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ASYMMETRIC SYNTHESIS OF (R)-(-)-2-ACETYL-1,2,3,4-TETRAHYDRO-2-NAPHTHOL: A MODEL STUDY FOR THE SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLINONES

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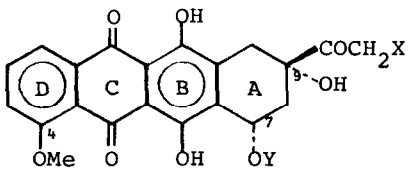
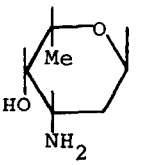
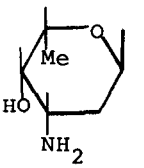
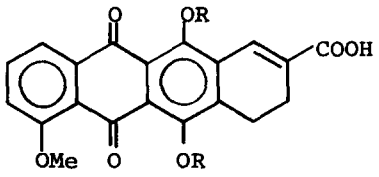
The anthracycline antibiotics daunorubicin(1) and adriamycin(2) have recently attracted much attention because of their promising antineoplastic activity against a variety of experimental tumors and certain types of human cancer.[1] Due to their potent clinical utility, various synthetic routes to racemic anthracyclinone (±)-daunomycinone((±)-3)[2] and an efficient procedure for transforming daunomycinone(3) into adriamycinone(4),[3] have been reported. Coupling of the suitably protected aminosugar with the aglycone (3 or 4) to afford natural antibiotic glycoside(1 or 2), have been described to proceed in a good yield.[3,4] To date, however, little attempts have been made to exploit a practical method which can make possible the large scale preparation of these aglycones and their analogues in an optically active form.[5,6]

Recently we have developed the highly efficient asymmetric bromolactonization reaction which can produce optically active α-hydroxy acid from α,β-unsaturated acid in more than 89% optical yield.[7] Considering the reaction mechanism and steric course of the asymmetric bromolactonization, which have been revealed by our studies,[7] an application of the asymmetric synthesis to the large scale preparation of optically active anthracyclinones(3 and 4) is anticipated quite promising if the tetracyclic α,β-unsaturated acid such as 5 is available. Optically active α-hydroxy ketone moiety, being present at the C-9 position of 3 or 4, can be easily derived from the corresponding optically active α-hydroxy acid, and stereoselective introduction of hydroxy



1: X=H, Y=  ; 2: X=OH, Y=  ;

3: X=Y=H; 4: X=OH, Y=H



R=H or alkyl

5

group at the C-7 position has been known to be achieved under an influence of the chiral center at the C-9 position.[3)]

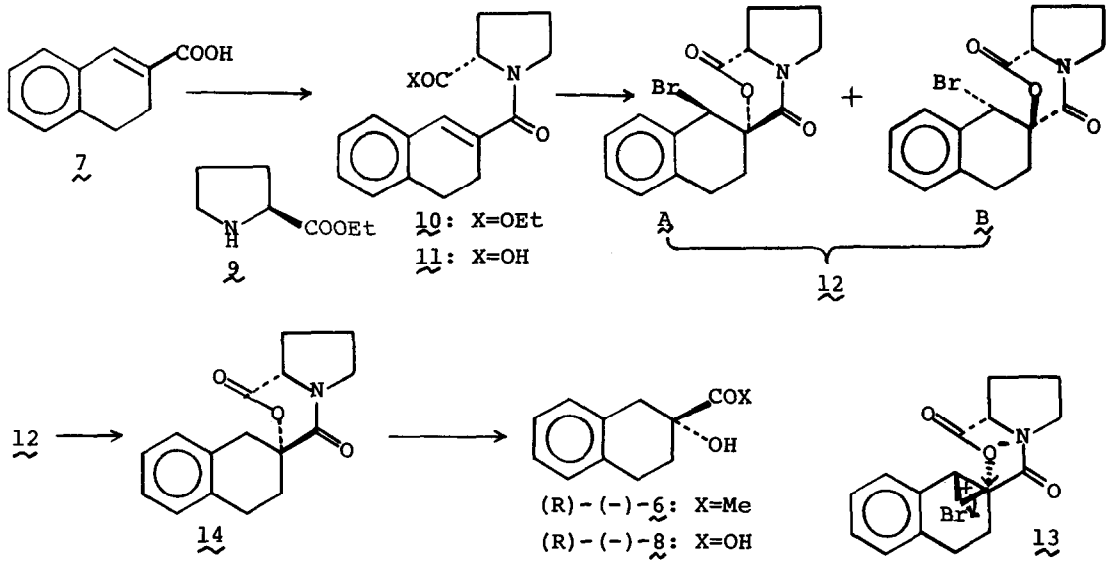
In order to elucidate whether our expectation could be realized, preparation of optically active (R)-2-acetyl-1,2,3,4-tetrahydro-2-naphthol((R)-6), a model compound for anthracyclinone AB ring system, by the use of the asymmetric bromolactonization was attempted.

This report concerns our successful synthesis of (R)-(-)-6, being 92% optically pure, from achiral 3,4-dihydro-2-naphthoic acid(7) by way of (R)-(-)-2-hydroxy-1,2,3,4-tetrahydro-2-naphthoic acid((R)-(-)-8).

Condensation of (S)-(-)-ethyl prolinate(9),[7a)] $[\alpha]_D^{20}$-42.6°(c=2.03, EtOH), with 7,[8)] mp 117-119°C, (diethyl phosphorocyanidate(DEPC)[9)] and triethylamine in dimethylformamide(DMF), 0°C, 2 hr, then r.t., 48 hr) afforded (S)-(-)-ethyl N-acylprolinate(10)[10)] (91%) as colorless needles(recrystallized from ether-hexane), mp 56-57°C, $[\alpha]_D^{20}$-18.6°(c=1.03, EtOH). Subsequent alkaline hydrolysis of 10(KOH(1.3 eq.) in H_2O-EtOH(1:1), r.t., 5 hr) quantitatively yielded (S)-(-)-N-acyl proline(11)[10a)] as a colorless caramel, $[\alpha]_D^{20}$-93.3° (c=2.16, $CHCl_3$).

Bromolactonization of the potassium salt of 11,[11)] which was obtainable by treating 11 with KO-t-Bu(1.0 eq.) in DMF, was effected by using N-bromosuccinimide(NBS)(2.0 eq.) in DMF(-20°C, 2 hr, then r.t., 48 hr). Aqueous work-up and evaporation of the ethyl acetate extracts in vacuo gave crude bromolactone(12)[10a)] (79%), yellow needles, mp 166-170°C, $[\alpha]_D^{20}$-68.6°(c=1.01, $CHCl_3$), as the sole reaction product. Since the crude 12 could be converted to (R)-(-)-8 which was 92% optically pure(vide infra), it became evident that the crude 12 contained two diastereomers(12A and 12B) in a ratio of 96:4. The absolute configurations of 12A and 12B, and that of (-)-8 derivable from the predominantly formed diastereomer(12A)(vide infra), were tentatively assigned according to the previous mechanistic studies[7b)] which had established that the asymmetric bromolactonization could preferentially proceed via the transition state such as 13. Recrystallization of the crude 12 from ether-hexane gave pure 12A[10)] as colorless needles, mp 196-197°C, $[\alpha]_D^{20}$-88.8° (c=1.02, $CHCl_3$).

Debromination of the crude 12((n-Bu)$_3$SnH(4.0 eq.) and azobisisobutyronitrile(4.5 mol %) in bromobenzene, 65°C, 9 hr),[12)] followed by successive removing bromobenzene in vacuo(4 mmHg, bath temp.<60°C) and organotin compounds with a silica gel column(solvent, first hexane, then ether), afforded crude lactone(14)[10a)] (76%) as pale yellow needles, mp 165-173°C, $[\alpha]_D^{20}$-156°



(c=0.502, $CHCl_3$). The crude lactone(14) was submitted to acidic hydrolysis (36% HCl, reflux, 3 hr), giving (R)-(-)-8[10a] (93%) as colorless needles, mp 71-76°C, $[\alpha]_D^{20}$-15.0°(c=2.06, acetone), after extractive isolation with ethyl acetate and evaporation in vacuo. Spectral(ir and nmr) and chromatographic (tlc) behavior of (R)-(-)-8 was completely identical with those of the racemic α-hydroxy acid((±)-8)[13] prepared from 2-tetralone[14] according to the reported method.

On the other hand, when the pure 12A was debrominated in a similar manner to that described above, pure lactone(14)[10] (79%), mp 173-175°C, $[\alpha]_D^{20}$-154° (c=0.500, $CHCl_3$), was obtained as colorless needles(recrystallized from ether-hexane). Similar acidic hydrolysis of the pure 14 gave pure (R)-(-)-8[10a] (94%), mp 94-96°C, $[\alpha]_D^{20}$-16.3°(c=2.07, acetone), as colorless needles after repeated recrystallizations from ether-hexane. Since the optical purity of pure (R)-(-)-8, derived from the pure 12A, is considered to be 100%, it is evident that the optical purity of (R)-(-)-8, directly prepared from the crude 12, and the formation ratio of 12A and 12B, can be calculated as 92% and 96:4, respectively.

Treatment of (R)-(-)-8, mp 72-76°C, $[\alpha]_D^{20}$-15.0°(c=1.98, acetone), 92% optically pure, with methyl lithium(10 eq.) in ether(r.t., 2 hr),[15] followed by careful quenching with aq. hydrochloric acid(H_2O:36% HCl 40:3) and purification with a silica gel column(solvent, ether:hexane 2:1), gave (R)-(-)-6[10a,16] (67%), $[\alpha]_D^{20}$-33.1°(c=3.22, $CHCl_3$), as a colorless oil. This oily ketone((R)-(-)-6) showed identical spectral(ir and nmr) and chromatographic (tlc) properties with those of the racemic ketone((±)-6)[10a,17] similarly prepared from (±)-8.

Since the practical synthetic route to (R)-(-)-6 has been exploited as described above, the preparation of optically active anthracyclinones (3 and 4) from the α,β-unsaturated acid such as 5 seems quite promising. Studies along this line are under progress in these laboratories.

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17) The semicarbazone of (±)-6,[10] mp 221-223°C(recrystallized from acetic acid-EtOH), was prepared according to the usual manner.