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AN IMPROVED ASYMMETRIC SYNTHESIS OF (R)-(-)-2-ACETYL-5,8-DIMETHOXY-1,2,3,4-TETRAHYDRO-2-NAPHTHOL. A VERSATILE KEY SYNTHETIC INTERMEDIATE OF OPTICALLY ACTIVE ANTHRACYCLINONES[1)]

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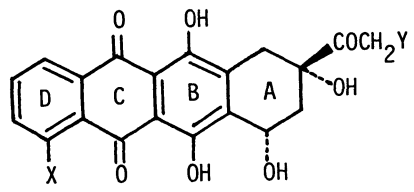
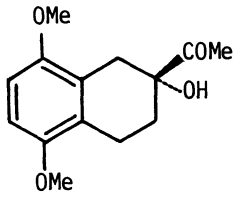
The bromolactonization of the (-)-acetals prepared from readily available 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene and (1R,2R)-(+)-tartaric acid diamide derivatives was found to proceed highly diastereoselectively, giving the seven-membered bromolactones. The bromolactones could be effectively converted to the title compound, >95%ee, in one-pot reaction.

Much synthetic efforts have been devoted to the anthracyclinones(1) in recent years[2)] because the anthracyclines, the glycoside of 1, exhibit promising antineoplastic activity against various types of human cancers.[3)] The title compound ((R)-(-)-2) corresponding to the AB ring system of 1, is considered to be one of the most versatile synthetic intermediates in the chiral synthesis of 1, from which both the natural(1a,b) and the unnatural optically active aglycones(1c,d) can be elaborated.[2,3a,4,5)] Therefore, various ingenious syntheses of (R)-(-)-2 have been hitherto reported by employing optical resolution[2,3a,5b)] or asymmetric synthesis.[2,4,5a,6)]



1

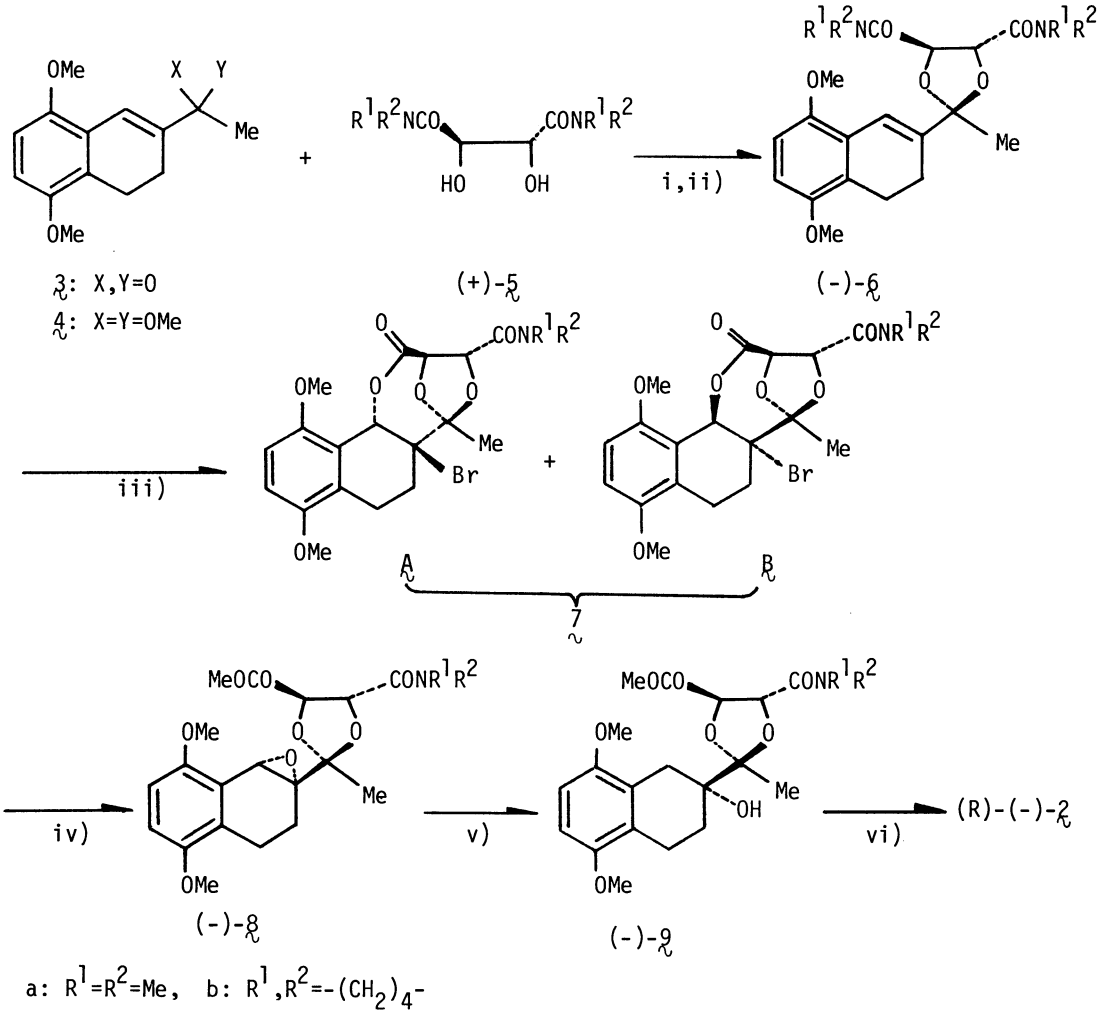
	X	Y
a:	OMe	OH
b:	OMe	H
c:	H	OH
d:	H	H



(R)-(-)-2

Previously, the authors explored the asymmetric synthesis of (R)-(-)-2 in which the bromolactonization of (S)-(-)-N-(5,8-dimethoxy-3,4-dihydro-2-naphthoyl)-proline constitutes the key diastereoselective reaction.[4)] Although we succeeded in preparing (R)-(-)-2 of 97%ee by sequential manipulations of the formed bromolactones, this asymmetric synthesis was found to be less practical because of long synthetic steps for the reaction substrate, 5,8-dimethoxy-3,4-dihydro-2-naphthoic acid, requirement of a stoichiometric amount of expensive (S)-proline as a chiral source, uses of various expensive reagents such as tributyltin hydride and methyllithium for converting the bromolactone to (R)-(-)-2, and rather low overall yield(<30%).

We wish to report here another efficient asymmetric synthesis of (R)-(-)-2



i) $CH(OMe)_3$-d-camphorsulfonic acid(CSA)(cat.) in MeOH, 0 °C ii) molecular sieves 3A in C_6H_6, reflux, then, CSA(cat.) in C_6H_6, reflux iii) MeCONHBr (4.0 equiv.) in DMF-H_2O(100:1), 0 °C, 21.5 h(for 7a), or 18 h(for 7b) iv) anhyd K_2CO_3(1.2 equiv.) in MeOH v) H_2-5% Pd/C in THF, rt vi) concd HCl in EtOH, reflux

which may overcome the above-mentioned impracticality. The explored asymmetric synthesis features the bromolactonization of the optically active (-)-acetals((-)-6), prepared from more readily available 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene(3) and (1R,2R)-(+)-tartaric acid diamide derivatives((+)-5).

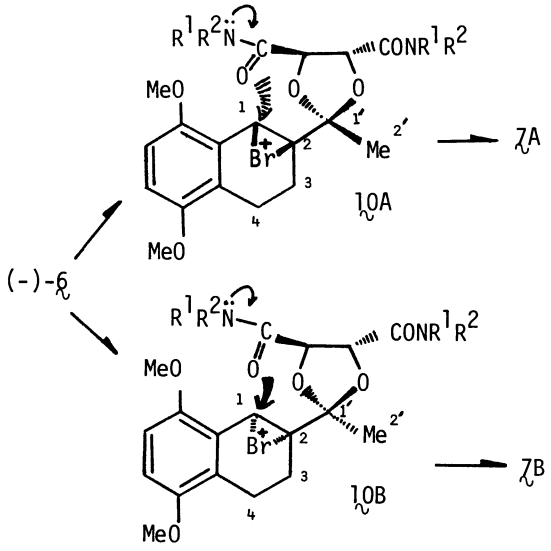
Thus, acetallization of 3[5a,7,10] with trimethoxymethane followed by trans-acetallization of the crude dimethyl acetal(4) with (+)-5a[8,9,10] gave a 92% yield of (-)-6a.[10] Treatment of (-)-6a with N-bromoacetamide in DMF-H_2O(100:1) afforded the crude seven-membered bromolactone(7a)[11] as a mixture of the two diastereomers (7Aa and 7Ba), mp 140 °C(decomp) and $[\alpha]_D^{20}$-110°(c 1.02, $CHCl_3$), in 83% yield.[12,13] Recrystallization of crude 7a gave the major diastereomer(7Aa)[10] in a pure state. Since crude 7a produces (R)-(-)-2, >95%ee(vide infra), the formation ratio of 7Aa to 7Ba can be estimated to be more than 97.5:2.5. The absolute configuration of 7Aa and 7Ba can be deduced by the assumption that the bromolactonization and the epoxide formation(vide infra) proceed in a trans fashion and an S_N2 manner,

respectively.

Alkaline treatment of 7Aa readily produced the (-)-epoxide((-)-8a),[10] in 90% yield. The reduction of (-)-8a quantitatively afforded the (-)-alcohol((-)-9a),[10] which on acidic hydrolysis produced (R)-(-)-2,[4-6] mp 127.5-129 °C and $[\alpha]_D^{20}$-48.4° (c 0.977, $CHCl_3$), 100%ee,[13] in 89% yield. Recrystallization of this sample from Et_2O gave pure (R)-(-)-2, mp 129.5-130.5 °C and $[\alpha]_D^{20}$-48.7°(c 0.368, $CHCl_3$)(lit.,[4] mp 128-129 °C and $[\alpha]_D^{20}$-48.2°(c 0.982, $CHCl_3$)). On the other hand, when crude 7a was successively treated in methanol under the conditions for epoxide formation, catalytic hydrogenation, and acidic hydrolysis without isolation of the intermediates(one-pot reaction), (R)-(-)-2, mp 129.5-130.5 °C and $[\alpha]_D^{20}$-49.0°(0.988, $CHCl_3$), >95%ee,[13] could be obtained in 75% overall yield from crude 7a.

In place of (+)-5a, (+)-5b[10,14] was found to be similarly employable as a chiral source. The enone(3) was converted to (-)-6b[10] in 85% overall yield by the similar manner to that described for (-)-6a. The bromolactonization of (-)-6b under the same condition as described for (-)-6a produced crude 7b,[11] mp 150.5 °C (decomp) and $[\alpha]_D^{20}$-114°(c 1.04, $CHCl_3$), in 78% yield. The formation ratio of the two diastereomers(7Ab and 7Bb) could be similarly determined as more than 97.5:2.5 by the optical purity of (R)-(-)-2 derived from this sample(vide infra). Recrystallization of crude 7b readily afforded the major bromolactone(7Ab).[10] Similar three successive operations on crude 7b to those described for crude 7a produced (R)-(-)-2, mp 129.5-130 °C and $[\alpha]_D^{20}$-47.6°(c 1.02, $CHCl_3$), >95%ee,[13] in 81% overall yield.

The highly diastereoselective bromolactonization may be explained by the kinetically controlled mechanism. Thus, the two diastereomeric bromonium ions(10A and 10B) are anticipated as intermediates for the formation of the major and the minor bromolactones(7A and 7B). Examinations using molecular models disclose that the bond angle between the C_2-C_3 bond and the $C_{1'}$-$C_{2'}$ bond is clearly smaller in 10A than in 10B. That is, the $C_{2'}$-methyl group should be involved in the plane of the 3,4-dihydronaphthalene ring in the conformer of (-)-6 leading to 10A. On the other hand, the conformer of (-)-6 giving rise to 10B should have the $C_{2'}$-methyl group below the plane of the 3,4-dihydonaphthalene ring. Accordingly, less steric interaction between the incoming bromonium ion(Br^+) and the $C_{2'}$-methyl group may be expected for 10A, resulting in the formation of 7A as a kinetically more favored product.



Taking into account the following merits: 1) the reaction substrate(3) is readily available, 2) inexpensive (+)-5 can be used as chiral sources, 3) all reactions can be carried out above 0 °C and strictly anhydrous conditions are not required, 4) conventional cheap reagents are only necessary for converting 3 to (R)-(-)-2, and 5) the optical yields of (R)-(-)-2 are more than 95%ee and the overall chemical yields

of (R)-(-)-2 from 3 exceed 50%, the explored asymmetric synthesis should hold promise as a practical synthetic method of (R)-(-)-2.

References

1) This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.
2) S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 40, 20(1982).
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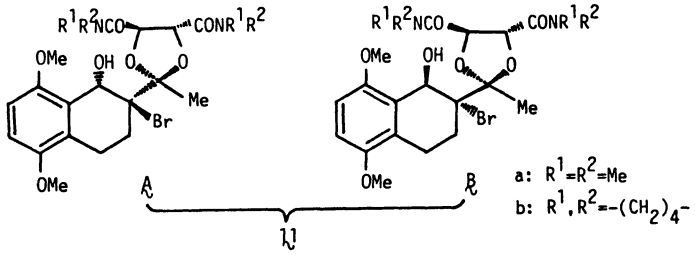
9) For other representative asymmetric synthesis where (+)-5a is used as a chiral auxiliary, see, J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, and H. Yamamoto, J. Am. Chem. Soc., 106, 5004(1984).
10) The following melting points(solvent for recrystallization) and optical rotations were recorded: 3: mp 106-106.5 °C(Et_2O)(lit.,[5a] mp 106-107 °C); (+)-5a: mp 184.5-188.5 °C(CH_2Cl_2-Et_2O), $[\alpha]_D^{20}$+44.3°(c 1.06, EtOH)(lit.,[9] mp 189-190 °C, $[\alpha]_D$+43°(c 3.0, EtOH)); (+)-5b: mp 132.5-135 °C(CH_2Cl_2-Et_2O), $[\alpha]_D^{20}$+34.2° (c 1.02, EtOH); (-)-6a: caramel, $[\alpha]_D^{20}$-4.0°(c 0.99, $CHCl_3$); (-)-6b: mp 163.5-164.5 °C(EtOAc-Et_2O-C_6H_{14}), $[\alpha]_D^{20}$-21.1°(c 1.03, $CHCl_3$); 7Aa: mp 140-140.5 °C (CH_2Cl_2-Et_2O), $[\alpha]_D^{20}$-114°(c 1.00, $CHCl_3$); 7Ab: mp 149.5-150.5 °C(decomp)(EtOAc-Et_2O), $[\alpha]_D^{20}$-116°(c 1.04, $CHCl_3$); (-)-8a: caramel, $[\alpha]_D^{20}$-132°(c 1.02, $CHCl_3$); (-)-9a: caramel, $[\alpha]_D^{20}$-58.1°(c 1.01, $CHCl_3$).
11) Detailed chemical and spectral studies which rigorously support the assigned structure of 7a, will be reported separately.
12) A small amount of bromohydrin(11), being a mixture of the two diastereomers (11A and 11B), was found to be produced as a byproduct(7% and 8% for 11a and 11b, respectively). Separation of 7 and 11 could be readily accomplished by column chromatography(SiO_2: EtOAc, then, EtOAc-MeOH 20:1). In the case of 11a, the formation ratio of 11Aa to 11Ba was determined as 85.5:14.5 by converting crude 11a to (R)-(-)-2, 71%ee, by the same sequential treatments as those described for 7.



13) The optical purity was determined by measuring the NMR spectrum in the presence of the chiral shift reagent(Eu(hfc)$_3$)(see Ref. 5a).
14) Prepared by allowing to react commercially available (1R,2R)-(+)-dimethyltartrate with excess pyrrolidine at room temperature for 18 h.

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