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Anthracyclines. X. The Enantiospecific Synthesis of (−)-(7*R*)-7-Acetyl-7-hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalen-1(4*H*)-one; a Type I Chiral Dienone for the Synthesis of 7-Deoxydaunomycinone

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Abstract

8-Benzyloxy-5-methoxy-3,4-dihydronaphthalene-2-carboxylic acid (34) has been prepared by a four-step sequence from 5-methoxy-8-hydroxy-3,4-dihydronaphthalen-1(2*H*)-one. Condensation of the unsaturated acid (34) with ethyl (*S*)-prolinate in the presence of dicyclohexylcarbodiimide afforded the amide (35) which was enantioselectively cyclized to the bromo lactone (37). Debromination with tributyltin hydride and subsequent reaction of the lactone with methyllithium afforded (−)-(2*R*)-2-acetyl-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol. Removal of the benzyl ether by catalytic hydrogenation and oxidation of the resulting phenol with thallium(III) nitrate afforded the title chiral dienone.

Introduction

The continuing development of new anthracycline antineoplastic agents[1–5] has resulted in the recognition of a number of clinically useful chemotherapeutic agents, including daunomycin (1),[6] adriamycin (2),[7] aclacinomycin A (3)[8] and the fully synthetic 4-demethoxydaunomycin (4).[9] The need for large quantities of these drugs for clinical use has led to a search for cheap, practical syntheses of these compounds.

[1] Arcamone, F., in 'Anticancer Agents Based on Natural Product Models' (Eds J. M. Cassidy and J. D. Pouros) (Academic Press: New York 1980).
[2] Yoshimoto, A., Matsuzawa, Y., Oki, T., Takeuchi, T., and Umezawa, H., *J. Antibiot.*, 1981, **34** (8), 951.
[3] Horton, D., and Priebe, W., *J. Antibiot.*, 1981, **34** (8), 1019.
[4] Arcamone, F., 'Doxorubicin—Anticancer Antibiotics' (Academic Press: New York 1981).
[5] El Khadem, H. S., (Ed.), 'Anthracycline Antibiotics' (Academic Press: New York 1982).
[6] Di Marco, A., Gaetini, M., Dorigott, L., Soldati, M., and Ballini, O., *Tumori*, 1963, **49**, 203.
[7] Di Marco, A., Gaetini, M., and Scarpinato, B. M., *Cancer Chemother. Rep.*, 1969, **53**, 33.
[8] Mathe, G., Bayssas, M., Gouvela, J., Dantcher, D., Ribaud, P., Machover, D., Misset, J. L., Schwarzenberg, L., Jasmin, C., and Hayat, M., *Cancer Chemother. Pharmacol.*, 1978, **1**, 259.
[9] Arcamone, F., Bernardi, L., Giardino, P., Patelli, B., Di Marco, A., Casazza, A. M., Pratesi, G., and Reggiani, P., *Cancer Treatment Rep.*, 1976, **60**, 829.

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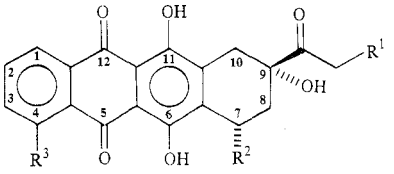
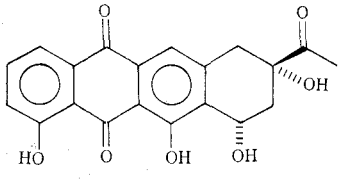
This synthetic task can be divided into three parts:[5] (i) a synthesis of the aglycone, (ii) a synthesis of the sugar residue and (iii) the linking of these two components. To date, the preparation of the aglycones has received most attention and two features, each requiring careful control, dominate the design and synthesis of these molecules. These are the incorporation of the correct regiochemistry in regard to the terminal substituents, and the introduction of the correct chirality into the molecule. Whilst Kishi[10] has achieved control of both these aspects in his recent synthesis of 11-deoxydaunomycinone (5), no comparable synthesis of the natural antipode of the first generation anthracyclinone, daunomycinone (6), has been reported. However, individual solutions to the control of regiochemistry and of chirality have each been described in the anthracycline area.



	R^1	R^2	R^3
(1)	H	ODa	OMe
(2)	OH	ODa	OMe
(4)	H	ODa	H
(6)	H	OH	OMe
(7)	H	OH	H
(20)	H	H	H



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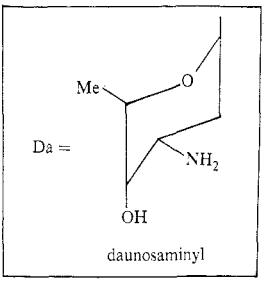
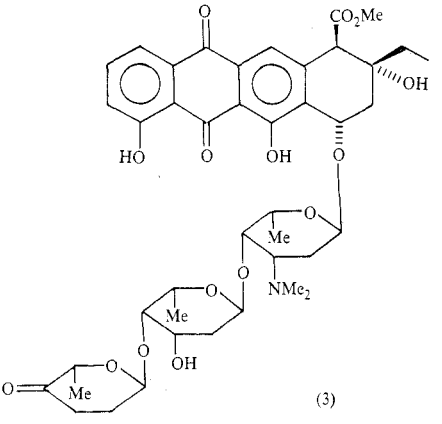


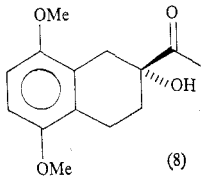
daunosaminyl



(3)

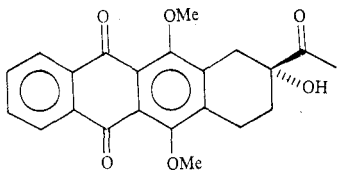
The preparation of the chiral (+)-4-demethoxydaunomycinone (7), a compound devoid of regiochemical challenge, has been achieved by Hassall[11,12] and Arcamone.[13] In both cases a resolution step was required at some stage in the synthesis. Some success has been achieved in recycling the unwanted enantiomer from the resolution step and this adds to the overall viability of these syntheses; however, the development of an efficient enantiospecific synthesis of (+)-4-demethoxydaunomycinone (7) and

[10] Sekizaki, H., Jung, M., McNamara, J. M., and Kishi, Y., *J. Am. Chem. Soc.*, 1982, **104**, 7372.
[11] Broadhurst, M., Hassall, C., and Thomas, G. J., *J. Chem. Soc., Perkin Trans. 1*, 1982, 2239.
[12] Broadhurst, M., Hassall, C., and Thomas, G. J., *J. Chem. Soc., Perkin Trans. 1*, 1982, 2249.
[13] Del Nero, S., Gandalfi, C., Lombardi, P., and Arcamone, F., *Chem. Ind. (London)*, 1981, 810.



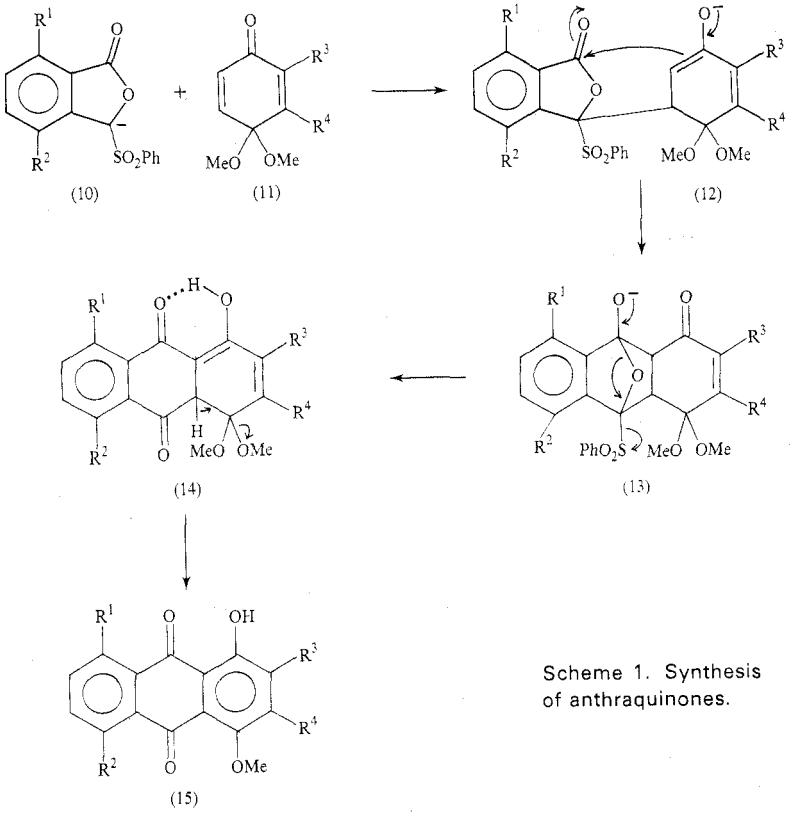
(8)

(−)-(*R*)-isomer



(9)

(+)-daunomycinone remains a challenge.[14] To this end, Terashima[15] has developed a synthesis of (+)-4-demethoxydaunomycinone (7) in which enhanced chiral selection (*c.* 75%) is achieved.[15] The strategy of this convergent synthesis involved the preparation of the hydroxy ketone (8) as a chiral AB ring synthon, either by chemical chiral induction[16] or by an enzyme-mediated reaction sequence.[17] The ketone (8) was of high chiral integrity since it was prepared with 'high chiral reaction efficiency'.[18] However, conversion to a tetracyclic intermediate by means of a

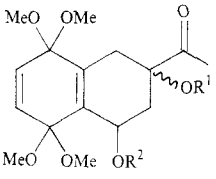


Scheme 1. Synthesis of anthraquinones.

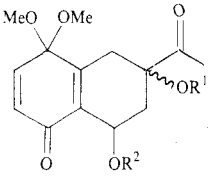
[14] Gupta, R. C., Harland, P. A., and Stoodly, R. J., *J. Chem. Soc., Chem. Commun.*, 1983, 754.
[15] Tanno, N., and Terashima, S., *Chem. Pharm. Bull.*, 1983, **31** (3), 821.
[16] Tanno, N., and Terashima, S., *Chem. Pharm. Bull.*, 1983, **31** (3), 837.
[17] Terashima, S., and Tamoto, K., *Tetrahedron Lett.*, 1982, **23**, 3715.
[18] Wilson, J. M., and Cram, D. J., *J. Am. Chem. Soc.*, 1982, **104**, 881.

modified Friedel–Crafts bisacylation resulted in partial racemization occurring at the C9 centre. A subsequent detailed study[19] has been carried out by Terashima and his coworkers and it is clear that Lewis acids or strong protic acids must be avoided if chirally pure compounds are to be obtained. Consequently, a new convergent step in the AB+CD strategy is required.

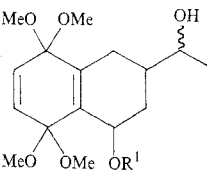
We have previously reported[20] a regiospecific synthesis of model anthraquinones based on the condensation of the anion of a 3-phenylsulfonylphthalide with a quinone monoacetal. This reaction, which is initiated by a Kraus[21]–Hauser[22,23] annulation step, leads directly to the anthraquinone nucleus (Scheme 1). The uniquely mild conditions of this synthesis are ideal for the preparation of chiral anthracyclines. Swenton[24] and Rodrigo[25] have subsequently described the application of this reaction to the synthesis of (±)-daunomycinone from the racemic dienones (17) and (19) respectively. In each case the dienones were prepared by selective hydrolysis of the respective bisacetals (16) and (18). These two syntheses demonstrate the value of the Kraus annulation reaction to achieve convergence in the reaction sequence. Neither synthesis is capable of controlling chirality, since the C7 and C9 (daunomycinone numbering) oxygens of (17) and (19) are introduced by non-enantiospecific reactions.



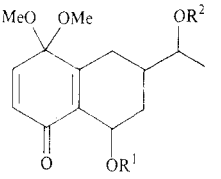
(±)-(16)



(±)-(17)



(±)-(18)

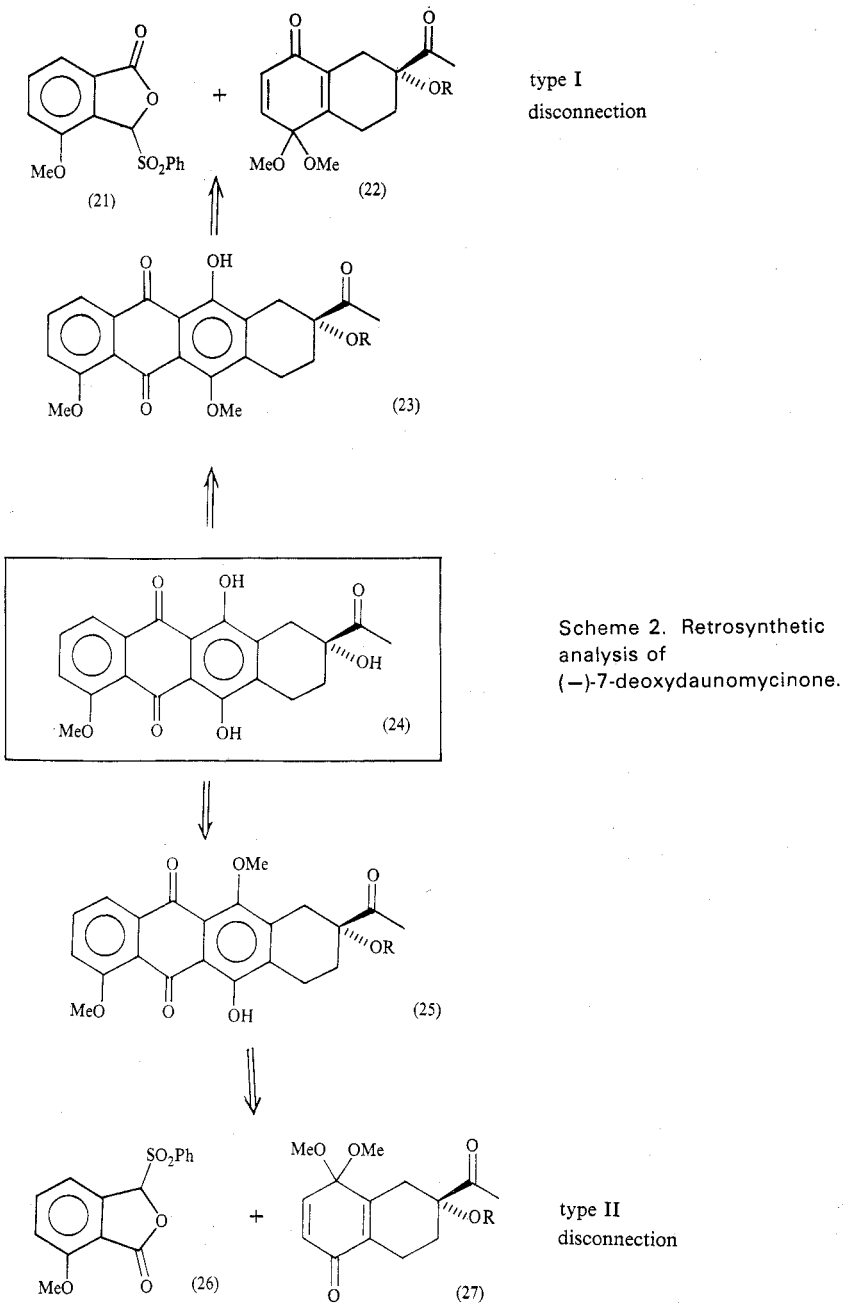


(±)-(19)

We have sought to combine both regiospecificity and enantiospecificity into the one synthesis, and chosen the dienone–phthalide anion condensation as our basis. (−)-7-Deoxydaunomycinone (24), an established[26] precursor to (+)-daunomycinone, has been chosen as our initial target.

Reterosynthetic analysis of target molecule (24) into phthalide anion and quinone acetal partners can be achieved in two modal forms (type I or type II: Scheme 2). In this series of papers we report first on the preparation of chiral dienones of both types I and II and subsequently on their evaluation in the synthesis of (−)-7-deoxydaunomycinone (24) and other chiral anthracyclines, e.g. (20). In this paper we report in detail[26] on the synthesis of the type I dienone (41) utilizing the bromolactonization[27] method of chiral induction.

[19] Terashima, S., and Tamoto, K., *Tetrahedron Lett.*, 1983, **24**, 2589.
[20] Russell, R. A., and Warrener, R. N., *J. Chem. Soc., Chem. Commun.*, 1981, 108.
[21] Kraus, G. A., and Sugimoto, H., *Tetrahedron Lett.*, 1978, 2263.
[22] Hauser, F. M., and Rhee, R. P., *J. Am. Chem. Soc.*, 1977, **99**, 4533.
[23] Hauser, F. M., and Rhee, R. P., *J. Am. Chem. Soc.*, 1979, **101**, 1628.
[24] Polson, M. G., Chenard, B. L., and Swenton, J. S., *J. Am. Chem. Soc.*, 1981, **103**, 5263.
[25] Keay, B. A., and Rodrigo, R., *Can. J. Chem.*, 1983, **61**, 637.
[26] Warrener, R. N., Gee, P. S., and Russell, R. A., *J. Chem. Soc., Chem. Commun.*, 1981, 1100.
[27] Jew, S. S., Terashima, S., and Koga, K., *Chem. Pharm. Bull.*, 1979, **27**, 2351.

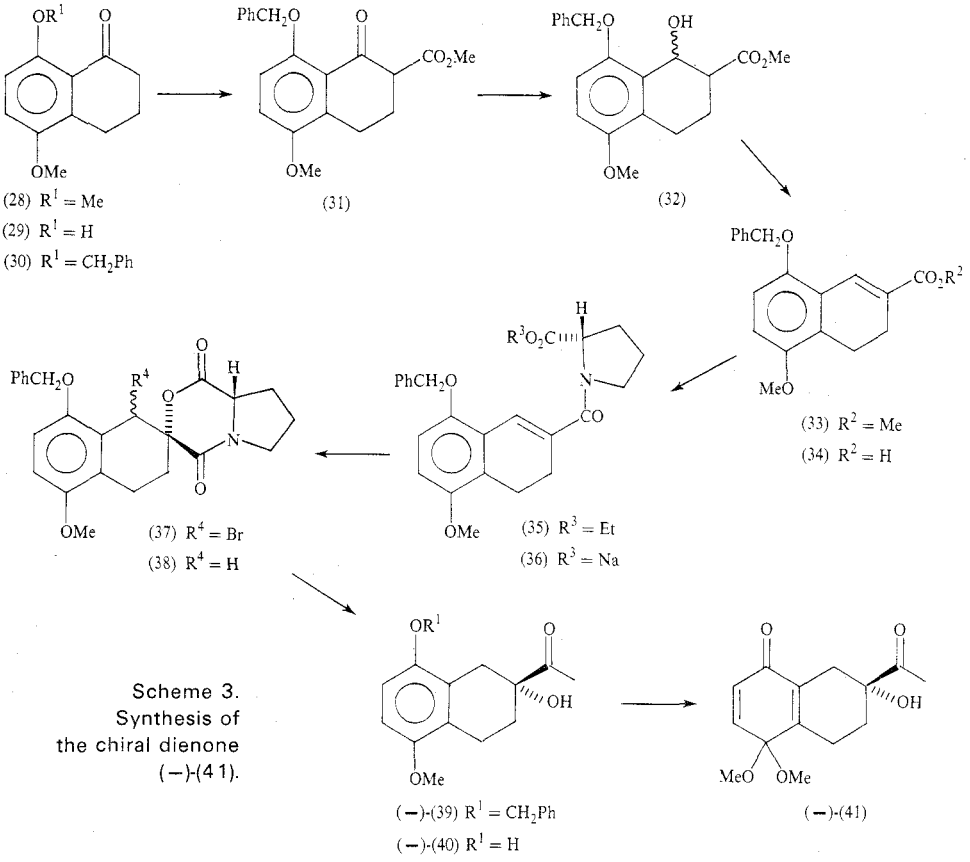


Scheme 2. Retrosynthetic analysis of (−)-7-deoxydaunomycinone.

Results and Discussion

Unlike other workers[24,25] in this field who have used the selective hydrolysis of quinone bisacetals to form the required dienone, we have approached the construction of our dienones by direct synthesis. This involves site-selective location of the incipient

carbonyl group of the dienone as the phenolic group of a monoalkylated hydroquinone. Oxidation of this substrate with thallium(III) yields the dienone; chiral phenol (40) (Scheme 3) illustrates this approach.



Scheme 3. Synthesis of the chiral dienone (−)-(41).

The preparation of key intermediate (40) commenced from 5,8-dimethoxytetralone (28)[28] which was selectively demethylated by reaction with potassium iodide in formic acid to yield the known phenol (29).[29] The anion of this phenol was benzylated with benzyl bromide in dimethylformamide to yield (30). Reaction of the ketone (30) with sodium hydride followed by dimethyl carbonate produced the keto ester (31) which was selectively reduced by sodium borohydride[30] to yield the hydroxy ester (32). Subsequent dehydration of this alcohol, with *p*-toluenesulfonic acid in benzene, afforded the α,β-unsaturated ester (33) which yielded the corresponding carboxylic acid (34) upon treatment with alkali.

Condensation of the acid (34) with ethyl (*S*)-prolinate to form amido ester (35) was achieved, by reaction with dicyclohexylcarbodiimide, in quantitative yield.

[28] Moore, J. A., and Rahm, M., *J. Org. Chem.*, 1961, **26**, 1109.
[29] Crawford, M., and Supanekar, V. R., *J. Chem. Soc.*, 1960, 1985.
[30] Johnson, D. W., and Mander, L. M., *Aust. J. Chem.*, 1978, **31**, 1561.

Controlled alkaline hydrolysis of this ester, followed by reaction of the resulting sodium carboxylate (36) with *N*-bromosuccinimide in dimethylformamide, resulted in the slow formation of a mixture of bromo lactones, from which the main isomer (37) could be separated with difficulty. The absolute stereochemistry of (37) was assigned by analogy with the known dimethoxy derivative and ultimately (see subsequent paper) by comparison with related synthetic products. Debromination of (37) with tributyltin hydride proceeded in high yield to afford lactone (38). The purification of this latter compound, either by chromatography or repeated crystallization was hampered by the presence of tenacious tin-containing by-products. Reaction of the lactone (38) with an excess of methyllithium led directly to the chiral hydroxy ketone (39) in 69% yield. This was superior to the alternative two-step sequence based upon hydrolysis of the lactone and subsequent conversion of a hydroxy acid into the corresponding ketone as reported by Terashima in the original report of this type of reaction. The enantiomeric purity of the hydroxy ketone (39) ($[\alpha]_D$ $-22{\cdot}9°$) was determined by high-field ^{1}H n.m.r. spectroscopy in the presence of the chiral shift reagent tris[(trifluoromethyl)hydroxymethylene-(+)-camphorato]-europium(III), [Eu(tfc)$_3$] with the ketonic methyl resonance serving as a probe in these measurements. Optimally, an 0·16 M solution of the ketone containing 8·5 mole % Eu(tfc)$_3$ gave an 0·025 ppm separation of the two ketone methyl groups in their diasteriomerically complexed forms. Integration of these resonances indicated an enantiomeric excess of 92% or greater. A more precise estimation of the optical purity was subsequently obtained by h.p.l.c. on a chiral phase and indicated an enantiomeric excess of 94%. This result represents the best chiral induction obtained in a series of preparations of the hydroxy ketone (39) where specific rotations varied from $-18{\cdot}4°$ to $-22{\cdot}9°$, indicative of enantiomeric excess in the range 76–94%. This indicates the poor reproducibility of this chiral induction sequence.

Hydrogenolysis of the benzyl group in the chiral ketone (39) gave the related phenol (47) which was immediately oxidized with thallium(III) nitrate in methanol to yield the chiral dienone (41). This oxidation step required particular attention to experimental detail and was best performed in the presence of a mixture of trimethyl orthoformate and solid sodium hydrogen carbonate. Together, but not individually, these reagents effectively removed nitric acid produced during the reaction, thereby preventing racemization or *in situ* hydrolysis of the dimethyl acetal.

The structure of the dienone (41) was confirmed by ^{1}H n.m.r. spectroscopy. Two characteristic low-field doublets (δ 6·44, 6·90, J 10 Hz) and two diastereotopic methoxyl resonances (3·26, 3·34) were observed in the spectrum in accordance with expectation for structure (41).

This reaction sequence represents the first successful synthesis of a chiral type I dienone; however, a number of features detract from its wider use. First, the route leading to the key intermediate (34) is limited to type I dienones, by the initial site-selective demethylation of the tetralone (28). Furthermore, the overall yield for the 13-step conversion (28) → (41) is a modest 10%, and the reaction sequence is time-consuming and involves numerous chromatographic separations. Finally, there remains the variable optical purity of the hydroxy ketone (39), which we consider is due to the difficulties associated with purifying the bromo lactone (37). A combination of these features suggests that a practical synthesis of chiral dienones must be based on an alternative strategy. One such alternative which overcomes all the abovementioned problems is reported in a following communication.

Conclusion

The chiral dienone (41), which represents the first such chiral intermediate for the synthesis of anthracyclinones has been prepared from the readily available α,β-unsaturated acid (34). Chiral-phase h.p.l.c. is shown to be a more sensitive analytical technique than the use of chiral shift reagents for assessing the optical purity of anthracycline AB ring precursors.

Experimental

General Methods

All melting points were recorded on a Reichert hot-stage microscope and are uncorrected. Infrared spectra were, unless otherwise stated, run on Nujol mulls in a Perkin–Elmer 283 spectrometer. ^{1}H n.m.r. spectra were obtained for $CDCl_3$ solutions at 80 MHz on a Varian CFT-20, or at 100 MHz on a Jeolco Minimar n.m.r. spectrometer. Unless otherwise stated ^{1}H n.m.r. spectra are reported at 100 MHz. ^{13}C n.m.r. spectra were recorded at 67·89 MHz on a Bruker HFX-270 n.m.r. spectrometer. All chemical shifts are reported relative to tetramethylsilane (internal) on the appropriate δ scale. Low-resolution mass spectra were measured on a Varian MAT CH7 or an AEI MS902 mass spectrometer. Accurate mass measurements were made on the latter instrument. Unless otherwise stated optical rotations were measured for chloroform solutions in a 10-cm cell of a Perkin–Elmer 241 polarimeter. All preparative thin-layer chromatography was carried out on plates coated with silica gel (Merck HF_{254}) as adsorbant. Unless otherwise stated, column chromatography was conducted on Merck 60 silica gel. H.p.l.c. was conducted on 25-cm columns of μ-Porasil and chiral-phase chromatography was carried out on a 25-cm Bakerbond DNPG (ionic) column. Unless otherwise stated flow rates were in the range 2·5–3 ml min^{-1}, and u.v. detection was at 254 nm. All solvents were distilled and where necessary dried prior to use. Light petroleum refers to the hydrocarbon fraction, b.p. 40–70°. Microanalyses were performed by the A.N.U. Microanalytical Service.

8-Benzyloxy-5-methoxy-3,4-dihydronaphthalen-1(2H)-one (30)

Method A.—A solution of the phenol (29) (7·68 g, 40 mmol) in dry dimethylformamide (25 ml) was added to a stirred, ice-cold, suspension of sodium hydride (1·6 g, 55–60% NaH in oil; *c.* 40 mmol NaH) in dry dimethylformamide (15 ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 15 min, and benzyl bromide (7·7 g, 45 mmol) added. The mixture, still under a nitrogen atmosphere, was stirred at room temperature for 18 h and poured into water (400 ml). The product was extracted into ether (3 × 100 ml) and the combined extracts washed with water (3 × 100 ml) and brine (2 × 50 ml). The solvent was removed from the dried extracts to afford an oil (12·3 g) which was dissolved in dichloromethane and filtered through a bed of alumina (150 g) to remove unchanged starting material. The filtrate yielded an orange-coloured oil (10·3 g) which crystallized after being set aside at room temperature overnight. The resulting solid was recrystallized from heptane to afford the *product* as fine pale yellow-coloured needles (6·3 g, 56%), m.p. 88–89° (Found: C, 76·7; H, 6·5. $C_{18}H_{18}O_3$ requires C, 76·6; H, 6·4%). ^{1}H n.m.r. δ 2·06, dd, *J* 7 Hz, 2H, H3; 2·63, t, *J* 7 Hz, 2H, H2,4; 2·88, t, *J* 7 Hz, 2H, H4,2; 3·82, s, 3H, OCH_3; 5·14, s, 2H, $PhCH_2O$; 6·82, d, *J* 9 Hz, 1H, H6,7; 6·98, d, *J* 9 Hz, 1H, H7,6; 7·44, m, 5H, ArH. Mass spectrum *m/z* 283 (8%), 282 (M, 33), 265 (5), 264 (17), 206 (2), 205 (3), 204 (2), 191 (8), 187 (10), 135 (11), 120 (5), 105 (5), 103 (6), 92 (12), 91 (100), 77 (8), 65 (17), all other peaks less than 5%.

Method B.—To a stirred solution of sodium ethoxide, prepared by the reaction of sodium (1·15 g) with absolute ethanol (50 ml), was added a solution of phenol (29) (9·6 g, 50 mmol) in ethanol. After stirring at room temperature for 0·5 h, the solvent was evaporated at 30°/1 mm and the residue dried at 30°/1 mm for 4 h. The remaining sodium phenolate was dissolved in dimethylformamide (50 ml), benzyl bromide (6·0 ml, 50·5 mmol) added, and the mixture stirred overnight at room temperature. The solution was poured into brine (500 ml) and aqueous sodium hydroxide (200 ml, 2 M), extracted with ether (3 × 250 ml), and the combined organic phase washed with brine (3 × 200 ml). The solvent was removed from the dry ethereal solution to afford a residue which

crystallized from a mixture of ether and light petroleum to afford the title compound (5·80 g) as colourless needles. Decolorization of the mother liquors (charcoal, methanol) followed by column chromatography (acetone/petrol 1 : 5) afforded a second batch (6·21 g; total 11·52 g, 85%) which upon successive crystallization from a mixture of ether and light petroleum followed by aqueous methanol afforded colourless needles, m.p. 89–90°. This product was identical with that obtained by method A.

Methyl 8-Benzyloxy-5-methoxy-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (31)

Sodium hydride (1·15 g, 55–60% in oil, *c.* 27 mmol) was washed, under an argon atmosphere, with anhydrous tetrahydrofuran (2 × 20 ml). The remaining powder was suspended in a mixture of anhydrous tetrahydrofuran (15 ml) and dimethyl carbonate (1·8 g, 20 mmol). Whilst still under an inert atmosphere, this suspension was heated to 80°, stirred and treated dropwise, over a period of 75 min, with a solution of the ketone (30) (2·82 g, 10 mmol) in dry tetrahydrofuran. The reaction mixture was heated under reflux for a further 90 min, and set aside at room temperature for 12 h. The resulting solid mass was acidified with glacial acetic acid (3 ml) and diluted with water (50 ml). The product was extracted into dichloromethane (2 × 25 ml) and the combined organic extracts washed with aqueous sodium carbonate solution (25 ml, 5%) followed by water (2 × 25 ml). The dried organic phase was freed of solvent to afford an oil (3·32 g, 97%) which crystallized after being cooled. This solid was triturated with a mixture of n-hexane and ether (1 : 1) to afford a crystalline *product* suitable for use in subsequent steps. An analytical sample was purified by preparative t.l.c. (dichloromethane) and recrystallized from a mixture of ether and n-hexane, m.p. 85–86° (Found: C, 70·2; H, 5·9. $C_{20}H_{20}O_5$ requires C, 70·6; H, 5·9%). I.r. ν_{max} 1740, 1688, 1674, 1590, 1504, 1310, 1270, 1237, 1210, 1197, 1179, 1155, 1104, 1093, 1070, 1045, 1040, 1035, 1010, 988, 940, 910, 890, 880, 830, 818, 804, 757, 746, 734, 700, 675 cm^{-1}. ^1H n.m.r. (90 MHz) δ 2·21–3·68, m, 5H, H2, H3, H4; 3·76, s, 3H, OCH_3; 3·79, s, 3H, OCH_3; 5·12, s, 2H, $PhCH_2O$; 6·79, dd, *J* 9 Hz, 1H, H6, 7; 6·90, dd, *J* 9 Hz, 1H, H7,6; 7·21–7·57, m, 5H, ArH. Mass spectrum *m/z* 341 (5%), 340 (M, 23), 263 (5), 249 (11), 218 (5), 217 (16), 190 (7), 189 (9), 175 (5), 163 (6), 92 (10), 91 (100), 65 (9), 59 (7), 45 (5), 41 (5), all other peaks less than 5%.

Methyl 8-Benzyloxy-1-hydroxy-5-methoxy-1,2,3,4-tetrahydronaphthalene-2-carboxylate (32)

A solution of the keto ester (31) (83·7 g, 0·246 mol) in a mixture of tetrahydrofuran (300 ml) and methanol (600 ml) was cooled to 2° and treated with sodium borohydride (9·5 g, 0·25 mol) at such a rate (*c.* 30 min.) that the temperature remained below 5°. The mixture was maintained between 0 and 5° and stirred for 1·5 h. A further portion of sodium borohydride (0·5 g, 13 mmol) was added and the mixture maintained at 0–5° until t.l.c. showed no remaining starting material. The mixture was partitioned between water (1 l.) and ether (3 × 500 ml) and the combined ether extracts washed with water (3 × 300 ml), followed by brine (2 × 300 ml). The dried ether solution was freed of solvent to yield the crude alcohol (79 g, 94%), m.p. 104–105°, which was of satisfactory purity for use in the subsequent step. An analytical sample was purified by recrystallization from a ternary mixture of ether, dichloromethane and n-hexane. The pure product was obtained as colourless *prisms*, m.p. 113–114° (Found: C, 70·5; H, 6·7. $C_{20}H_{22}O_5$ requires C, 70·2; H, 6·5%). I.r. ν_{max} 3586, 1740, 1605, 1335, 1320, 1308, 1264, 1228, 1190, 1174, 1150, 1118, 1087, 1072, 1056, 1014, 980, 958, 930, 920, 900, 880, 840, 808, 790, 774, 766, 734, 700 cm^{-1}. ^1H n.m.r. (90 MHz) δ 2·05–3·2, m, 5H, H2, H3, H4; 3·77, s, OCH_3; 5·10, s, $PhCH_2O$; 5·45, t, *J* 3·2 Hz, 1H, H1; 6·71, s, 2H, H6, H7; 7·38, br s, 5H, ArH. Mass spectrum *m/z* 343 (6%), 342 (M, 15), 324 (4), 311 (6), 235 (12), 324 (70), 219 (3), 206 (3), 202 (4), 192 (3), 191 (17), 190 (4), 176 (13), 175 (62), 174 (23), 165 (5), 163 (9), 159 (6), 107 (6), 92 (10), 91 (100), 77 (8), 65 (14), 55 (9), all other peaks less than 5%.

Methyl 8-Benzyloxy-5-methoxy-3,4-dihydronaphthalene-2-carboxylate (33)

A solution of the hydroxy ester (32) (78·0 g, 0·23 mol), and *p*-toluenesulfonic acid monohydrate (1 g) in benzene (500 ml) was heated to reflux under a Dean–Stark apparatus until *c.* 4 ml of water was produced. The solution was freed of solvent to afford the crude ester which was suitable for subsequent hydrolysis (see below). Chromatography of the crude product on alumina followed by recrystallization from methanol yielded the *product* as colourless prisms, m.p. 75–76° (Found:

C, 74·2; H, 6·2. $C_{20}H_{20}O_4$ requires C, 75·1; H, 6·2%). I.r. ν_{max} 1695, 1632, 1598, 1335, 1329, 1294, 1264, 1236, 1197, 1167, 1106, 1054, 1027, 1000, 963, 915, 844, 800, 776, 755, 730, 696 cm^{-1}. ^1H n.m.r. δ 2·39–3·25, m, 4H, H3, H4; 3·77, s, 3H, OCH_3; 3·79, s, 3H, OCH_3; 5·06, s, 2H, $PhCH_2O$; 6·74, s, 2H, H6, H7; 7·28–7·46, m, 5H, aromatic; 7·96, t, *J* 1·4 Hz, 1H, H1. Mass spectrum *m/z* 324 (M, 42%) (Found: $M^{+\cdot}$, 324·1363. $C_{20}H_{20}O_4$ requires 324·1362), 293 (15), 264 (14), 234 (15), 233 (100), 202 (9), 174 (21), 173 (21), 159 (11), 150 (9), 145 (6), 131 (7), 115 (7), 103 (7), 92 (10), 91 (100), 77 (7), 65 (10), 59 (8), all other peaks less than 5%.

8-Benzyloxy-5-methoxy-3,4-dihydronaphthalene-2-carboxylic Acid (34)

A solution of the abovementioned crude ester (33) (75·4 g) in methanol (650 ml) was treated with a solution of potassium hydroxide (60 g) in water (50 ml). The resulting mixture was heated under reflux for 2 h, and set aside at room temperature for 12 h. The supernatant was decanted from a small quantity of resinous material and poured into water (2 l.). The mixture was extracted with ether and the aqueous phase acidified to pH 1 with concentrated hydrochloric acid. The resulting solid was collected by filtration, washed with water and dried to afford the crude acid (56 g, 78%) as a tan coloured solid. Recrystallization from ethyl acetate afforded the product as colourless *plates*, m.p. 198–198·5° (Found: C, 73·4; H, 6·0. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·9%). I.r. ν_{max} 3000br; 1670, 1620, 1595, 1485, 1440, 1340, 1325, 1305, 1265, 1200, 1120, 1090, 1050, 1030, 955, 800, 762, 700, 733, 695 cm^{-1}. ^1H n.m.r. (90 MHz) δ 2·71, m, 4H, H3, H4; 3·79, s, 3H, OCH_3; 5·07, s, 2H, $PhCH_2O$; 6·69, dd, *J* 9 Hz, 1H, H6,7; 6·82, dd, *J* 9 Hz, 1H, H7,6; 7·35, m, 5H, ArH; 8·12, t, *J* 1·3 Hz, 1H, H1. Mass spectrum *m/z* 311 (10%), 310 (M, 46), 265 (5), 264 (22), 220 (13), 219 (81), 203 (4), 202 (7), 175 (6), 174 (6), 173 (11), 160 (11), 159 (11), 150 (13), 145 (5), 131 (9), 115 (12), 103 (8), 92 (10), 91 (100), 77 (8), 65 (14), 51 (5), all other peaks less than 5%.

Ethyl (−)-(2′S)-N-(8-Benzyloxy-5-methoxy-3,4-dihydro-2-naphthoyl)prolinate (35)

To a suspension of the acid (34) (21·7 g) in acetonitrile (250 ml) was added a solution of ethyl (*S*)-prolinate (10·8 g) in dichloromethane (250 ml) and the mixture cooled to 0°. Dicyclohexylcarbodiimide (15·6 g) was added, and the mixture allowed to stir in the thawing cold bath overnight. The mixture was filtered and the filtrant washed with dichloromethane (2 × 50 ml). The filtrate was diluted with dichloromethane (150 ml) and washed successively with a mixture (4 : 1) of sodium bicarbonate solution and brine (2 × 150 ml), dried and the solvent evaporated. The residue was redissolved in ether (100 ml) and allowed to stand for 2 days, filtered, and the solvent evaporated to yield the *title compound* as a brown oil (30·0 g, 100%). Column chromatography (acetone/petrol 1 : 4) afforded an analytical sample as a colourless syrup, $[\alpha]_D$ −16·6° (*c*, 1·06) (Found: C, 72·0; H, 6·8; N, 3·2. $C_{26}H_{29}NO_5$ requires C, 71·7; H, 6·7; N, 3·2%). I.r. (film) ν_{max} 1740, 1640, 1612, 1484, 1466, 1454, 1440, 1410, 1263, 1185, 1090 cm^{-1}. ^1H n.m.r. δ 1·25, m, 3H, CH_2CH_3; 1·70–3·00, m, 3H, H3, H3′, H4, H4′; 3·50–3·80, m, 2H, H5′; 3·85, s, 3H, OCH_3; 4·00–4·60, m, 2H, CH_2CH_3; 4·61, m, 1H, H2′; 5·11, s, 2H, $PhCH_2O$; 6·84, s, 2H, H6, H7; 7·20–7·64, m, 6H, H1, aromatics.

(−)-(2′S)-N-(8-Benzyloxy-5-methoxy-3,4-dihydro-2-naphthoyl)proline (36)

To a stirred solution of the crude ester (35) (35·0 g) in ethanol (48 ml) at 5° was added sodium hydroxide (58 ml, 2 M). The mixture was stirred at room temperature for 21 h, diluted with sodium hydroxide (500 ml, 0·05 M), and extracted with ethyl acetate (200 ml, 100 ml). The aqueous phase was acidified (pH 1) with 2 M hydrochloric acid, extracted with ethyl acetate (3 × 75 ml) and the combined extracts washed with brine (2 × 100 ml), dried, and the solvent evaporated to give the title compound as a solid (26·6 g, 86%). Recrystallization from ethyl acetate afforded colourless *blades*, m.p. 142·5°; $[\alpha]_D$ −98·6° (*c*, 1·04) (Found: C, 70·8; H, 6·2; N, 3·2. $C_{24}H_{25}NO_5$ requires C, 70·7; H, 6·2; N, 3·4%). I.r. ν_{max} 2680, 2570, 1710, 1632, 1602, 1440, 1410, 1360, 1347, 1322, 1307, 1298, 1275, 1263, 1212, 1225, 1136, 1290, 1068, 794, 730, 692 cm^{-1}. ^1H n.m.r. δ 1·8–2·5, m, 5H, CO_2H, H3′, H4′; 2·5–3·0, m, 4H, H3, H4; 3·67, m, 2H, H5′; 3·79, s, 3H, OCH_3; 4·68, dd, *J* 7·2 Hz, 4·5 Hz, 1H, H2′; 5·04, s, 2H, $PhCH_2O$; 6·75, s, 2H, H6, H7; 7·28, s, 1H, H1; 7·36, m, 5H, aromatics. Mass spectrum *m/z* 408 (14%), 407 (M, 48), 316 (13), 310 (22), 293 (12), 266 (10), 219 (33), 203 (19), 202 (62), 201 (83), 187 (16), 173 (14), 159 (14), 131 (13), 115 (13), 103 (11), 91 (100), 70 (12), 65 (15), all other peaks less than 10%.

(−)-[3′S-3′α(S*),8′aβ]-*8-Benzyloxy-1-bromo-5-methoxy-3,4,6′,7′,8′,8′a-hexahydrospiro[naphthalene-2(1H),3′(4′H)-[1H]pyrrolo[2,1-c][1,4]oxazine]-1′,4′-dione* (*37*)

The sodium salt of the unsaturated amido acid (36) was prepared by extraction of the acid into a 1 : 1 mixture of saturated aqueous sodium bicarbonate solution and water, filtration of unchanged acid, and freeze-drying the filtrate for 40–70 h.

A solution of the salt (4·5 g) and *N*-bromosuccinimide (3·9 g) in dimethylformamide (20 ml) was stirred under a nitrogen atmosphere for 24 h, the mixture was poured into brine (150 ml) and extracted with ethyl acetate (4 × 100 ml). The combined organic phase was washed successively with brine (50 ml), saturated sodium bicarbonate solution (2 × 50 ml), brine (50 ml) and water (50 ml), and dried; the solvent was evaporated. Column chromatography of the residue (4·92 g) (acetone/light petroleum 1 : 3) afforded the *title compound* as an unstable yellow syrup; (4·0 g, 75%) $[\alpha]_D$ −9·0° (*c*, 1·07) (Found: C, 59·3; H, 5·4; N, 2·5. $C_{24}H_{24}BrNO_5$ requires C, 59·3; H, 5·0; N, 2·9%). I.r. ν_{max} 1760, 1677, 1348, 1264, 1240, 1047 cm^{-1}. ^1H n.m.r. δ 1·60–2·50, m, 6H, H3, H7′, H8′; 3·0, m, 2H, H4; 3·70, m, 2H, H6′; 3·80, s, 3H, OCH_3; 4·32, m, 1H, H8a′; 5·10, s, 2H, $PhCH_2O$; 5·54, d, 1H, *J* 2 Hz; H1, 6·75, s, 2H, H6, H7; 7·25–7·60, m, 5H, aromatics.

(−)-(3′S-cis)-*8-Benzyloxy-5-methoxy-3,4,6′,7′,8′,8′a-hexahydrospiro[naphthalene-2(1H),3′(4′H)-[1H]pyrrolo[2,1-c][1,4]oxazine]-1′,4′-dione* (*38*)

A solution of the bromolactone (37) (1·5 g) and 2,2′-azobis(2-methylpropionitrile) (180 mg) in bromobenzene (40 ml) was stirred with tributyltin hydride (3·9 ml) under a nitrogen atmosphere at 70° for 14 h. The mixture was cooled, and filtered to yield the *title compound* as colourless prisms (0·957 g) which were washed thoroughly with light petroleum. Concentration of the filtrate in a vacuum and trituration with light petroleum afforded a second crop of product which was filtered and washed with light petroleum, then ether (0·24 g; total 1·19 g; 94%). Recrystallization from a mixture of dichloromethane and ethyl acetate gave colourless *needles*, m.p. 224–225°; $[\alpha]_D$ −166·9° (*c*, 0·99) (Found: C, 70·7; H, 6·4; N, 3·3. $C_{24}H_{25}NO_5$ requires C, 70·8; H, 6·2; N, 3·4%). I.r. ν_{max} 1745, 1660, 1310, 1262, 1245, 1065 cm^{-1}. ^1H n.m.r. δ 1·60–2·56, m, 6H, H3, H7′, H8′; 2·72–3·24, m, 4H, H1, H4; 3·64, m, 2H, H6′; 3·78, s, 3H, OCH_3; 4·24, m, 1H, H8a′; 5·0, s, 2H, $PhCH_2O$; 6·69, m, H6, H7; 7·38, m, 5H, aromatics.

(−)-(2R)-*2-Acetyl-8-benzyloxy-5-methoxy-1,2,3,4-tetrahydronaphthalen-2-ol* (*39*)

To a stirred suspension of the lactone (38) (300 mg) in ether (9 ml) under a nitrogen atmosphere was added, dropwise, methyllithium in ether (9 ml, 0·88 M). The mixture was stirred at 20° for 1 h, poured into a mixture of hydrochloric acid (55 ml, 10%) and brine (50 ml), and extracted with ethyl acetate (20 × 50 ml). The combined extracts were washed sequentially with 50% brine (50 ml), sodium carbonate (50 ml, 5%) and brine, dried, and the solvent evaporated. Preparative t.l.c. of the residue (ether/hexane 3 : 7) gave the title compound as a pale amber oil (166 mg, 69%). Crystallization from a mixture of ether and hexane afforded colourless *needles*, m.p. 84·5–85°; $[\alpha]_D$ −22·9° (*c*, 1·03) (Found: C, 73·5; H, 6·9. $C_{20}H_{22}O_4$ requires C, 73·6; H, 6·8%). I.r. ν_{max} 3510, 3460, 1693, 1601, 1359, 1340, 1330, 1250–1270, 1228, 1105, 1086, 1070, 1028, 792, 788, 760, 731, 699 cm^{-1}. ^1H n.m.r. δ 1·80–2·05, m, 2H, H3; 2·31, s, 3H, $COCH_3$; 2·70–3·05, m, 4H, H1, H4; 3·63, s, 1H, OH; 3·78, s, 3H, OCH_3; 5·00, s, 2H, $PhCH_2$; 6·68, m, 2H, H6, H7; 7·30–7·45, m, 5H aromatics. ^{13}C n.m.r. δ 19·4, C3; 24·0, C2′; 29·8, C4; 32·6, C1; 55·6, OCH_3; 70·3, $PhCH_2O$; 76·5, C2; 107·3, C6,7; 108·6, C7,6; 123·3, C9,10; 125·7, C10,9; 127·3, 2C, aromatic; 127·9, 1C, aromatic, 128·5, 2C, aromatic, 137·6, 1C, aromatic, 150·7, C5,8; 151·4, C8,5; 212·5, C1′. Mass spectrum *m/z* 327 (10%), 326 (M, 45), 217 (58), 192 (10), 191 (11), 91 (100), 43 (20), all other peaks less than 10%.

(−)-(7R)-*7-Acetyl-7-hydroxy-4,4-dimethoxy-5,6,7,8-tetrahydronaphthalen-1(4H)-one* (*41*)

A solution of the ether (39) (145 mg) in tetrahydrofuran (5 ml) and acetic acid (4·5 ml) was stirred under a hydrogen atmosphere with 10% palladium on charcoal (73 mg) for 4·5 h. The mixture was diluted with ethyl acetate, filtered, washed with 10% sodium bicarbonate and the combined aqueous phase washed with ethyl acetate (25 ml). The organic phase was washed with brine, dried and evaporated, to yield the phenol (40) as a pale pink-coloured solid, m.p. 175–176°. This crude

product (87 mg) and sodium bicarbonate (100 mg) were stirred at 0° in a mixture of methanol (5 ml), tetrahydrofuran (5 ml), trimethyl orthoformate (5 ml) and thallium(III) nitrate trihydrate (167 mg) added. The mixture was stirred at 0° for 0·25 h, diluted with dichloromethane (50 ml) and washed with 50% brine. The aqueous phase was washed with dichloromethane (10 ml) and the combined organic phase dried and the solvent evaporated to yield the *title dienone* as a pale amber syrup (91 mg, 77%); $[\alpha]_D$ −48·8° (*c*, 1·09) (Found: C, 63·2; H, 6·7. $C_{14}H_{18}O_5$ requires C, 63·1; H, 6·8%). I.r. (neat) ν_{max} 3460, 2940, 2817, 1710, 1672, 1643, 1620, 1420, 1400, 1360, 1300, 1260, 1240, 1223, 1210, 1100, 1060, 945, 825 cm^{-1}. ^1H n.m.r. δ 1·76–1·96, m, 2H, H6; 2·35, s, 3H, $COCH_3$; 2·40–2·70, m, 4H, H5, H8; 3·26, s, 3H, OCH_3; 3·34, s, 3H, OCH_3; 3·88, s, 1H, OH; 6·54, d, *J* 10 Hz, 1H, H3; 6·90, d, *J* 10 Hz, 1H, H2. Mass spectrum *m/z* 266 (M, 3%), 224 (15), 223 (100), 222 (17), 217 (18), 205 (20), 193 (12), 192 (51), 191 (29), 167 (47), 163 (14), 150 (14), 149 (21), 91 (11), 57 (10), 55 (11), 43 (50), all other peaks less than 10%.

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