

Synthesis of 2-acetyl-5,8-dimethoxytetralin — an important anthracycline intermediate

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Received 30 March 1990

The important anthracycline intermediate, 2-acetyl-5,8-dimethoxytetralin, has been synthesized in five steps in an overall yield of 51% starting from 5,8-dihydroxy-1,4-dihydronaphthalene. Since all the steps are straightforward the method lends itself to multigram synthesis.

Die belangrike antrasiklinoon-'uitgangstof', 2-asetiel-5,8-dimetoksitetralien, is in vyf stappe vanuit 5,8-dihidroksi-1,4-dihidronaftaleen in 'n algehele opbrengs van 51% gesintetiseer. Omdat al die stappe redelik maklik is, kan die prosedure aangewend word vir die sintese van multigram hoeveelhede.

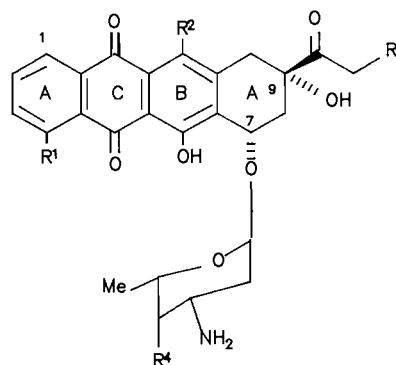
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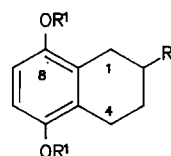
For almost the past two decades attempts to improve the therapeutic effect of the first-generation anthracycline anti-tumour antibiotics, daunomycin (1) and adriamycin (2), have been rewarded with reasonably encouraging results. New anthracyclines and derivatives thereof, both of natural and synthetic origin, such as 4-demethoxydaunomycin (3), 4-demethoxy-11-deoxydaunomycin (4), 11-deoxydaunomycin (5), and 4'-deoxydaunomycin (6) as well as many others, have been demonstrated to be either more potent or less toxic than the first-generation antitumour anthracyclines.¹ However, a major problem is that cardiotoxicity remains a critical side-effect, and this severely restricts the dosages, and hence, the long-term use of these drugs.

That the anthracycline intermediate, 2-acetyl-5,8-dimethoxytetralin (7) is a valuable precursor of the AB portion of the tetracycline system, can be attested by a proliferation in the literature of various methods for its synthesis.² These methods generally employed classical chemistry and usually involved at least five steps with overall yields ranging between 25 and 35%.

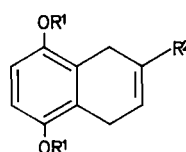
A most attractive route to ketone (7) presented itself in reports by Russell *et al.*,³ in which 5,8-dihydroxy-1,4-dihydronaphthalene (10)* was converted into the conjugated diacetate (14) in a one-pot reaction sequence under the influence of a powerful base. This technique has also been used by Rao *et al.*,⁴ who converted the non-conjugated dimethyl ether (11) into the conjugated ether (17). Addition of acetyl chloride to the diacetate (14) in the presence of aluminium chloride, formed a stereoisomeric mixture of the chloroketones (18) which were not isolated but immediately dehydrochlorinated to afford the enone (15). Base hydrolysis of this diacetate followed by *in situ* methylation produced the



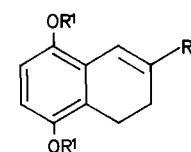
- (1) R¹ = OMe; R² = R⁴ = OH; R³ = H
 (2) R¹ = OMe; R² = R³ = R⁴ = OH
 (3) R¹ = R³ = H; R² = R⁴ = OH
 (4) R¹ = R² = R³ = H; R⁴ = OH
 (5) R¹ = OMe; R² = R³ = H; R⁴ = OH
 (6) R¹ = OMe; R² = OH; R³ = R⁴ = H



- (7) R¹ = Me; R² = COCH₃
 (8) R¹ = Me; R² = CH(OH)CH₃
 (9) R¹ = R² = COCH₃

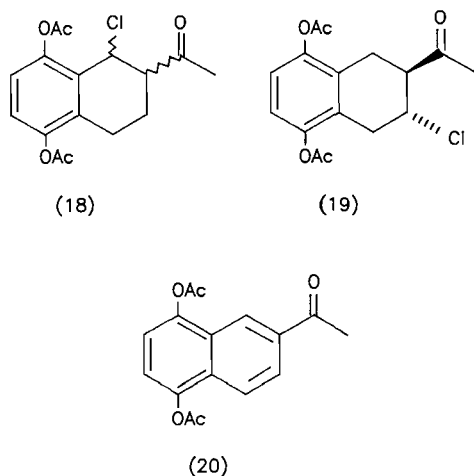


- (10) R¹ = R² = H
 (11) R¹ = Me; R² = H
 (12) R¹ = COCH₃; R² = H
 (13) R¹ = R² = COCH₃



- (14) R¹ = COCH₃; R² = H
 (15) R¹ = R² = COCH₃
 (16) R¹ = Me; R² = COCH₃
 (17) R¹ = Me; R² = H

* For clarity and consistency, the numbering of all naphthalene derivatives in this paper is as drawn in structure (7), although strictly speaking the principal functional group in each compound should be assigned the lowest locant [e.g. 5,8-dihydroxy-1,4-dihydronaphthalene (10)].



enone (16) which we hoped could be readily hydrogenated to yield the desired target ketone (7).

In our hands, great difficulty was experienced in converting the quinol (10) into the conjugated diacetate (14), the best yield being 16% as opposed to 53% quoted by Russell *et al.*³ In spite of this, the sequence of reactions was followed according to the literature to afford enone (16).

Catalytic hydrogenation of the enone (16) over platinum produced the desired ketone (7) but in only 51% yield, together with the alcohol (8) in 46% yield. The structure of the alcohol (8) was obvious from the i.r. spectrum which lacked a carbonyl absorption and showed instead a strong absorption at 3350 cm^{-1} for the hydroxy group, and in the ^1H n.m.r. spectrum, the methyl group of the hydroxyethyl side chain appeared as a doublet at δ 1,36 (J 7 Hz). The 1'-H proton of the side chain appeared as a broad quartet at δ 4,46 (J 7 Hz). Confirmation of the coupling between these two signals was obtained by irradiation of this signal, which caused the doublet at δ 1,36 to collapse into a singlet. Additionally, oxidation of this material using pyridinium dichromate afforded an almost quantitative yield of the ketone (7) analogous to work done by Corey and Schmidt⁵ as well as Reddy and Rao.⁷ This route also involved five steps but, owing to the low yielding conjugation step $10 \rightarrow 14$, a very poor overall yield of 9% was achieved and thus other options had to be considered.

Conversion of the quinol (10) into the dimethyl ether (11) according to the method of Alexander and Mitscher,⁶ followed by treatment with acetyl chloride in the presence of aluminium chloride gave an intractable black oil and thus this option was also abandoned.

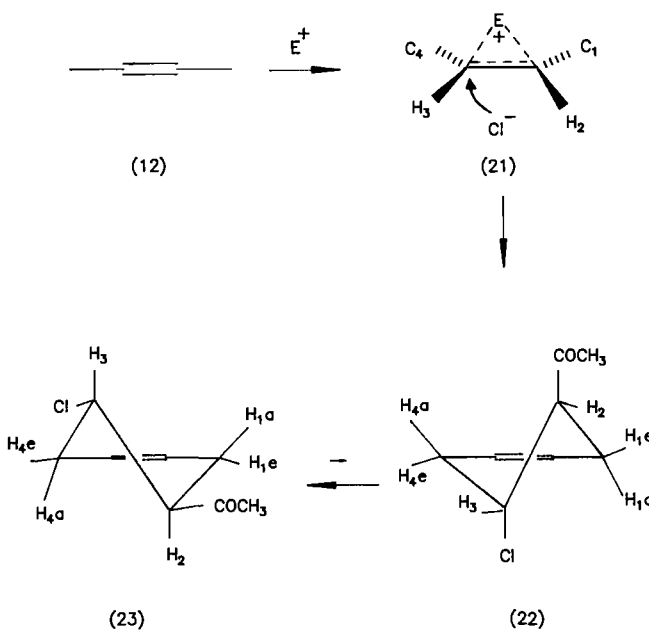
On the other hand, conversion of the quinol (10) into the non-conjugated diacetate (12) (100%), followed by treatment with acetyl chloride as before, afforded the chloroketone (19) in 75% yield. This adduct proved to be reasonably stable which is in marked contrast to the corresponding addition product (18) derived from the conjugated diacetate (14).³ This difference in stability may be attributed to the greater facility with which chloride is lost from C(1) in the case of compound (18), through both activation by the *peri* acetoxy group and also by virtue of the fact that C(1) is benzylic, neither of which is relevant to the isomer (19).

The ^1H n.m.r. spectrum of compound (19) permitted assignment of the *trans*-diequatorial stereochemistry (23) for

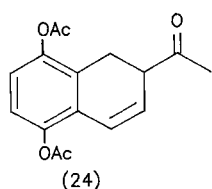
the acetyl and chlorine substituents at C(2) and C(3), since 3-H appeared at δ 4,30 as a symmetrical doublet of triplets with coupling constants of 11 and 6,3 Hz. The signal derived its appearance from the equal coupling of axial 3-H to both axial 2-H and *pseudo*-axial 4-H (11 Hz) and further coupling with *pseudo*-equatorial 4-H. A similar analysis could not be made for the axial 2-H since this signal was obscured by those of 1- and 4-H₂.

Presumably this stereochemistry arises as a result of initial attack by the electrophile, the acylium ion CH_3CO^+ , on the isolated double bond to give an intermediate carbocation of the type (21), which undergoes subsequent attack by either chloride or aluminium chloride anionic species, to afford the observed *trans*-stereochemistry as depicted in Scheme 1. Of the two possible half-chairs (22) or (23), the latter, with equatorial substituents at C(2) and C(3), is preferred.

Scheme 1



When dehydrochlorination was attempted at room temperature using lithium chloride in dimethylformamide,^{3b} the sole product isolated was the fully aromatized material, 2-acetyl-5,8-diacetoxynaphthalene (20). However, it was found that by lowering the temperature to 0°C , the desired enone (13) was produced in 81% yield, together with the diacetoxynaphthalene (20) obtained earlier in 6% yield. It was of interest to note that in the ^1H n.m.r. spectrum of the enone (13) there were basically three sets of signals, *viz.* the acetoxy and acetyl methyl signals at $\pm \delta$ 2,32 (9H), a four-proton signal at δ 3,40 accounting for the benzylic 1- and 4- protons, and thirdly, a broadened singlet at δ 6,92 (3H) which implies that the olefinic 3-H proton has a very similar chemical shift to the aromatic protons. A comparison of the i.r. and ^1H n.m.r. spectral data for the isomers (13) and (15)^{3b} showed that the two compounds were indeed different as integration of the ^1H n.m.r. spectrum of isomer (13) confirmed the presence of three rather than four protons in the olefinic and aromatic region. This effectively excluded the alternative isomer (24) which was a very likely product based upon a bimolecular elimination mechanism.



Careful catalytic hydrogenation of enone (13) afforded the expected ketone (9) in quantitative yield, which was conveniently converted into the target ketone (7) upon treatment with base followed by dimethyl sulphate.

Thus, the useful intermediate in tetracycline synthesis, the acetyltetralin (7) has been synthesized by a modified route which makes use of a clean reduction step, in an overall yield of 51% involving five easy steps, all of which lend themselves to scaling-up for multigram synthesis.

Experimental

Melting points are uncorrected. I.r. spectra were measured as Nujol mulls on a Pye–Unicam SP 300 spectrophotometer and the ^1H n.m.r. spectra were measured on either a Varian EM 360 at 60 MHz or a Bruker FT 90 spectrometer at 90 MHz. Column chromatography was carried out on dry columns using silica gel (70–230 mesh). Light petroleum refers to that fraction of boiling range 60–80°C. The phrase 'residue obtained upon work-up' refers to the material remaining when the organic layer was separated, dried (MgSO_4), and evaporated under reduced pressure.

2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (7) and 2-(1-hydroxyethyl)-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (8)

The enone (16)³ (620 mg; 2,67 mmol) in ethanol (70 ml) containing platinum(IV) oxide (20 mg) was hydrogenated at room temperature and atmospheric pressure until the uptake of hydrogen ceased. The filtrate was stripped of solvent and the residue was chromatographed using ethyl acetate–light petroleum (1:5) as eluent. The first fraction afforded the ketone (7) (320 mg; 51%) as white crystals, m.p. 83,5–84°C (from methanol) (lit.^{2b,2d} m.p. 81–82°C). Later fractions were shown to contain the alcohol (8) (290 mg; 46%) as white rosettes, m.p. 81–82°C (from light petroleum); ν_{max} 3350 cm^{-1} ; δ 1,36 (3H, d, J 7 Hz, 2'- CH_3), 2,0–3,0 (7H, m, 1-, 3-, and 4- H_2 , and 2-H), 3,78 (6H, s, 2 \times OCH_3), 4,46 (1H, br. q, J 7 Hz, 1'-H), and 6,59 (2H, s, 6- and 7-H) (Found: C, 71,4; H, 8,45. Calc. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: C, 71,2; H, 8,5%).

5,8-Diacetoxy-1,4-dihydronaphthalene (12)

Quinol (10)⁸ (5 g; 3,09 mmol) in acetic anhydride (50 ml) containing dry pyridine (20 ml) was stirred in a closed vessel for 12 h and the mixture was then poured into water (300 ml). The solid was filtered and dried to yield the diacetate (12) (7,6 g; 100%) as white crystals, m.p. 124,5–125,5°C (from ethanol) (lit.⁸ m.p. 124–125°C).

Trans-5,8-diacetoxy-2-acetyl-3-chloro-1,2,3,4-tetrahydronaphthalene (19)

Aluminium chloride (5 g) in dry dichloromethane (20 ml) at

–5°C was stirred and treated dropwise with acetyl chloride (4 ml). The resulting mixture was then treated with the diacetate (12) (2 g; 8,13 mmol) in dichloromethane (10 ml) at such a rate that the internal temperature did not exceed 0°C. Thereafter, the reaction mixture was stirred for 12 h at 20°C, then poured into cold (5°C) 0,5M-hydrochloric acid (120 ml). The organic phase was separated and the aqueous phase was extracted with dichloromethane (5 \times 50 ml). The combined organic phase (purple) was washed with saturated sodium hydrogen carbonate (3 \times 50 ml) and the residue obtained upon work-up was chromatographed using ethyl acetate–light petroleum (1:5) as eluent to give the chloroketone (19) (1,99 g; 75%) as white needles, m.p. 134–135°C (from ethanol); ν_{max} 1763 and 1715 cm^{-1} ; δ 2,27 (3H, s, COCH_3), 2,3 (6H, s, 2 \times OCOCH_3), 2,6–3,46 (5H, m, 1- and 4- H_2 , and 2-H), 4,3 (1H, dt, $J_{3a,4a} = J_{3a,2a}$ 11 Hz, $J_{3a,4a}$ 6,3 Hz, 3- H_{ax}), and 6,92 (2H, s, 7- and 8-H) (Found: C, 59,3; H, 5,4. Calc. for $\text{C}_{16}\text{H}_{17}\text{ClO}_5$: C, 59,2; H, 5,2%).

5,8-Diacetoxy-2-acetylnaphthalene (20)

Chloroketone (19) (350 mg; 1,08 mmol) in anhydrous dimethylformamide (3,5 ml) containing lithium chloride (180 mg; 4,25 mmol) was stirred at room temperature for 20 h after which the reaction mixture was poured into water (20 ml), and the yellow precipitate was collected by filtration and dried, to give the ketone (20) (300 mg; 97%) as canary-yellow needles, m.p. 135–136°C (from ethanol); ν_{max} 1760 and 1700 cm^{-1} ; δ 2,27 (3H, s, COCH_3), 2,35 (6H, s, 2 \times OCOCH_3), 6,92 (2H, s, 6- and 7-H), 8,1 (1H, dd, J 8 and 2 Hz, 3-H), 8,33 (1H, d, J 8 Hz, 4-H), and 8,9 (1H, d, J 2 Hz, 1-H) (Found: C, 67,15; H, 4,95. Calc. for $\text{C}_{16}\text{H}_{14}\text{O}_5$: C, 67,1; H, 4,9%).

5,8-Diacetoxy-2-acetyl-1,4-dihydronaphthalene (13)

The chloroketone (19) (1,50 g; 4,62 mmol) in anhydrous dimethylformamide (15 ml) containing lithium chloride (800 mg; 19 mmol) was stirred at 0°C for 20 h and the reaction mixture was then poured into water (100 ml). The precipitate was filtered and dried to afford a crude mixture (1,20 g) which was chromatographed using ethyl acetate–light petroleum (3:10) as eluent. The first fraction isolated was the acetylnaphthalene (20) (80 mg; 6%), identical in all respects to the material obtained before, followed by the enone (13) (1,08 g; 81%) as fine, white needles, m.p. 147–148°C (from ethanol); ν_{max} 1760 and 1705 cm^{-1} ; δ 2,29 (3H, s, COCH_3), 2,32 and 2,34 (each 3H, s, OCOCH_3), 3,4 (4H, m, 1- and 4- H_2), and 6,92 (3H, br.s, 3-, 6-, and 7-H) (Found: C, 66,9; H, 5,65. Calc. for $\text{C}_{16}\text{H}_{16}\text{O}_5$: C, 66,7; H, 5,6%).

5,8-Diacetoxy-2-acetyl-1,2,3,4-tetrahydronaphthalene (9)

The enone (13) (2 g; 6,94 mmol) in ethanol (300 ml) containing platinum(IV) oxide (50 mg) was hydrogenated at atmospheric pressure and room temperature until hydrogen uptake ceased. The ethanol solution was filtered, and evaporation of the solvent afforded the ketone (9) (2 g; 100%) which crystallized with difficulty, to give white rosettes, m.p. 82–84°C (from light petroleum); ν_{max} 1760 and 1716 cm^{-1} ; δ 2,27 (3H, s, COCH_3), 2,35 (6H, s, 2 \times OCOCH_3), 2,45 (1H, m, 2-H), 2,67 (6H, m, 1-, 3-, and 4- H_2), and

7,0 (2H, s, 6- and 7-H) (Found: C, 66,4; H, 6,1. Calc. for $C_{16}H_{18}O_5$: C, 66,2; H, 6,2%).

2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene (7)

The diacetate (9) (2 g; 6,9 mmol) in methanol (80 ml) was heated under reflux under a nitrogen atmosphere and was then slowly treated, with stirring, with aqueous sodium hydroxide (6,9 ml of a 5M-solution; 34,5 mmol). After addition, the solution was heated under reflux for an additional 10 min and then treated with dimethyl sulphate (4,41 g; 35 mmol) and heated under reflux for 2 h. Further aliquots of sodium hydroxide (2 ml of a 5M-solution; 10 mmol) were added, and the mixture was heated under reflux for 10 min followed by the addition of dimethyl sulphate (1,26 g; 10 mmol) and further reflux of 2 h, before the addition sequence was repeated once more. The cooled reaction mixture was poured into ammonium chloride (120 ml of a 3M-solution) and extracted with ether. The residue obtained upon work-up was chromatographed using ethyl acetate–light petroleum (3 : 10) as eluent to afford the target ketone (7) (1,36 g; 84%) identical in all respects to the material isolated before.

Acknowledgements

The authors thank the Foundation for Research Development as well as the Councils of the Universities of Cape Town and the Western Cape for financial support.

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