na_2CO_3. The combined aqueous washes were back-extracted with 75 ml of ether and then acidified by saturating with solid NaH_2PO_4 producing an amorphous solid that was filtered and then crystallized from ether to yield 3 g (50%) of **33** in several crops with m.p. 156–160°; λ_{max}^{EtOH} 252 nm (ε 9,600); IR ($CHCl_3$) 2·8–3·2, 6·00, 6·25μ. (Found: C, 63·85; H, 6·87. Calc. for $C_9H_{12}O_3$: C, 64·27; H, 7·19%).

Enol methyl ether of **33** prepared by addition of CH_2N_2 in ether to **33** in MeOH, m.p. 86–90° (from ether–hexane); λ_{max}^{MeOH} 253 nm (ε 12,000); IR ($CHCl_3$) 5·85, 6·15, 6·30μ. (Found: C, 65·69; H, 7·52. Calc. for $C_{10}H_{14}O_3$: C, 65·91; H, 7·74%).

trans - 2 - *Methoxalyloxycyclopentane aldehyde* **32a**. O_3 was passed into a soln of 470 mg of **33** in 10 ml pyridine[9] and 50 ml CH_2Cl_2 at − 70° until a deep blue color persisted. N_2 was bubbled through the mixture until excess O_3 was removed and continued while the temp was allowed to rise to 25°. Concentration *in vacuo* afforded the corresponding α-keto lactone as a semi-solid mass (IR C=O 5·65–5·8μ; positive $FeCl_3$ test) which was enol acetylated directly with Ac_2O and pyridine at room temp. The excess reagents were removed *in vacuo* and the residue was crystallized from ether–hexane to give 440 mg (82%) of lactone enol acetate (m.p. 65–68°; IR ($CHCl_3$) 5·65, 5·75 and 6·10μ; UV λ_{max}^{MeOH} 212 nm (ε 8,200).

To a stirred soln of lactone enol acetate (400 mg) in 40 ml MeOH was added 1·2 ml of 1% OsO_4 aq and the mixture was stirred for 1 h. The black mixture was treated with 860 mg pulverized $NaIO_4$ and stirred overnight at room temp. The mixture was diluted with 100 ml ether, filtered, dried over $MgSO_4$ and concentrated at 25° to afford essentially pure **32a** (410 mg, 100%) as an oil; IR ($CHCl_3$) 3·7, 5·64, 5·72, 5·80μ; NMR ($CDCl_3$) δ 3·87 (3H, s), 5·50 (1H, m), 9·77 (1H, d, J = 2).

The above product on treatment with methanolic 2,4-dinitrophenylhydrazine reagent afforded in quantitative yield the 2,4-dinitrophenylhydrazone of cyclopentene aldehyde,[16] m.p. and mixed m.p. 210–213°.

trans 2 - *Hydroxy* - 1 - (3 - *oxo* - trans - *oct* - 1 - *enyl*)*cyclopentane methyl oxalate* **34**. Under anhydrous conditions and a N_2 atmosphere a stirred suspension of 96 mg of NaH (49% in oil) in 25 ml dry THF at 0° was treated with a soln of 480 mg of dimethyl 2-ketoheptylphosphonate in 5 ml of THF and the mixture stirred at 0° for 30 min. A soln of **32a** (400 mg) in 5 ml THF was added and the mixture allowed to warm to room temp and stirred for 1 h. The mixture was poured into a stirred mixture of ice and sat NaH_2PO_4 aq and extracted with EtOAc. The extract was washed with NaH_2PO_4 aq, dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. The latter was chromatographed on 18 g silica gel H eluting with 5% acetone in chloroform. There was obtained 386 mg (66%) of **34** as a pale yellow oil; IR ($CHCl_3$) 5·65, 5·73, 5·82, 5·98 and 6·13μ. A sample was evaporatively distilled at 125–130° at 0·02 mm for analysis. (Found: C, 64·45; H, 8·16. Calc. for $C_{16}H_{24}O_5$: C, 64·87; H, 8·15%).

Conversion of **34** *to prostaglandin model end products* **35** *and* **35a**. A stirred soln of **34** (386 mg) in 30 ml of MeOH was treated with 78 mg of ethylenediamine[10] and stirred at room temp for 45 min (isolation at this stage afforded **34a**; λ_{max}^{MeOH} 230 nm (8900).

The mixture was then cooled to 0° and 98 mg of $NaBH_4$ was added and stirring continued for 30 min. Cold sat NaH_2PO_4 aq (50 ml) was added and the mixture was extracted thoroughly with EtOAc. The extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield 216 mg of epimeric diols (TLC R_f 0·4 and 0·6, 20% Me_2CO–$CHCl_3$). Dry column chromatography of the mixture on 20 g of silica gel H and elution as above afforded: *trans*-**35a** (54 mg) with R_f 0·6 and *trans*-**35** (60 mg) with R_f 0·4 as colorless oils. The configurational assignments are based on analogy with the R_f values of related prostaglandins. The respective IR spectra ($CHCl_3$) are very similar and relatively featureless, 2·75, 2·90μ (OH); NMR ($CDCl_3$) **35** δ 0·87 (3H, t, J = 7), 3·8 (2H, broad m), 5·60 (2H, asym m); **35a** δ 0·87 (3H, t, J = 7), 3·8 (2H, broad m), 5·48 (2H, sym m).

2α - (2 - *Carboxyethyl*) - 3β - *hydroxy* - 5 - *oxo* - 1β - *cyclopentaneheptanoic acid methyl ester, δ-lactone,* 5-*cyclic ethylene acetal* **29**. Intermediates **27**, **28** and **28a** were prepared as described previously.[2] *Nat* series **27** had $[\alpha]_D^{Chf}$ − 26·0°. *Nat* series **28a** had $[\alpha]_D^{Chf}$ + 14·7°. *Ent* series **28a** had $[\alpha]_D^{Chf}$ − 13·3°.

Traces of moisture were removed from a soln of **28a** (2·05 g) in benzene (375 ml) by distilling off 30 ml of solvent. t-BuOK in t-BuOH (0·20 ml of 0·96M) was added and the mixture was refluxed with slow distillation. In 3 h 230 ml of distillate was collected, the mixture was chilled, added to sat NaH_2PO_4 aq and extracted with benzene. The organic extract was washed with sat NaCl aq, dried

*We are grateful to R. D. Hoffsommer for the first preparation of this compound.

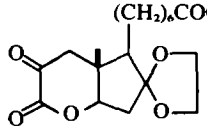
over Na_2SO_4 and concentrated to dryness under vacuum to give **29** as a colorless oil, 1·82 g (100%); TLC single spot R_f 0·5 (20% acetone–$CHCl_3$); IR ($CHCl_3$) 5·75, 5·78, 10·55μ; NMR ($CDCl_3$) δ 3·70 (3H, s), 3·93 (4H, broad s), 4·2 (1H, m).

2α - (2 - Carboxy - 2 - formylethyl) - 3β - hydroxy - 5 - oxo - 1β - cyclopentaneheptanoic acid methyl ester, δ-lactone, 5-cyclic ethylene acetal **36**. To a stirred soln of **29** (1·82 g) in methyl formate (38 ml) under N_2 at 0° was added in 4 portions 50% NaH-white oil dispersion (285 mg). After 2 h at 0° and 3 h at room temp the mixture was concentrated to dryness under vacuum. The gummy residue on trituration with ether at 0° crystallized, yielding the yellow brown Na salt of **36** which was filtered off and washed with ether. Concentration of the filtrate gave 350 mg of a mixture of **28a** and the corresponding formate. Presumably reaction of **29** with methoxide generated from methyl formate during the formylation yields **28a** and subsequent transesterification yields the corresponding formate. Treatment of this mixture with methanolic NaOMe gave **28a** (IR, TLC) which was efficiently recycled to **29**.

The Na salt of **36** was partitioned between EtOAc and cold conc NaH_2PO_4 aq. The aqueous layer was extracted further with 1:1 EtOAc–C_6H_6. The organic extract was dried over Na_2SO_4 and concentrated under vacuum to yield **36** as a solid residue (1·62 g–80%) which was ozonized without further purification. Crystallization of an aliquot from ether–hexane gave plates, m.p. 88–90°; λ_{max}^{MeOH} 229 nm (ε 9550), $\lambda_{max}^{MeOH\,OH^-}$ 286 nm (ε 16,800); IR ($CHCl_3$) 2·8–3·3, 5·78, 6·00, 6·22, 10·55μ; deep purple color with 1% methanolic $FeCl_3$. (Found: C, 62·17; H, 7·70. Calc. for $C_{19}H_{28}O_7$: C, 61·94; H, 7·66%).

Nat series **36** had m.p. 80–81°.

2α - (2 - Acetoxy - 2 - carboxyvinyl) - 3β - hydroxy - 5 - oxo - 1β - cyclopentaneheptanoic acid methyl ester, δ-lactone, 5-cyclic ethylene acetal **37**. A soln of **36** (1·80 g) in CH_2Cl_2 (20 ml) and pyridine (14 ml)[9] was ozonized (~5% O_3 in O_2) at ~ −70° until the characteristic blue color of O_3 appeared. Excess O_3 was removed by bubbling N_2 through the mixture, which was then concentrated to dryness. In one run an aliquot of the product, α-keto–lactone ii, was crystallized from ether–hexane, m.p. 107–115°, UV (MeOH) no max above 200 nm; IR ($CHCl_3$) 5·68, 5·72, 10·55μ. This material decomposed on standing at room temp.



ii

Normally the total O_3 product (~ 1·7 g) was directly acetylated in Ac_2O (3 ml) and pyridine (6 ml) for 18 h at room temp. Xylene (15 ml) was added and volatiles were removed on the oil pump. The residue was chromatographed on 75 g silica gel H eluting with 5% acetone–$CHCl_3$ to yield **37** (800 mg, 42%), m.p. 82–84° (from ether); λ_{max}^{MeOH} 229 nm (ε 9100); IR ($CHCl_3$) 5·65, 5·75, 6·10, 11·55μ; NMR ($CDCl_3$) δ 2·22 (3H, s), 3·70 (3H, s), 3·92 (4H, m), 4·43 (1H, m), 6·67 (1H, d, J = 2). (Found: C, 60·49; H, 7·16. Calc. for $C_{20}H_{28}O_8$: C, 60·59; H, 7·12%).

Nat series **37** was a colorless oil; $[\alpha]_D^{CHCl_3}$ + 29°. *Ent* series **37** had $[\alpha]_D^{CHCl}$ − 30°.

2α - Formyl - 3β - hydroxy - 5 - oxo - 1β - cyclopentaneheptanoic acid methyl ester, 5-cyclic ethylene acetal **38a** *and its 3-methoxalyl ester* **38**. To a soln of **37** (700 mg) in MeOH (25 ml) stirred at room temp was added 2·1 ml of 1% OsO_4 in MeOH. After 15 min powdered $NaIO_4$ was added in portions over 3 h to the stirred soln. After an additional 2 h EtOAc was added, the mixture was filtered and the pptated $NaIO_3$ washed with EtOAc. The filtrate was concentrated to dryness, the residue taken up in EtOAc-benzene 1:1 and the latter soln washed with water, sat NaCl aq, decolorized with charcoal and dried over Na_2SO_4. Concentration under vacuum gave **38** + **38a** (650 mg) as a viscous yellow oil; IR ($CHCl_3$) 2·80, 3·68, 5·62, 5·70, 5·78, 10·52μ; NMR ($CDCl_3$) δ 3·66 (s, $-OCH_3$), 3·90 (m, $-OCH_3$ and $-OCH_2CH_2O-$), 5·32 (m, $-\overset{|}{H}-\overset{||}{C}-O-\overset{||}{C}-\overset{|}{C}-OMe$) 9·80 (J = 2, d, HC–). TLC–R_f (30% O O O) acetone–$CHCl_3$), 0·6 (~ 85–90% methoxalyl aldehyde **38**) and 0·4 (~ 10–15% hydroxy aldehyde **38a**).

15-Dehydroprostaglandin E_1 *methyl ester cyclic ethylene acetal* (**39a**). Dimethyl 2-oxoheptylphosphonate (350 mg) in THF (4 ml) was added by syringe to a suspension of 75 mg 50% NaH–white oil dispersion in THF (11 ml) at 0° under N_2. After stirring 30 min at 0°, aldehyde **38** + **38a** (630 mg) in THF (6 ml) was added. After 2 h at room temp, the mixture was added to cold conc NaH_2PO_4 aq and extracted with EtOAc. The latter extract was dried over Na_2SO_4 and concentrated to dryness. The residue [**39** (major) and **39a** (minor by TLC)] was dissolved in MeOH (6 ml) at 0° and ethylenediamine (100 mg)[10] in MeOH (4 ml) was added. After 45 min at room temp MeOH was removed on the water pump and the residue partitioned between EtOAc and conc NaH_2PO_4 aq. The aqueous phase was extracted with EtOAc, and the combined organic extracts dried over Na_2SO_4 and concentrated under vacuum. The residue in which **39** was absent (TLC) was chromatographed on 35 g of silica gel H eluting with 30% acetone–$CHCl_3$ to give pure **39a** as a colorless oil (315 mg); λ_{max}^{MeOH} 232 nm (ε 12,300); IR ($CHCl_3$) 2·85, 5·80, 5·92, 6·00, 6·18, 10·55μ; NMR ($CDCl_3$) δ 0·83 (3H, t, J = 6), 3·63 (3H, s), 3·92 (5H, m, $-OCH_2CH_2-O$ and H–C–OH), 6·17 ($C_{14}H$, d, J = 16), 6·73 ($C_{13}H$, dd, $J_{13,14}$ = 16, $J_{13,12}$ = 8). An additional 80 mg of slightly less pure **39a** was also obtained (55% from **37**).

Nat series **39a** had $[\alpha]_D^{CHCl_3}$ + 9·4°. *Ent* series **39a** had $[\alpha]_D^{CHCl_3}$ − 8·0°.

Prostaglandin E_1 *methyl ester cyclic ethylene acetal* **40** *and its 15-epimer* **40a**. To a soln of **39a** (180 mg) in pyridine (3 ml) and benzene (3 ml) at 0° was added 1 ml of O,N-*bis*-(trimethylsilyl)trifluoroacetamide containing 1% trimethyl chlorosilane. After 2 h at room temp TLC (25% acetone–$CHCl_3$) of a probe showed complete conversion to **39b**. Xylene (10 ml) was added to the mixture which was then taken to dryness under oil pump vacuum. To the residue (**39b**) at − 5° was added a soln of $NaBH_4$ (30 mg) in MeOH (5 ml) precooled to − 5°. The mixture was stirred 35 min at − 5°, added to cold conc NaH_2PO_4 aq and extracted with EtOAc. The extract was dried over Na_2SO_4 and the solvent removed on the water pump. MeOH (4·5 ml) and water (3 ml) were added, and the mixture was warmed on the steam bath 20 min. Toluene was added and the solvents were then removed under vacuum to give 170 mg of reduction product **40** + **40a**. The components were cleanly separated by dry column chromatography on silica gel H (40 g) eluting with 50% acetone–$CHCl_3$. The more mobile component **40a** was obtained as a colorless

oil (51 mg, 28%) R_f 0·5; IR ($CHCl_3$) 2·75, 2·90, 5·78, 10·30, 10·55μ; NMR ($COCl_3$) δ 0·90 (3H, t), 3·67 (3H, s), 3·93 (4H, broad s), 4·13 (1H, m), 5·62 (2H, m).

The more polar component **40** (90 mg, 50%) R_f 0·4 was obtained crystalline, m.p. 54–56° (ether–hexane); IR ($CHCl_3$) similar to that of **40a** except for minor differences in the fingerprint region; NMR ($CDCl_3$) δ 0·90 (3H, t), 3·67 (3H, s), 3·95 (5H, m), 5·53 (2H, m). Mass spec. bis–$SiMe_3$ ether; M^+ found 556; calc. 556. (Found: C, 66·96; H, 9·77. Calc. for $C_{23}H_{40}O_6$: C, 66·56; H, 9·64%).

Nat series **40** had $[\alpha]_D^{CHCl_3} = 0°$.

Prostaglandin E_1 *cyclic ethylene acetal* **41**. To a stirred soln of **40** (65 mg) in MeOH (1·1 ml) at 0° was added 60 mg of KOH in 2·5 ml H_2O. The mixture was stirred 3 h at room temp. It was then added to cold dil $KHCO_3$ aq and extracted once with 1:1 ether–hexane. NaH_2PO_4 was added in portions to pH ~ 5 and the mixture was extracted with EtOAc. The organic extract was dried over Na_2SO_4 and taken to dryness on the water pump to give single spot **41** (R_f 0·3, F_6 system[17]) which crystallized in ether–hexane, m.p. 81–83° (racemic)[2], 79–81° (*nat* series).

Nat (−) *Prostaglandin* E_1 **42**. A soln of *nat* series **41** (total product − 58 mg) was treated with 1:1 AcOH–H_2O (3 ml) at room temp as previously described for the racemic series.[2] The crystalline residue (50 mg), essentially single spot (−) **42** (R_f 0·35, F_6 system[17]), on crystallization from EtOAc–hexane gave prismatic needles (31 mg), m.p. 112–113°; $[\alpha]_D^{THF}$ − 59° identical with an authentic sample. (Found: C, 67·82; H, 9·58. Calc. for $C_{20}H_{34}O_5$: C, 67·76; H, 9·67%).

An additional 8 mg of (−) **42**, (~ 80% combined yield) m.p. 109–112° was obtained as a second crop. TLC of the mother liquor indicated the major component to be **42** with minor mobile impurities.

Ent series **42** had $[\alpha]_D^{THF} + 58°$.

REFERENCES

[1]For a preliminary account of part of this work see: H. L. Slates, Z. S. Zelawski, D. Taub and N. L. Wendler, *Chem. Comm.* 304 (1972)

[2]D. Taub, R. D. Hoffsommer, C. H. Kuo, H. L. Slates, Z. S. Zelawski and N. L. Wendler, *Ibid.* 1258 (1970); *Tetrahedron* **29**, 1447 (1973)

[3]*Organic Reactions* Vol. 4, p. 44; Wiley., N.Y., 1948, O. Diels and K. Alder, *Liebigs Ann.* **470**, 62 (1929)

[4]G. P. Kugatova-Shein-Yakina, U. M. Andrew and S. A. Kazaryan, *Zh. Org. Chim.* **2**, 2025 (1966) (Engl. Trans.)

[5]N. L. Wendler, D. Taub and C. H. Kuo, *J. Org. Chem.* 1510 (1969)

[6]D. H. R. Barton, N. K. Basu, R. H. Hesse, F. S. Morehouse and M. M. Pechet, *J. Am. Chem. Soc.* **88**, 3016 (1966)

[7]*Cf Organic Reactions* Vol. 17, p. 155, Wiley, N.Y. (1969)

[8]E. Taschner and B. Liberek, *Roczniki Chemii* **30**, 323 (1956); F. Elsinger, J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta* **43**, 113 (1960)

[9]*Cf* D. Yang and S. W. Pelletier, *Chem. Comm.* 1055 (1968)

[10]R. D. Hoffsommer, H. L. Slates, D. Taub and N. L. Wendler, *J. Org. Chem.* **27**, 353 (1962)

[11]B. H.. Mahoud and K. N. Greenlee, *Ibid.* **27**, 2369 (1962)

[12]J. J. Bloomfield and P. V. Fennessey, *Tetrahedron Letters* 2272 (1964)

[13]E. E. Van Tamelen and M. Shamma, *J. Am. Chem. Soc.* **76**, 2315 (1964)

[14]J. T. DeBoer and H. J. Backer, *Org. Syn. Coll.* Vol. IV, p. 250 (1963)

[15]S. Dev and C. Rai, *J. Indian Chem. Soc.* **34**, 226 (1957)

[16]I. Heilbron, E. R. H. Jones, J. B. Toogood and B. C. L. Weedon, *J. Chem. Soc.* 1827 (1949)

[17]N. H. Anderson, *J. Lipid Research* **10**, 316 (1969)