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A NOVEL SYNTHESIS OF (±)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL, A KEY INTERMEDIATE FOR THE SYNTHESIS OF ANTHRACYCLINONES

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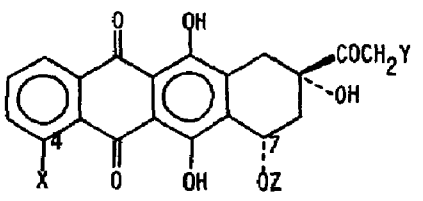
Summary: The title compound((±)-3) was prepared from readily available 5,8-dimethoxy-3,4-dihydro-2-naphthoic acid(4), according to the novel synthetic route visualized in Scheme I.

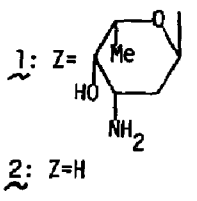
The anthracycline antibiotics, adriamycin(1a) and daunorubicin(1b), are of current interest because of their clinically useful anti-cancer activity.[1] Studies on the structure-activity relationships have uncovered that 4-demethoxy analogues of 1a,b, 4-demethoxyadriamycin (1c) and 4-demethoxydaunorubicin(1d), show reduced cardiotoxicity.[1,2]

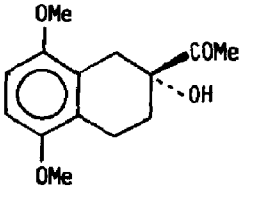
Although various syntheses of the anthracyclinones(2), the aglycones of the anthracyclines (1), have been reported,[3] the synthetic route exploited by Wong, et al.,[4] in which the tetracyclic system is produced by successive inter- and intramolecular Friedel-Crafts acylation, is anticipated most versatile since, in addition to the natural aglycones(2a,b),[4] various structural types of the unnatural anthracyclinones including 4-demethoxyadriamycinone(2c) and 4-demethoxydaunomycinone(2d)[1b,2,5] can be elaborated in racemic or optically active forms from the common synthetic intermediate, racemic or optically active 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol((±)- or (R)(-)-3). The key intermediate((±)-3) was originally synthesized from 2,5-dimethoxybenzaldehyde in seven or nine steps,[4] and various improved syntheses of (±)-3 have been reported.[6,7] Preparation of optically active (R)(-)-3 has also been accomplished either by the optical resolution of (±)-3[5] or by the asymmetric synthesis featuring halolactonization reaction.[8]

We wish to describe here a novel synthesis of (±)-3, presumably more efficient than those reported.[4,6,7]



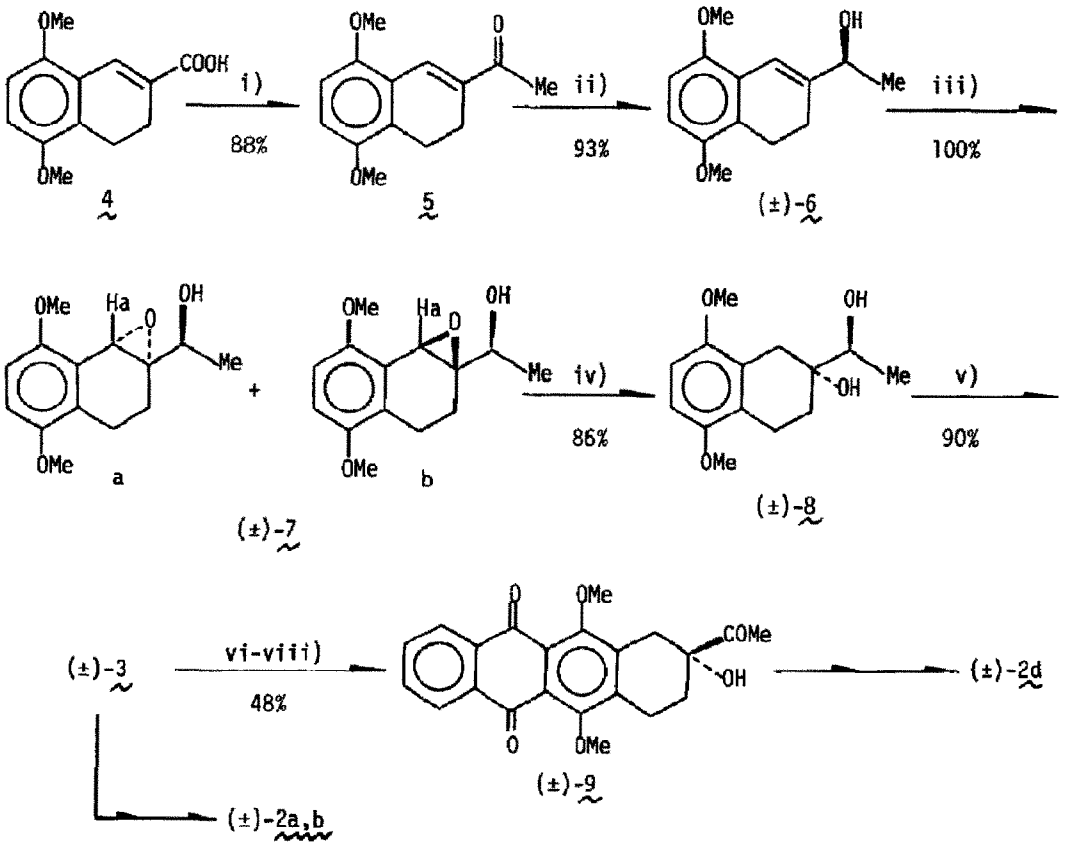
a: X=OMe; Y=OH c: X=H; Y=OH
b: X=OMe; Y=H d: X=H; Y=H





(±)-3
(R)(-)-3

Scheme I



i) MeLi(excess) in Et_2O, rt, 3 hr. ii) $NaBH_4$ in EtOH, rt, 4 hr. iii) t-BuOOH-VO(acac in C_6H_6, rt, 0.75 hr. iv) $LiAlH_4$ in THF, rt, 4 hr. v) Ag_2CO_3-celite(Fetizon reagent) in C_6H_6, reflux, 0.5 hr. vi) o-methoxycarbonylbenzoyl chloride-$AlCl_3$ in CH_2Cl_2, rt, 3 hr. vii) NaOH in aq EtOH. viii) HF, 0-10°C, 20 hr.

As shown in Scheme I, 5,8-dimethoxy-3,4-dihydro-2-naphthoic acid(4), mp 234-237°C(lit., mp > 220°C), readily prepared from 1,4-dimethoxybenzene following to the procedure previously reported from these laboratories,[8] was converted to the methyl ketone(5),[9,10] mp 104-105°C (from isopropyl ether), which, on reduction, afforded the allylic alcohol((±)-6),[9] mp 78-79 (from hexane). Epoxidation of (±)-6 was effected according to the reported procedure,[11] to give the crude α,β-epoxyalcohol((±)-7) as an unstable oil,[9a] showing the epoxide proton (Ha) as two singlets at 4.50 and 4.41 ppm with an integration ratio of 96 to 4 in its NMR spectrum. Since the preferential formation of the allylic alcohol((±)-7a) is reasonably expected from the reported results of the catalytic epoxidation examined by using various structural types of allylic alcohols,[12,13] it might be assumed that (±)-7 consists of two stereomers((±)-7a and (±)-7b) in a ratio of 96 to 4. Without purification, (±)-7 was di

rectly subjected to the condition for reductive cleavage of the epoxide, giving the vicinal-diol((±)-8),[9] mp 145-146°C, after recrystallization from ether. After several unsuccessful attempts,[14] it was finally found that oxidation of (±)-8 was effectively carried out by using Fetizon reagent.[19] Recrystallized (±)-3, mp 100-101°C(from chloroform-ether)(lit.,[4a] mp 100-102°C; lit.,[7] mp 97°C) showed identical spectral properties with those reported.[4a,7,8b] According to the reported method,[4a,5] (±)-3 was further converted to (±)-7-deoxy-4-demethoxy-daunomycinone dimethyl ether((±)-9), mp 187-188°C(from methanol)(lit.,[4a] mp 184-186°C), which was an intermediate for the synthesis of (±)-2d from (±)-3.

Due to its operational simplicity and directness, the overall process exemplified above might have practical values in synthesizing various structural types of racemic and optically active anthracyclinones. We have also succeeded in the synthesis of optically pure (R)(-)-3 by the asymmetric reduction of 5. This is a subject of the accompanying communication.[20]

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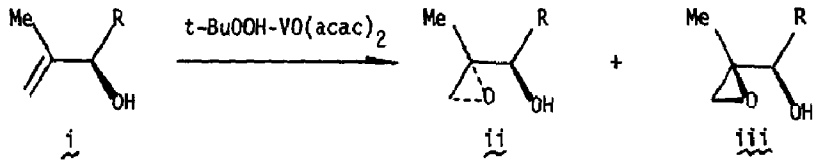
13) The epoxides(i) having the structures similar to that of (±)-6 were reported to give the α,β-epoxyalcohols(ii and iii) in a ratio of 99-95:1-5.[12b,c)]



i
R=Me or n-Bu

ii

iii

14) Attempted oxidations of (±)-8 with chromium trioxide-dipyridine complex(Collins reagent), pyridinium chlorochromate,[15)] and pyridinium dichromate[16)] were found to give 5,8-dimethoxy-2-tetraline[9a)] as a major reaction product in stead of the desired α-hydroxy ketone((±)-3) A combination of N-chlorosuccinimide-dimethylsulfide-triethylamine, being reported to be quite effective for preparing α-hydroxy ketones from vicinal-diols,[17)] simply recovered starting (±)-8. Complex reaction products involing (±)-3 as a minor component could be obtained by usual Jones oxidation and Moffatt oxidation.[18)]

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