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A STEREOCONVERGENT SYNTHESIS OF (+)-4-DEMETHOXYDAUNOMYCIN[1]

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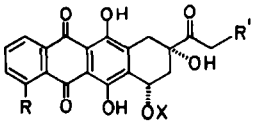
Abstract—Sharpless kinetic asymmetric epoxidation on (±)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (**8**) followed by LAH reduction gave *R*-2-(*S*-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene and the undesired antipode. The former was converted to *R*-(−)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene[*R*-(−)-**5**], while the latter was epimerized and recycled. *R*-(−)-**5** has been exploited for the synthesis of (+)-4-demethoxydaunomycin.

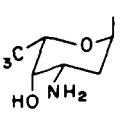
During the past decade the anthracycline antibiotics such as daunomycin (**1a**) and adriamycin (**2a**) have emerged as the most effective drugs for the treatment of a broad spectrum of human cancers.[2] However, like other anticancer agents, these compounds also display various side effects, the most serious being the cumulative dose dependent cardiotoxicity.[3] To overcome this major drawback, there has been a continued interest in the total synthesis of these antibiotics including one of its analogues, 4-demethoxydaunomycin (**3a**), which has now assumed considerable clinical importance as it is found to be 8 to 10 times more effective than daunomycin or adriamycin.[4] Further, 4-demethoxydaunomycin (**3a**) is orally active. As there is no possibility of obtaining **3a** by fermentation, and many suitable methods[5a] for the synthesis of L-daunosamine including two of our approaches[5] either starting from glucose or glucosamine and its coupling to the aglycone, [4-demethoxydaunomycinone (**3b**)] have already been accomplished,[6] our main efforts have been directed towards evolving a convenient synthesis of the aglycone moiety, 4-demethoxydaunomycinone (**3b**). During the last 3 to 4 years, we have evolved various approaches[7–9] for the synthesis of different aglycones such as daunomycinone (**1b**),[7] 11-deoxydaunomycinone,[8] and 4-demethoxydaunomycinone (**3b**).[9] The distinguishing features of our approaches are their simplicity, flexibility and conceptually novel which can be adopted for the preparation of anthracyclinone analogues. In spite of the fact that we have evolved innumerable methods for the synthesis of 4-demethoxydaunomycinone (**3b**), our primary objective of obtaining 4-demethoxydaunomycin (**3a**) in gram quantities remained as an unsolved task mainly due to non-availability of a suitable method for the preparation of enantiomerically pure aglycone (−)-4-demethoxydaunomycinone. As (−)-4-demethoxy-7-deoxydaunomycinone[(−)-**4**] can be conveniently transformed[10] into optically active aglycone (**3b**), most of the researchers from various schools have directed their efforts for the preparation of (−)-**4**, either by resolution[11] of (±)-**4** or by asymmetric synthesis.[12] However, these methods suffer from the severe drawback in the conversion of the undesired antipode to either racemic or the desired antipode.

Other reported procedures[6] make use of an optically active 2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [*R*-(−)-**5**] by adopting it as an AB synthon which is then transformed into the desired (−)-**5** by adopting Wong's procedure.[13] The *R*-(−)-**5** has been obtained either by resolution[14] of (±)-**5** or by microbial[12a] or chemical reduction[15] to the products which were then converted to *R*-(−)-**5** by appropriate reactions. However, in all these methods the conversion of the undesired antipode to the desired compound is impractical.

We envisaged that Sharpless asymmetric epoxidation[16] on a suitable allylic alcohol would provide us with an optically active epoxy alcohol that could be readily converted to the desired (−)-**5** which can then



a : X =

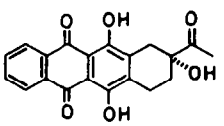


b : X = H

1 : R = OMe, R' = H

2 : R = OMe, R' = OH

3 : R = R' = H



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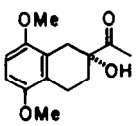

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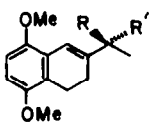
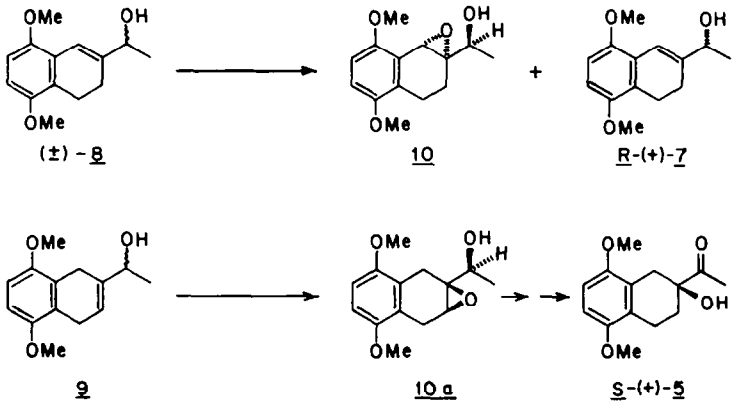


6 : R = OH, R' = H

7 : R = H, R' = OH

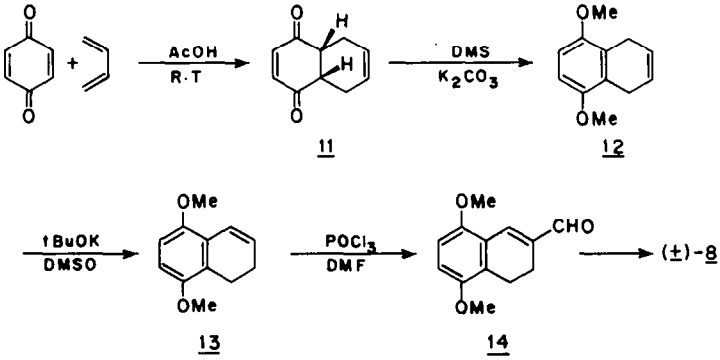


Scheme 1.

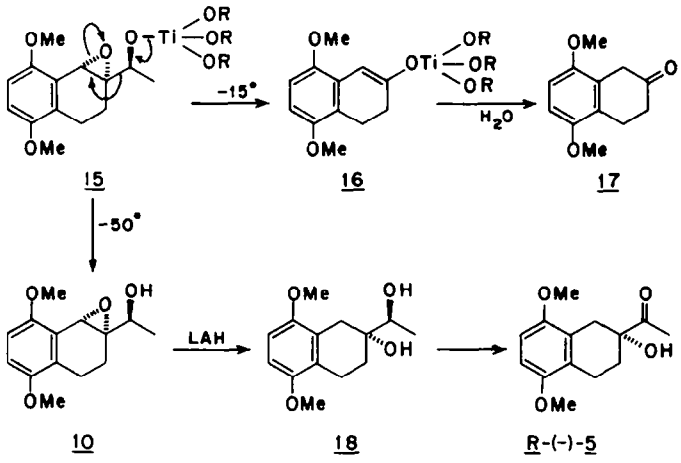
be built up to the tetracyclic system (4). For this purpose allylic alcohols, 8 and 9 were considered as they can be kinetically resolved into a mixture of epoxide and *R*-alcohol based on the fact that the *S*-enantiomer reacts much faster compared to the *R*-enantiomer when natural L(+)tartaric acid ester is used in the epoxidation reaction with t-butylhydroperoxide (TBHP) in the presence of titanium tetraisopropoxide (TIP). Thus alcohol **8** is expected to give the desired epoxide (**10**) (Scheme 1) whereas alcohol (±)-**9** will yield the undesired epoxide (**10a**), because titanium alkoxide tartrate catalyst strongly favours *erythro* product. The epoxide **10** can be transformed to *R*-(−)-**5** by appropriate reactions and the undesired *R*(+)alcohol (**8**) can be inverted to the desired '*S*' alcohol **6** which can be recycled to *R*-(−)-**5**. Based on the above prediction our attention has been directed to the preparation of the required allylic alcohol **8**.

The reported procedures[17] for the preparation of **8** are lengthy and require chromatographic separation. We delineate a process (Scheme 2) for the synthesis of allylic alcohol (**8**), which is simple in operation and may be carried out in large scale. Diels–Alder reaction of benzoquinone with butadiene in acetic acid at room temperature afforded the adduct **11** which was methylated with dimethylsulfate in the presence of potassium carbonate in refluxing acetone to afford 5,8-dimethoxy-1,4-dihydronaphthalene (**12**) as colourless solid in quantitative yield.[19] Vilsmeier formylation[20] of **12** with phosphorous oxychloride and dimethylformamide failed under various reaction conditions to afford the formylated product at the olefinic carbon enroute to **14**. We therefore decided to isomerize the double bond in **12** to a more reactive position as in **13**. Thus **12** was treated with potassium t-butoxide in dimethylsulfoxide at room temperature under nitrogen atmosphere to afford 5,8-dimethoxy-3,4-dihydronaphthalene (**13**) in quantitative yield. **13** when subjected to Vilsmeier formylation reaction conditions[18] produced the expected 5,8-dimethoxy-3,4-dihydro-2-naphthaldehyde (**14**)[17b] as a single crystalline product, m.p. 91–92°. Grignard reaction on aldehyde **14** with methylmagnesium iodide in ether was straightforward and gave racemic 2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (**8**)[17] in 90% yield. The above sequence of reactions gave the desired racemic alcohol (**8**) in 66% overall yield from benzoquinone, thereby providing a method for obtaining sufficient amounts of **8** for enantioselective epoxidation studies.

First, kinetic resolution of (±)-**8** by using the Sharpless asymmetric epoxidation procedure[15] was studied at −15°. Thus allylic alcohol (**8**) was treated with titanium tetraisopropoxide (TIP), L(+)-diisopropyl tartrate (DIPT) and t-butyl hydroperoxide (TBHP) in the molar ratio of 1:1:0.6 respectively at −15°. The progress of the reaction was monitored by titrating the concentration of TBHP in the reaction mixture. Initially the reaction was very fast and became sluggish after 4 hr. After 10 hr, reaction was almost complete as indicated by the presence of two compounds, one of which had the R_f value corresponding to the starting material while other was faster moving than the allylic alcohol. This mixture was subjected to silica gel column chromatography using benzene as eluant; the faster moving component was



Scheme 2.



Scheme 3.

obtained in almost 40% yield and was characterized as 5,8-dimethoxy-2-tetralone (**17**)[22] by comparison (spectral as well as m.p.) with an authentic sample. The slower moving component was crystallised from hexane and characterized as *R* - (+) - 2 - (1 - hydroxyethyl) - 5,8 - dimethoxy - 3,4 - dihydronaphthalene (**7**). The *R*-configuration of **7** was given by comparison of its m.p. (88–89°) and $[\alpha]_D$ value [+20.4°, (*c*, 1.55 EtOH)] with the known data for *S*-(−)-**6**[15b,21] [m.p. 88–89° $[\alpha]_D$ −20.4 (*c*, 1.55 EtOH)].

The isolation of optically active *R*-(+)-**7** from the reaction mixture clearly indicated that asymmetric epoxidation had taken place as expected. (*S*)-Allylic alcohol (**6**) had epoxidized but unfortunately the epoxyalcohol had undergone a fragmentation reaction under these reaction conditions to give tetralone (**17**). The formation of tetralone (**17**) may be explained by assuming the intermediate **15** undergoing Grob type fragmentation[23] to enolate (**16**). **16** on work up produces tetralone (**17**) (Scheme 3). To our knowledge this type of cleavage has not been reported under Sharpless epoxidation conditions.

To circumvent the fragmentation reaction we decided to repeat the above epoxidation at lower temperature; thus the allylic alcohol (**8**) was subjected to kinetic resolution under the Sharpless asymmetric epoxidation conditions described earlier at below −50°. After completion of the reaction in 10 hr, aqueous acetone was added to the reaction mixture maintained at the same temperature (−55 to −50). The product obtained after removal of inorganic salts and solvent, was worked up as usual. TLC of the product indicated absence of tetralone (**17**) and presence of a slightly slower moving compound besides starting material. The separation of the mixture was unsuccessful because of their close R_f values as well as the unstable nature of the epoxide. The crude reaction mixture was reduced with LAH in tetrahydrofuran to give a semisolid (containing two products with distinct R_f values 0.6 and 0.3 which was subjected to chromatographic separation (silica gel) to obtain allylic alcohol *R*-(+)-**7**, m.p. 88–89 $[\alpha]_D^{20}$ + 20.3 (*c*, 0.5, EtOH) and *R*-(−)-2-(*S*-1-hydroxyethyl-2-hydroxy-5,8-dimethoxy - 1,2,3,4 - tetrahydronaphthalene (**18**),[21] m.p. 154–155° $[\alpha]_D^{20}$ −49.7 (*c*, 0.5, EtOH) each in 35% yield.

The undesired antipode *R*-(+)-**7** was inverted by treating it with triphenylphosphine, diethyl azodicarboxylate and benzoic acid in THF[24] to give the benzoate of (−)-**6** which was de-O-benzoylated with a catalytic amount of sodium methoxide in methanol to obtain (−)-**6** in overall 70% yield. The asymmetric epoxidation of (−)-**6** with TIP, L-(+)-DIPT and TBHP followed by reduction with LAH gave **18** in 83% yield, m.p. 152–154°, $[\alpha]_D$ −47.6 (*c*, 0.5 EtOH).

Oxidation of (−)-**18** with Fetizon's reagent[25] gave *R*-(−)-**4** m.p. $[\alpha]_D^{20}$ −48.8 (*c*, 0.5 $CHCl_3$) which was fused with phthalic anhydride in an intimate mixture of $AlCl_3$—NaCl (5:1) at 180° for 2 min and usual work up gave (−)-4-demethoxy-7-deoxydaunomycinone[6] (**4**) (m.p. 227–228°) $[\alpha]_D^{20}$ −84° (*c*, 0.1, $CHCl_3$).

As the conversion of **4** to 4-demethoxydaunomycinone (**3b**)[10] and subsequently to 4-demethoxydaunomycin (**3a**)[6] by convenient methods have already been discussed, we consider that our present approach can constitute a practical total synthesis of optically active **3a**.[26]

EXPERIMENTAL

M.ps were determined in open capillaries and are uncorrected. Optical rotations were measured on JASCO DIP 181 polarimeter in $CHCl_3$ or EtOH. IR spectra were recorded in nujol mulls unless stated to the contrary on Perkin–Elmer Infracord model 683 spectrometer with NaCl optics. ^{1}H-NMR spectra recorded in $CDCl_3$ using TMS as internal standard on Varian T-60 or Varian FT-80A spectrometers (δ = 0 ppm). Mass spectra (MS) were obtained with a CEC spectrometer model 21-110B, using an ionising voltage of 70 eV and a direct inlet system.

Column chromatography was performed using silica gel (100–200 mesh, Acme make). Progress of the reactions was checked by TLC on 0.2 mm layers of silica gel, using an iodine chamber for visualisation.

5,8-Dimethoxy-1,4-dihydronaphthalene (**12**). To a soln of *p*-benzoquinone (54.0 g, 0.5 mol) in glacial AcOH (500 ml), liquid butadiene (108 g, 2 mol) was added while stirring and the clear soln was allowed to stand at room temp for 36 hr. The contents were poured on crushed ice with stirring. The colourless ppt was filtered, washed with ice-cold water and dried (72.2 g, 90%).

A mixture of the above adduct (64.8 g, 0.4 mol), Me_2SO_4 (126.0 g, 1 mol) and K_2CO_3 (200 g) in dry acetone (1.0 lit) was refluxed for 36 hr (TLC, benzene). Acetone was distilled off and the contents were cooled. Crushed ice was added to the mixture, the solid was filtered, washed with water (till free from

carbonate) and dried to give **12** (68.3 g, 90%) as colourless solid, m.p. 51° (lit.[19] 50°) ^{1}H-NMR: 3.26 (br s, 4H, CH_2 – 1 & 4); 3.76 (s, 6H, OMe), 5.90 (br s, 2H, 2- & 3-H), 6.53 (s, 2H, aromatic).

5,8 - *Dimethoxy*-3,4-*dihydronaphthalene* (**13**). To a soln of **12** (57.0 g, 0.3 mol) in dry DMSO (250 ml), t-BuOK (4.0 g, 0.038 mol) was added while stirring. The contents were further stirred under a N_2 atm for 6 hr (TLC, benzene). The mixture was poured over crushed ice with stirring. The colourless solid was filtered, washed with ice-cold water and dried to afford **13** (56.0 g, 98%), which crystallised from hexane as colourless crystals, (m.p. 70°). ^{1}H-NMR: (CCl_4) 2.1–2.7 (m, 4H, CH_2 – 3 & 4), 3.80 (s, 6H, —OMe), 5.85 (m, 1H, H-2), 6.63 (s, 2H, – 6 & 7-H), 6.83 (m, 1H, – 1-H). M^+ 190. (Found: C, 75.72; H, 7.42%. $C_{12}H_{14}O_2$ Requires: C, 75.79; H, 7.36%).

5,8-*Dimethoxy*-3,4-*dihydro*-2-*naphthaldehyde* (**14**). To a precooled (0°) soln of **13** (38.0 g, 0.2 mol) in DMF (80 ml), Vilsmeier reagent [prepared from $POCl_3$ (46.0 g, 0.3 mol) and DMF (36.5 g, 0.5 mol)] was added. The mixture was heated at 80° for 4 hr and after cooling it was poured over crushed ice. The contents were allowed to attain room temp and the solid was filtered, washed with water and dried to give **14**[17b] (39.0 g, 90%). Crystallisation from MeOH gave light yellow crystals m.p. 91–92°. ^{1}H-NMR: 2.43–2.86 (m, 4H, CH_2 – 3 & – 4), 3.76 (s, 3H, OMe), 3.83 (s, 3H, OMe), 6.60 (d, J = 8 Hz, 1H, – 6-H), 6.82 (d, J = 8 Hz, 1H, 7-H), 7.66 (s, 1H, 1-H). 9.63 (s, 1H, –CHO); IR: 1660 cm^{-1} (C=O); M^+ 218. (Found: C, 71.60; H, 6.47%. $C_{13}H_{14}O_3$ Requires: C, 71.55; H, 6.42%).

2 - (1 - *Hydroxyethyl*) - 5,8 - *dimethoxy* - 3,4 - *dihydronaphthalene* (**8**). To an ethereal soln of MeMgI (60.0 ml, 24.9 g, 0.15 mol) a dilute soln of **14** (21.8 g, 0.1 mol) in ether (600 ml) was added dropwise under vigorous stirring, at 10 to 15°, under an atmosphere of N_2. After complete addition of the ether soln (15–20 min) the contents were stirred at room temp for 1 hr. After completion of the reaction (TLC, benzene) saturated NH_4Cl aq (100 ml) was added and the contents were stirred for 20 min. The organic layer was separated, washed with water, dried over Na_2SO_4 and concentrated to give **8** as semi solid. It solidified on addition of hexane. The solid was filtered and recrystallised from hexane to give pure **8** (21.15 g, 90%) as colourless crystalline product m.p. 78–79° (lit.[17b] m.p. 78–79°). ^{1}H-NMR: 1.30 (d, J = 6 Hz, 3H, $\underline{CH_3}$—CHOH), 1.83 (br s, 1H, –OH), 2.16–2.43 (m, 2H, CH_2—3), 2.66–2.97 (m, 2H, CH_2—4), 3.76 (s, 6H, OMe), 4.43 (9, 1H, C$\underline{H}$OH), 6.63 (s, 2H, aromatic), 6.76 (s, 1H, vinylic). IR: 3470 cm^{-1} (OH), M^+: 234. (Found: C, 71.91; H, 7.73%. $C_{14}H_{18}O_3$ Requires: C, 71.79; H, 7.69%).

5 - 8 - *Dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* - 2 - *one* (**17**) *and* R(+)2 - (1 - *hydroxyethyl*) - 5,8 - *dimethoxy* - 3,4 - *dihydronaphthalene* (**7**). To precooled (– 15°) CH_2Cl_2 (40 ml), was added in sequence titanium tetraisopropoxide (1.48 ml, 5 m.mole), a soln of (+) diisopropyl tartrate (1.46 ml, 6 m.mol) in CH_2Cl_2 (2 ml), the racemic alcohol **8** (1.17 g, 5 m.mole) in CH_2Cl_2 (5 ml) and t-butyl hydroperoxide (0.56 ml, 3.0 m.mol, 5.33 M-CH_2Cl_2 soln) with an interval of 5 min. Progress of the reaction was monitored by iodometric titration for the concentration of t-butylhydroperoxide in the mixture. After 10 hr, 90% of the added t-butyl hydroperoxide was consumed. The reaction was quenched by the addition of precooled (0°) aqueous acetone (97%) and while stirring the contents were brought to room temp. Inorganic ppt was filtered off and washed with CH_2Cl_2 (50 ml). TLC (benzene) showed two products, one corresponding to starting material and other faster than the former. The combined filtrate was concentrated under reduced pressure to give a gummy material. This was dissolved in ether (100 ml) and stirred with 1N NaOH (15 ml) at 0° for 30 min. Organic layer was separated, washed with water and dried (Na_2SO_4). Purification by column chromatography (benzene) afforded two fractions A & B.

Fraction 'A' afforded colourless crystalline product identified as **17** m.p. 97–98° (lit.[22] m.p. 98–99°). ^{1}H-NMR (CCl_4): 2.23 (t, 2H, 3-H), 2.90 (t, 2H, 4-H), 3.23 (s, 2H, 1-H), 3.63 (s, 6H, OMe), 6.23 (s, 2H, aromatic); IR: 1710 cm^{-1} (C=O); M^+ 206.

Fraction 'B' afforded a colourless solid, crystallised from hexane (0.47 g, 40%), (m.p. 88–89°). $[\alpha]_D^{20}$ + 20.8° (*c* 1.5, EtOH) ^{1}H-NMR and IR identical with (±)**8**. It was identified as (+)**7**.

R - (–) - 2 - (S - 1 - *Hydroxyethyl*) - 2 - *hydroxy* - 5,8 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**18**). To precooled (– 50 to – 55°) CH_2Cl_2 (40 ml) was added in sequence titanium tetraisopropoxide (2.96 g, 0.01 mole) in CH_2Cl_2 (5 ml), racemic alcohol **8** (2.34 g, 0.01 mol) in CH_2Cl_2 (5 ml) and t-butyl hydroperoxide (1.16 ml, 6.25 m.mole, 5.33 M CH_2Cl_2 soln), under a N_2 atm, with an interval of 5 min. Reaction was stirred at – 50 to – 55° for 10 hr.

The reaction was quenched by the addition of precooled (– 50 to – 55°) aqueous acetone (97%) and the contents were stirred for 2 hr to attain ambient temp. Inorganic salts were filtered off and the ppt washed with CH_2Cl_2 (50 ml). Combined filtrate was concentrated on a rotary evaporator to give a colourless oily compound. TLC (benzene) indicated formation of a new product along with starting material. The contents were dissolved in ether (150 ml) and a precooled (0°) soln of 1N NaOH (25 ml) was added at 0°. The two phase mixture was stirred at 0° for 30 min and the organic layer separated, washed with water and dried (Na_2SO_4). Concentration of the solvent gave a colourless thick mass (2.36 g). It was dissolved in dry THF (50 ml) and lithium aluminium hydride (0.305 g, 8 m.mol) added in portions. Contents were stirred at room temp for 4 hr (TLC, benzene, acetone). A sat Na_2CO_3 aq was added to the mixture and the contents were stirred vigorously for 30 min. Inorganic ppt was filtered off and washed with $CHCl_3$. Combined filtrate was concentrated under reduced pressure and the semisolid was chromatographed on a silica gel column with benzene as solvent. Fractions 'A' and 'B' were collected.

Fraction 'A' afforded a colourless solid, (m.p. 86–89°), which on crystallisation from hexane furnished a crystalline product (0.82 g, 38%), (m.p. 88–89°), $[\alpha]_D^{20}$(+)20.3° (*c* 0.5 EtOH) which was in concurrence with *R*(+)-2-(1-hydroxyethyl)-5,8-dimethoxy - 3,4 - dihydronaphthalene (**7**).

Fraction 'B' afforded a colourless solid, which on crystallisation from ether furnished needles of **18** (0.880 g, 40%), m.p. 154–155°, $[\alpha]_D^{20}$ – 49.4° (*c* 0.50, EtOH), (lit.[21] m.p. 154–155°) $[\alpha]_D^{20}$ – 49.7° (*c* 0.50, EtOH). ^{1}H-NMR: 1.36 (d, J = 6 Hz, 3H, $\underline{CH_3}$—CHOH) 1.83–2.33 (m, 4H, CH_2 and –OH), 2.46–2.96 (m, 4H, CH_2 1- & 4-), 3.76 (q, 1H, merged with singlet, C$\underline{H}$—OH), 3.79 (s, 3H, OMe), 3.80 (s, 3H, OMe), 6.63 (s, 2H, aromatic).

S - (–) - 2 - (1 - *Hydroxyethyl*) - 5,8 - *dimethoxy* - 3,4 - *dihydronaphthalene* (**6**). To a soln of (+)**7** [0.94 g, 4 m.mol, $[\alpha]_D^{20}$ + 20.3 (*c* 0.5, EtOH)] and triphenylphosphine (1.15 g, 4.4 m.mol) in dry THF (15 ml) was added benzoic acid (0.54 g, 4.4 m.mol) in THF (4 ml) and diethyl azodicarboxylate (DEAD) (0.66 g, 4.4 m.mol) in THF (4 ml) at room temp. The mixture was stirred for 2 hr at room temp. Excess solvent was removed under reduced pressure and the residue after dissolving in benzene was passed through a short silica gel column to obtain pure benzoate of (–)**6** as semisolid. ^{1}H-NMR: 1.53 (d, J = 6 Hz, 3H, $-CH_3$), 2.23–2.43 (m, 2H, CH_2), 2.90–3.16 (m, 2H, CH_2), 3.70 (s, 6H, OMe), 5.66 (q, J = 6 Hz, 1H, C$\underline{H}$OAr), 6.43 (s, 2H, aromatic), 6.73–8.00 (m, 5H, aromatic).

Crude benzoate (0.68 g, 2m.mole) was stirred with NaOMe (0.12 g, 2 m.mole) in MeOH (10 ml) at room temp for 5 hr. Solvent was removed on a rotary evaporator and the compound extracted with $CHCl_3$. The organic layer was washed with brine and dried over Na_2SO_4. On filtration and concentration it gave a semisolid. On silica gel chromatography (hexane: acetone, 9:1), it afforded crystalline (–)**6** (0.42 g, 90%), m.p. 86–88°, $[\alpha]_D^{20}$ – 18.6 (*c*, 0.5, EtOH).

R - 2 - (s - 1 - *Hydroxyethyl*) - 2 - *hydroxy* - 5,8 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**18**) *by epoxidation of* S(–)**6**. To be precooled (– 50 to – 55°) soln of CH_2Cl_2 (20 ml), were sequencially added titanium tetraisopropoxide (0.9 g, 3 m.mol), L(+)diisopropyl-tartrate (0.88 g, 3 m.mol in 2 ml CH_2Cl_2), S(–) allyl alcohol **6** (0.70 g, 3 m.mol) in CH_2Cl_2 (2 ml) and t-butylhydroperoxide (0.56 ml, 3.0 m.mol, 5.33 M in CH_2Cl_2) under a N_2 atm with the interval of 5 min for each addition. The mixture was stirred at – 50 to – 55° for 10 hr.

Work up as usual provided **10** (620 mg) which was reduced with lithium aluminium hydride (0.19 g, 5 m.mole) to afford **18** (0.464 g, 74%) as a solid, $[\alpha]_D^{20} - 34.6$ (*c*, 0.5, EtOH), which on two crystallisations from ether furnished colourless needles of **18**, m.p. 151–153° $[\alpha]_D^{20} - 47.6$ (*c*, 0.5 EtOH).

R - (−) - 2 - *Acetyl* - 2 - *hydroxy* - 5,8 - *dimethoxy* - 1,2,3,4 - *tetrahydronaphthalene* (**5**). To an aqueous $AgNO_3$ soln (20.0 g, 0.12 mol, in 120 ml water), celite was added while magnetic stirring and to this was added Na_2CO_3 aq (16.0 g, 0.15 mole in 160 mol water) dropwise while stirring. The thick yellow slurry was filtered, washed free of carbonate and dried on rotavapour at 100°.

To this powder was added **18** (7.5 g, 0.03 mole) in 300 ml benzene. The contents were refluxed with vigorous stirring for 4 hr. TLC (silica gel, benzene : acetone 9 : 1) indicated absence of starting material. The benzene soln was filtered hot, the residue washed with a little hot benzene and the filtrate after concentration was chromatographed on a silica gel column to afford **5** (6.0 g, 80%). It was crystallised from hexane (m.p. 128–129°, $[\alpha]_D^{20} - 48.8°$, (*c*, 1.0 $CHCl_3$); lit.[6] m.p. 130–132°, $[\alpha]_D^{20} - 50°$ (*c*, 1.0 $CHCl_3$) ^{1}H-NMR : $CDCl_3$ 1.85, (*t*, 2H, CH_2), 2.30 (*s*, 3H, $COCH_3$), 2.80 (*bs*, 2H, $ArCH_2$), 2.76 (*t*, 2H, $ArCH_2$), 3.40 (*s*, 1H, OH), 3.66 (*s*, 3H, OMe) 3.73 (*s*, 3H, OMe), 6.60 (*s*, 2H, ArH), IR : 1685 cm^{-1} (C=O); M^+ 250.

(−)-4-*Demethoxy*-7-*deoxydaunomycinone* (**4**). A homogeneous mixture of phthalic anhydride (11.0 mg, 0.75 m.mol), *R*(−)**5** (125.0 mg, 0.5 m.mol), anhyd $AlCl_3$ (1.0 g) and NaCl (0.20 g) was immersed in an oil bath preheated to 180°. The contents were stirred for 2 min and cooled. The solid red mass was treated with cold aqueous saturated oxalic acid soln (100 ml). After heating (70°) for 10 min, the contents were cooled, extracted with CH_2Cl_2 (50 ml), and after drying the solvent was evaporated. The orange–red residue (150 mg, 85%) was dissolved in benzene and chromatographed on short silica gel column. The eluate on concentration and crystallisation from benzene afforded optically pure (−)-**4** m.p. 227–228°, $[\alpha]_D^{20} - 84°$ (*c*, 0.1 $CHCl_3$); lit.[6] m.p. 228–230, $[\alpha]_D^{20} - 87°$ (*c*, 0.1, $CHCl_3$). ^{1}H-NMR : 1.95 (m, 2H, CH_2), 2.37 (s, 3H, $\overset{O}{\overset{\|}{C}}-CH_3$), 3.00 (m, 4H, $ArCH_2$), 3.76 (s, 1H, OH), 7.78 (m, 2H, ArH), 8.31 (m, 2H, ArH), 13.39 (s, 2H, ArOH). IR : (nujol) : 1690 (free C=O), 1640 (bonded C=O) cm^{-1} M^+ 352.

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