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A SIMPLE AND EFFICIENT SYNTHESIS OF KEY SYNTHETIC INTERMEDIATES OF 4-DEMETHOXYANTHRACYCLINONES, (±)- AND (R)-(-)-7-DEOXY-4-DEMETHOXYDAUNOMYCINONE

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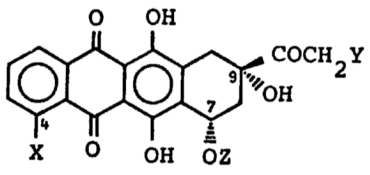
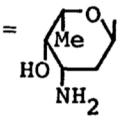
(±)-2,5,12-Trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione-2-carboxylic acid was found to readily afford the racemic title compound by successive treatments with N,N'-carbonyldiimidazole and methylmagnesium bromide in the presence of trimethylsilyl triflate. The same reaction scheme could also furnish the optically pure title compound from the (R)-carboxylic acid produced by the optical resolution.

The 4-demethoxyanthracyclines, 4-demethoxyadriamycin(1a) and 4-demethoxydaunorubicin(1b), attract much attention since these modified antibiotics are expected to show more improved therapeutic indices than natural anthracyclines (1c,d).[1] (±)- and (R)-(-)-7-Deoxy-4-demethoxydaunomycinone((±)- and (R)-(-)-3) hold pivotal positions in the synthesis of 4-demethoxyanthracyclinones(2a,b), the aglycones of 1a,b.[1,2] Numerous methods have been hitherto explored for preparing these racemic and optically active key intermediates.[1-4]

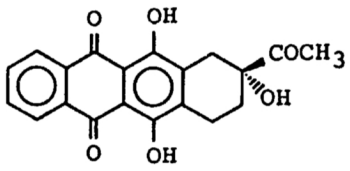
In connection with our continuing synthetic studies on optically active 2a,b, we have recently developed the efficient preparation method of 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione(4).[5] The method for introducing the C_7-hydroxy group into (R)-(-)-3 in a highly stereoselective manner has also been explored.[4,6] Considering the simplicity and directness of the reaction scheme, the synthesis of (±)- and (R)-(-)-3 from (±)- and (R)-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphtacene-6,11-dione-2-carboxylic acid((±)- and (R)-6) readily accessible from 4, has been anticipated to be one of the most promising large scale



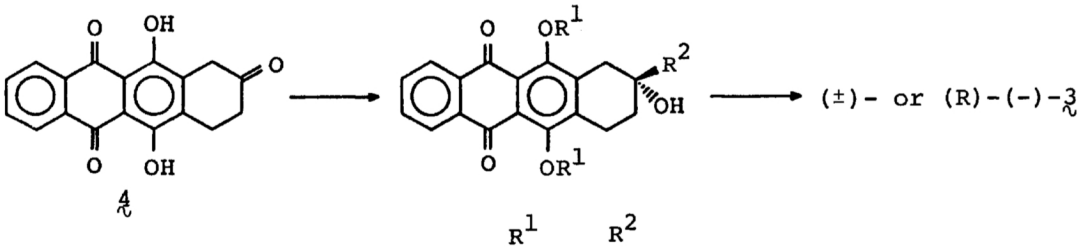
	X	Y
a:	H	OH
b:	H	H
c:	OMe	OH
d:	OMe	H

1: Z = 

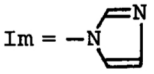
2: Z = H



(±)- or (R)-(-)-3



	R^1	R^2
(±)-5:	H	CN
(±)- or (R)-6:	H	COOH
(±)- or (R)-7:	H	COIm
(R)-(-)-8:	H	COOMe
(R)-(+)-9:	Me	COOMe
(R)-(+)-10:	Me	COOH

Im = 

preparation methods of these key intermediates.[7] However, this has never met a success probably due to the lack of the efficient reaction which can directly transform the carboxyl groups of (±)- and (R)-6 into the corresponding methyl ketones.

We wish to report here that (±)-6 can afford a good yield of (±)-3 in one pot reaction by sequential treatments with N,N'-carbonyldiimidazole and methylmagnesium bromide in the presence of trimethylsilyl triflate(TMSOTf). Moreover, since (±)-6 can be effectively resolved into (R)-6 by the use of (-)-N-methylephedrine, the explored overall process is found to be applicable to the preparation of optically pure (R)-(-)-3 from 4.

Preparation of (±)-6 from 4 was performed according to a conventional method. Thus, cyanohydrin formation of 4 (KCN(15 equiv.)-AcOH(20 equiv.) in EtOH-THF(1:1), rt, overnight, then 1 mol dm^{-3} HCl) gave the unstable product((±)-5) in 83% yield. This was directly hydrolyzed (concd HCl-AcOH(1:2), reflux, 10 h) to give (±)-6 in 94% yield, mp 251-252 °C(from nitrobenzene)(lit.,[8] mp 253-258 °C).

With a large quantity of (±)-6 in hand, various methods were examined which had been reported to give a methyl ketone from the corresponding carboxylic acid. After several unsuccessful attempts, it was finally found that the reaction of N-acylimidazole((±)-7) with methylmagnesium bromide[9] could afford the promising result. Thus, the reaction of (±)-6 with N,N'-carbonyldiimidazole(2.0 equiv.) in THF containing hexamethylphosphoric triamide(HMPA)(8.0 equiv.)(rt, 18 h) furnished (±)-7.[10,11] Without isolation, (±)-7 was immediately treated with TMSOTf(1.0 equiv.)(-20 °C), then with methylmagnesium bromide(14.0 equiv.)(3 mol dm^{-3} in Et_2O, -40 °C, 3h), to give (±)-3 in 65% yield after quenching (1 mol dm^{-3} HCl), extractive isolation (EtOAc), and filtration with a short column (SiO_2: EtOAc/C_6H_6=1/9),[12] mp 213-215 °C(from C_6H_6)(lit.,[3b] mp 214-216 °C). In the absence of TMSOTf, the addition of the Grignard reagent to (±)-7 begins to occur only at -20 °C, affording a lower yield(at most 40% yield) of (±)-3. Therefore, (±)-7 seems to be activated with TMSOTf by silylation of the N^3-position of the imidazole ring.

In order to apply the explored one pot process to the preparation of (R)-(-)-3, the optical resolution of (±)-6 was next examined. (-)-N-Methylephedrine was found to be the best optically active amine being necessary for the salt formation with (±)-6. A mixture of (±)-6 and (-)-N-methylephedrine[13] (mp 85-86 °C, $[\alpha]_D^{20}$

-30.2°(c 4.48, MeOH))(1.2 equiv.) in ethanol was heated at reflux for 2 h. The hot mixture was filtered to remove a small amount of insoluble materials, concentrated to half volume, then kept standing (rt, overnight), to precipitate the crude salt of (R)-6 in 51%(102%)[14] yield, mp 200-204 °C, $[\alpha]_D^{20}$ -63.6°(c 0.10, $CHCl_3$). The crude salt was recrystallized twice from ethanol containing 0.2 equiv. of (-)-N-methylephedrin, to give the pure salt of (R)-6 in 31%(62%)[14] yield, mp 217.5-220 °C, $[\alpha]_D^{20}$ -12.0°(c 0.05, $CHCl_3$). Regeneration of optically pure (-)-6 was simply achieved stirring a suspension of the pure salt in an aqueous acid (1 mol dm^{-3} HCl, 17 h), to give optically pure (R)-6 in a quantitative yield, mp >280 °C. Unfortunately, the optical rotation could not be measured because of the extremely low solubility of (R)-6 to almost all solvents.

While the absolute configuration and optical purity of optically active 6 could be determined by the successful synthesis of (R)-(-)-3 (vide supra), the independent determination of these physical indices was examines at this stage by transforming optically active 6 into its derivatives. Esterification (MeOH-DMSO (5:1)-concd H_2SO_4, reflux, 4 h) of optically active 6 gave the (-)-methyl ester ((-)-8) in 81% yield, mp 206.5-210 °C, $[\alpha]_D^{20}$ -55.0°(c 0.10, $CHCl_3$), after purification by column chromatography (SiO_2: C_6H_6/EtOAc=5∿3). Recrystallization of this sample from toluene gave optically pure (-)-8, mp 210.5-211.5 °C, $[\alpha]_D^{20}$ -60.0° (c 0.10, $CHCl_3$). Methylation (Me_2SO_4(3.9 equiv.)-K_2CO_3(3.9 equiv.) in Me_2CO, reflux, 5.5 h) of (-)-8 ($[\alpha]_D^{20}$ -55.0°(c 0.10, $CHCl_3$)) followed by purification by column chromatography (SiO_2: Et_2O) produced the (+)-dimethoxy ester ((+)-9) in 90% yield, mp 152-154 °C(lit.,[3a] mp 154-155 °C), $[\alpha]_D^{20}$ +11.7°(c 0.22, $CHCl_3$).[15] Measurement of the NMR spectrum of (+)-9 in the presence of the chiral shift reagent($Eu(hfc)_3$) clearly disclosed that (+)-9 was optically pure. Accordingly, the optical purity of optically active 6 obtained by the resolution was established to be 100% ee.

In order to determine the absolute configuration, (+)-9 was further hydrolyzed (KOH(1.5 equiv.) in MeOH-THF-H_2O, rt, 3 h) to give the (+)-dimethoxy acid ((+)-10) in 82% yield, mp 202-207 °C(from hexane-EtOAc), $[\alpha]_D^{20}$ +16.9°(c 0.20, $CHCl_3$)(lit.,[3a] mp 200-201 °C, $[\alpha]_D^{20}$ +13.6°(c 0.43, $CHCl_3$); lit.,[8] mp 200-205 °C, $[\alpha]_D^{20}$ +14.0°(c 0.20, $CHCl_3$)). Since (+)-10 had been reported to belong to (R)-series,[3a] optically active 6 was definitely established to have (R)-configuration.

Finally, the synthesis of (R)-(-)-3 from optically pure (R)-6 was carried out following the reaction scheme explored by the use of (±)-6. The same treatments of (R)-6 as those described for (±)-6 readily gave (R)-(-)-3 in 58% yield, mp 195-203 °C, $[\alpha]_D^{20}$ -85.7°(c 0.11, $CHCl_3$), after filtration through a short silica gel column. Recrystallization from benzene gave optically pure (R)-(-)-3, mp 214-216 °C, $[\alpha]_D^{20}$ -90.6°(c 0.11, $CHCl_3$)(lit.,[4] mp 218-219 °C, $[\alpha]_D^{20}$ -90.3°(c 0.11, $CHCl_3$)).

As mentioned above, we have succeeded in developing the efficient synthetic scheme which could convert 4 into (±)- and (R)-(-)-3 by way of (±)- and (R)-6. Numerous synthetic approaches to anthracyclinones hitherto reported, terminate at or proceed through 1,2,3,4-tetrahydronaphthacene-2,6,11-trione derivatives.[2] Taking into account the operational simplicity and directness, the exprored process is considered to be one of the best synthetic routes which can add the racemic

or optically active C_9-α-hydroxy ketone moiety to those tetracyclic systems.

References

1) F. Arcamone, "Doxorubicin," Academic Press, New York(1981), pp. 259-299; M.B. Naff, J. Plowman, and V.L. Narayanan, "Anthracycline Antibiotics," ed by H.S. El Khadem, Academic Press, New York(1982), pp. 1-57.
2) S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 40, 20(1982).
3) a) S-s. Jew, S. Terashima, and K. Koga, Chem. Pharm. Bull., 27, 2351(1979); b) N. Tanno and S. Terashima, ibid., 21, 811, 821(1983); c) S. Terashima and K. Tamoto, Tetrahedron Lett., 23, 3715(1982); Chem. Pharm. Bull. in press and references cited therein.
4) a) S. Terashima, K. Tamoto, and M. Sugimori, Tetrahedron Lett., 23, 4107(1982); Tetrahedron in press and references cited therein; b) K. Tamoto and S. Terashima, Proceeding of the 43th Symposium on the Synthetic Organic Chemistry, Tokyo, June 1983, Abstr., No. 2-8.
5) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, Chem. Lett., 1984, 473.
6) Acetallization of (R)-(-)-3 with ethylene glycol (p-TsOH - C_6H_6, reflux, 5 h, 98%) followed by bromination (Br_2 - $CHCl_3$-CCl_4-H_2O, hν) and treatment with 10% NaOH stereoselectively afforded crude (+)-2b in 48% yield (2 steps)(the ratio of (+)-2b to its C_7-epimer >20:1). Direct recrystallization of this sample readily gave optically pure (+)-2b, mp 184-185 °C, $[\alpha]_D^{20}$ +156°(dioxane), in 34% yield (2 steps).
7) For the reported preparation method of (±)-3 from 4; see, M. Suzuki, Y. Kimura, and S. Terashima, Chem. Lett., 1984, 1543.
8) Japan Kokai Tokkyo Toho, JP 58-77844.
9) H.A. Staab, Angew. Chem., Int. Ed. Engl., 1, 351(1962).
10) Generation of (±)-7 was reasonably assumed according to the literature.[9] Isolation of (±)-7 was not examined due to the high reactivity of (±)-7 to water.
11) The use of HMPA seems to be inevitable for obtaining a higher yield of (±)-7.
12) This operation was required to remove a small amount of the tertiary alcohol, mp 234.5-237.5 °C, which was usually produced in less than 3% yield.
13) T. Mashiko, S. Terashima, and S. Yamada, Yakugaku Zasshi, 100, 319(1980).
14) Based on the amount of (R)-6 originally involved in (±)-6.
15) This sample showed the following optical rotations; $[\alpha]_D^{20}$ 0.0°(c 0.22, Me_2CO), $[\alpha]_D^{20}$ -5.2°(c 0.23, MeOH), $[\alpha]_D^{20}$ -13.1°(c 0.25, EtOH), and $[\alpha]_D^{20}$ -23.5°(c 0.22, C_6H_6). Although $[\alpha]_D^{20}$ -7.8°(c 0.613, Me_2CO) was reported for this compound in the previous report,[3a] this rotation value should be corrected.

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