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# Novel Ethynylcerium(III) Reagents as Efficient Tools for Constructing the α-Hydroxy Methyl Ketone Moiety of Anthracyclinones[1)]

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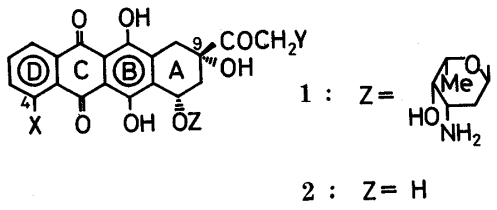
The title cerium(III) reagents (**7**—**10**) were found to react with 5,8-dimethoxy-2-tetralone (**11a**) and 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (**15**) more efficiently than the corresponding lithium and magnesium reagents (**3**, **5**, and **4**, **6**), giving the addition products (**12a**, **13a**, and **17**) in high yields. Hydration of these adducts readily afforded the α-hydroxy methyl ketones, 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**14a**), and 2-acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (4-demethoxy-7-deoxydaunomycinone) (**18**), which are versatile synthetic intermediates for optically active 4-demethoxyanthracyclinones.

**Keywords**——anthracycline; anthracyclinone; 4-demethoxyanthracycline; 4-demethoxyanthracyclinone; ethynylcerium(III) reagent; ethynyl- and 2-trimethylsilylethynylcerium(III) chloride; triethynyl- and tris(2-trimethylsilylethynyl)cerium(III); 1,2-addition reaction; acetylene hydration

The anthracycline antibiotics, adriamycin (**1a**) and daunorubicin (**1b**), have attracted much attention in recent years because of their prominent anticancer activities.[2-4)] While various undesirable side effects, including cardiotoxicity, restrict the utility of **1a**, **b** for chemotherapy of human cancers,[2,4)] studies on the structure–activity relationship have revealed that unnatural 4-demethoxyanthracyclines, 4-demethoxyadriamycin (**1c**) and 4-demethoxydaunorubicin (**1d**), show therapeutic properties superior to those of natural **1a**, **b**.[2,5)]




| | X | Y |
|---|---|---|
| **a**: | OMe | OH |
| **b**: | OMe | H |
| **c**: | H | OH |
| **d**: | H | H |

In the synthesis of optically active 4-demethoxyanthracyclinones (**2c**, **d**), the aglycones of **1c**, **d**, introduction of an α-hydroxy methyl ketone moiety into 5,8-dimethoxy-2-tetralone (**11a**) and 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (**15**), which are readily accessible from *p*-benzoquinone[6,7)] and 1,4-dihydroxyanthracene-9,10-dione (quinizarin),[6,8)] is expected to constitute one of the key synthetic steps.[6)] The processes for converting 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (**14a**) and 2-acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (4-demethoxy-7-deoxydaunomycinone) (**18**), derived from **11a** and **15**, into optically active **1c**, **d** have been well established, *i.e.*, Friedel–Crafts reaction of **14a** with phthalic acid derivatives,[5,6,9)] optical resolution of **14a** and **18**,[5,6,9-11)] and stereoselective introduction of the $C_{7\alpha}$-hydroxy group (anthracycline numbering) into **18**.[10)]

Among various synthetic schemes for preparing **14a** and **18** from **11a** and **15**, re-

spectively, 1,2-addition of an ethynyl group to the ketonic function followed by hydration of the resulting acetylenic alcohol seems to be one of the most practical methods due to its directness and simplicity.[12,13] While this synthetic scheme was first introduced into anthracyclinone synthesis by Kende *et al.*,[14] a large excess amount of ethynylmagnesium bromide (**4**) is usually required to achieve the addition of an ethynyl group to **11a** and **15** in acceptable yields.[14-16] Taking into account this disadvantage, an efficient reagent was sought which

$(X\text{–}C\equiv C\text{–})_nM$

| | X | M | *n* |
|---|---|---|---|
| **3** | H | Li | 1 |
| **4** | H | MgBr | 1 |
| **5** | $Me_3Si$ | Li | 1 |
| **6** | $Me_3Si$ | MgBr | 1 |
| **7** | H | $CeCl_2$ | 1 |
| **8** | $Me_3Si$ | $CeCl_2$ | 1 |
| **9** | H | Ce | 3 |
| **10** | $Me_3Si$ | Ce | 3 |

could introduce an ethynyl group or its equivalent into the ketonic functions of **11a** and **15** more readily than **4**.

We have now found that novel ethynylcerium(III) reagents (**7**—**10**), especially 2-trimethylsilylethynylcerium(III) reagents (**8** and **10**), are quite promising for this purpose, and that, in the same way as the ordinary acetylenic alcohols (**12a** and **16**), the addition products (**13a** and **17**) carrying a 2-trimethylsilylethynyl group can be readily converted to **14a** and **18** by mercury(II)-catalyzed hydration. This report deals with **7**—**10** which should be useful in the synthesis of 4-demethoxyanthracyclinones.[8b,17,18]

## Results and Discussion

As described in the introduction, when **11a** was allowed to react with 10 eq of **4**, the addition product (**12a**) could be obtained in 86% yield (Table I, run 2). Since treatment of **11a** with 2.3 eq of **4** gave a 30% yield of **12a** with a 39% recovery of **11a** (Table I, run 3), it appears that the yield of **12a** depends strongly upon the amount of **4**. The requirement of a large excess amount of **4** may be explained by insufficient nucleophilicity of **4**.

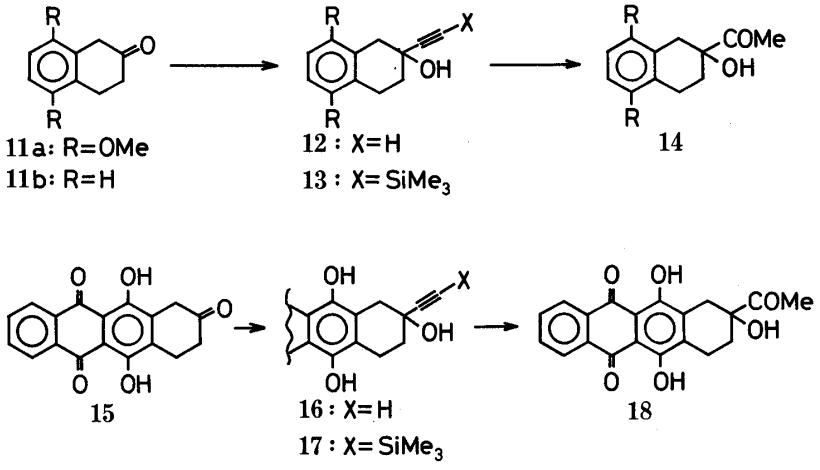



Chart 1

Recently, it was reported that alkylcerium(III) reagents prepared *in situ* by treating alkyllithium with cerium(III) halides, showed greater nucleophilicity than the parent organolithium reagents.[19,20] Since ethynylcerium(III) reagents such as **7**—**10** have never been

TABLE I. Addition Reactions of Ethynylmetal Reagents (**3**—**10**) to Ketones (**11a, b**, and **15**)

| Run | Ketone | Ethynylmetal reagent | | Reaction conditions[a] | | Addition product | |
|---|---|---|---|---|---|---|---|
| | | Reagent | Molar ratio of reagent to ketone | Temp. (°C) | Time (h) | Compound | Yield (%)[b] |
| 1 | **11a** | **3** | 2.0 | −78 | 2 | **12a** | 37 (58) |
| 2 | **11a** | **4** | 10 | r.t. | 15 | **12a** | 86[c] |
| 3 | **11a** | **4** | 2.3 | r.t. | 14.5 | **12a** | 30 (39) |
| 4 | **11a** | **5** | 2.2 | −78 | 3 | **13a** | 49 (44) |
| 5 | **11a** | **6** | 2.3 | 0; r.t. | 2.5; 14 | **13a** | 70 (10) |
| 6 | **11a** | **6** | 2.0 | −78 | 1 | **13a** | 18 (78) |
| 7 | **11a** | **7**[d] | 2.0 | −78 | 2 | **12a** | 81 (15) |
| 8 | **11a** | **7**[e] | 2.4 | −78——70 | 1 | **12a** | 64 (18) |
| 9 | **11a** | **8**[f] | 1.8 | −78 | 1 | **13a** | 100 (0) |
| 10 | **11a** | **8**[g] | 2.0 | −78 | 1 | **13a** | 72 (13) |
| 11 | **11a** | **9**[e] | 0.65 | −78——55 | 1 | **12a** | 57 (16) |
| 12 | **11a** | **10**[f] | 0.67 | −78 | 1 | **13a** | 93 (0) |
| 13 | **11b** | **8**[f] | 1.9 | −78 | 1 | **13b** | 85 (0) |
| 14 | **15** | **4** | 25 | r.t. | 41 | **16** | 48 (12) |
| 15 | **15** | **8**[f] | 6.1 | −78 | 3 | **17** | 62[h] |
| 16 | **15** | **10**[f] | 2.0 | −78——65 | 5 | **17** | 55[h] |

*a*) r.t. = room temperature. *b*) Isolated yields based on the ketones (**11a, b**, and **15**). Numbers in parentheses refer to recovery yields of the starting ketones. *c*) Recovery of **11a** was not carried out. *d*) This reagent was prepared from **3**. *e*) Preparation of this reagent was performed using **4**. *f*) This reagent was prepared using **5**. *g*) Preparation of this reagent was carried out using **6**. *h*) Recovery of **15** was not carried out.

explored, the preparation and reaction of these reagents were studied in the hope of exploiting their increased nucleophilicity.

According to the procedure reported for alkylcerium(III) reagents, preparation of 2-trimethylsilylethynylcerium(III) chloride (**8**) was examined by treating 2-trimethylsilylethynyllithium (**5**) with anhyd. cerium(III) chloride in 1 : 1 ratio at −78 °C in tetrahydrofuran (THF). Reaction of **11a** with 1.8 eq of **8** at −78 °C for 1 h was found to give **13a** in a quantitative yield (Table I, run 9). Comparisons of the yields of **13a** obtained by using **5** and 2-trimethylsilylethynylmagnesium bromide (**6**) (Table I, runs 4—6) with that obtained with **8**, indicate that the nucleophilicity of the ethynyl group is clearly enhanced in **8**. Although Grignard reagents were reported to be ineffective for producing alkylcerium(III) reagents,[19] it was found that **8** could be produced from **6**, and **13a** was obtained in 72% yield when **8** was reacted with **11a** (Table I, run 10). The lower yield of **13a** may be well explained by assuming that metal–metal exchange proceeds less effectively for **6** than for **5**. When **5** was treated with anhyd. cerium(III) chloride in 3 : 1 ratio, tris(2-trimethylsilylethynyl)cerium(III) (**10**) could be produced. Like **8**, this novel cerium(III) reagent (**10**) was also found to react with **11a**, giving **13a** in 93% yield (Table I, run 12).

Preparation of non-substituted ethynylcerium(III) reagents (**7** and **9**) from ethynyllithium (**3**), which is readily obtainable from cheap acetylene gas, was next attempted. Ethynylcerium(III) reagents (**7** and **9**) produced from **3** and **4** by the same procedures as those described for **8** and **10**, exhibited higher reactivity than **3** and **4** (Table I, runs 1, 3, 7, 8 and 11). As in the case of **8**, **7** prepared from **4** showed lower reactivity than that from **3** (Table I, runs 7 and 8). In terms of the chemical yields of **12a** and **13a** and operational simplicity, **8** and **10** seem to be superior to **7** and **9**.

When 2-tetralone (**11b**) was treated with 1.9 eq of **8**, the addition product (**13b**) was obtained in 85% yield (Table I, run 13). A 48% yield of **16** could be achieved with a 12%

TABLE II. Hydration Reactions of Various Acetylenic Alcohols (**12a**, **13a**, **b**, **16**, and **17**) Using Mercury(II) Oxide in aq. Sulfuric Acid

| Run | Acetylenic alcohol | Reaction conditions[a] | | Product | |
|---|---|---|---|---|---|
| | | Molar ratio of HgO to acetylenic alcohol | Time (h) | Compound | Yield (%)[b] |
| 1 | **12a** | 0.57 | 19 | **14a** | 83 |
| 2 | **13a** | 0.27 | 16.5 | **14a** | 100 |
| 3 | **13b** | 0.29 | 31 | **14b** | 92 |
| 4 | **16**[c] | 1.38 | 14 | **18** | 83 (40)[d] |
| 5 | **17** | 0.54 | 12 | **18** | 95 |
| 6 | **17**[e] | 0.47 | 24 | **18** | 100 (62)[f] |

*a*) All reactions were carried out at room temperature. *b*) Numbers in parentheses show the overall yield of **18** from **15**. *c*) Crude **16** was subjected to hydration. *d*) Since purification of crude **16** by column chromatography gave the pure sample in 48% yield (see Table I, run 14), the yield of hydration could be calculated as 83%. *e*) Hydration was performed using crude **17**. *f*) Since pure **17** could be obtained in 62% yield by purification of crude **17** by column chromatography (see Table I, run 15), the yield of hydration could be calculated as 100%.

recovery of **15** by allowing **15** to react with 25 eq of **4** (Table I, run 14). This result is almost the same as those reported elsewhere.[8,14a,21] Treatment of **15** with 5.9 eq of **8** or 2.0 eq of **10** successfully provided **17** in 62% and 55% yields, respectively (Table I, runs 15 and 16).

With three types of the addition products (**13a**, **b** and **17**) in hand, direct transformation of a 2-trimethylsilylethynyl group into a methyl ketone was next examined. This was found to be readily accomplished by treating these addition products with mercury(II) ion, similarly to the established transformation of **12a** and **16** into **14a** and **18**.[14,15,18] These results are summarized in Table II. Treatment of **13a** with 0.27 eq of mercury(II) oxide in a mixture of aqueous sulfuric acid and THF gave **14a** in quantitative yield (Table II, run 2). Similarly, **13b** and **17** were converted to **14b** and **18** in 92% and 95% yields, respectively (Table II, runs 3 and 5). When crude **17** prepared from **15** was immediately subjected to hydration without purification, **18** could be obtained in 62% overall yield from **15** (Table II, run 6). Taking into account the yield of **17** from **15** (Table I, run 15), the yield of the hydration step can be corrected to 100%. These results compare favorably with those obtained with **12a** and **16** carrying ethynyl groups (Table II, runs 1 and 4).

As mentioned above, we have succeeded in developing novel ethynylcerium(III) reagents (**7**—**10**) which are useful in the synthesis of 4-demethoxyanthracyclinones.[22,23] Numerous synthetic approaches to anthracyclinones hitherto reported terminate at or proceed through 1,2,3,4-tetrahydronaphthacene-2,6,11-trione derivatives corresponding to **15**,[6] and the ethynylcerium(III) reagents (**7**—**10**) developed here should hold promise for adding the $C_9$-α-hydroxy ketone moiety (anthracycline numbering) to those tetracyclic systems.

## Experimental[24]

**5,8-Dimethoxy-2-tetralone (11a)**——Prepared according to the reported method.[7b,16] mp 98.5—99 °C (lit.,[16] mp 98—99 °C).

**5,12-Dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione (15)**——This was synthesized following the method previously developed in this laboratory.[8] mp >250 °C (dec.) (lit.,[8] mp >250 °C (dec.), lit.,[21] mp >300 °C).

**Preparation of Ethynyllithium (3)**——A solution of **3** (2.0 mmol) was prepared by passing dry acetylene gas through a mixture of butyllithium (1.63 M hexane solution, 1.25 ml, 2.0 mmol) and THF (5.0 ml) with stirring at

−78 °C for 5 min.

**Preparation of Ethynylmagnesium Bromide (4)**——Ethyl bromide (28.8 g, 0.26 mol) was added over 2.2 h to a suspension of magnesium (5.89 g, 0.24 mol) in THF (86 ml) with stirring in a water bath, and the mixture was stirred for 1 h. The solution of ethylmagnesium bromide (0.24 mol) prepared above was added over 2.2 h to stirred THF (80 ml), through which dried acetylene gas was being passed, in a water bath to give a THF solution of **4** (0.24 mol).

**Preparation of 2-Trimethylsilylethynyllithium (5)**——A solution of **5** (16.3 mmol) was prepared by adding butyllithium (1.63 M hexane solution, 10.0 ml, 16.3 mmol) to a solution of trimethylsilylacetylene (1.73 g, 17.7 mmol) in THF (20 ml) with stirring at −78 °C under an argon atmosphere, followed by stirring of the whole mixture at the same temperature for 30 min.

**Preparation of 2-Trimethylsilylethynylmagnesium Bromide (6)**——A solution of ethylmagnesium bromide (2.3 mmol) was prepared by adding ethyl bromide (247 mg, 2.3 mmol) to a stirred suspension of magnesium (55 mg, 2.3 mmol) in THF (3.0 ml), followed by stirring of the mixture at room temperature for 1 h. Trimethylsilylacetylene (235 mg, 2.4 mmol) was added to the THF solution of ethylmagnesium bromide with stirring in an ice bath. The mixture was stirred for 10 min in an ice bath, then at room temperature for 30 min, giving a solution of **6** (2.3 mmol).

**Preparation of Ethynylcerium(III) Chloride (7)**——THF (4.0 ml) was added to anhyd. cerium(III) chloride[25] (499 mg, 2.0 mmol) under an argon atmosphere. The suspension was stirred overnight at room temperature,[26] then cooled at −78 °C, and added to a solution of **3** (1.9 mmol) prepared from butyllithium (1.63 M hexane solution, 1.15 ml, 1.9 mmol) and THF (5.0 ml). The mixture was stirred at −78 °C for 30 min to give a suspension of **7** (1.9 mmol).

A suspension of **7** (1.2 mmol) could be similarly prepared by adding a solution of **4** (1.2 mmol) in THF to a suspension of anhyd. cerium(III) chloride[25] (294 mg, 1.2 mmol) in THF (3.0 ml) with stirring at −78 °C, followed by stirring of the mixture at the same temperature for 1 h.

**Preparation of 2-Trimethylsilylethynylcerium(III) Chloride (8)**——A suspension of anhyd. cerium(III) chloride[25] (516 mg, 2.1 mmol) in THF (4.0 ml), prepared in a similar manner to that described above,[26] was cooled at −78 °C. A solution of **5** (1.8 mmol) [prepared from butyllithium (1.63 M hexane solution, 1.1 ml, 1.8 mmol) and trimethylsilylacetylene (217 mg, 2.2 mmol) in THF (5.0 ml)] was added to the suspension of anhyd. cerium(III) chloride with stirring at −78 °C, and the mixture was further stirred at the same temperature for 30 min to give a suspension of **8** (1.8 mmol).

A suspension of **8** (2.0 mmol) could be similarly prepared by adding a THF solution of **6** (2.0 mmol) to a suspension of anhyd. cerium(III) chloride[25,26] (529 mg, 2.1 mmol) in THF (4.0 ml) at −78 °C, followed by stirring of the whole mixture at the same temperature for 1 h.

**Preparation of Triethynylcerium(III) (9)**——A suspension of **9** (0.32 mmol) was prepared by adding a THF solution of **4** (1.2 mmol) to a suspension of cerium(III) chloride[25,26] (78 mg, 0.32 mmol) with stirring at −78 °C, followed by stirring of the mixture at the same temperature for 1 h.

**Preparation of Tris(2-trimethylsilylethynyl)cerium(III) (10)**——Preparation of a suspension of **10** (0.33 mmol) was carried out by adding a suspension of cerium(III) chloride[25,26] (96.5 mg, 0.39 mmol) in THF (3.0 ml) to a solution of **5** (0.98 mmol) with stirring at −78 °C, followed by stirring of the mixture at the same temperature for 1.5 h.

**2-Ethynyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (12a)**——a) Table I Run 1: A solution of **11a** (207 mg, 1.0 mmol) in THF (6.0 ml) was added to a solution of **3** (2.0 mmol) with stirring at −78 °C. After the mixture had been stirred at the same temperature for 2 h, the reaction was quenched by the addition of $H_2O$ (10 ml). The whole mixture was extracted with $Et_2O$, and the combined organic extracts were washed with $H_2O$. Filtration and concentration *in vacuo* gave a residue, which was separated by column chromatography ($C_6H_6$–EtOAc, 10:1) to afford **12a** (87.5 mg, 37%) and **11a** (120 mg, 58%). These samples were shown to be identical with an authentic sample[16] by spectral (NMR) comparisons.

b) Table I Run 2: A solution of **11a** (5.0 g, 24 mmol) in THF (80 ml) was added over 50 min to a solution of **4** (0.24 mol) in THF with stirring in an ice bath. Stirring was continued at room temperature for 15 h, then the mixture was worked up in a similar manner to that described in a), giving **12a** (4.84 g, 86%) after purification by column chromatography ($C_6H_6$–EtOAc, 5:1). This product was shown to be identical with authentic **12a**[16] by spectral (NMR) comparison.

c) Table I Run 3: Treatments of **11a** (210 mg, 1.0 mmol) with a solution of **4** (2.3 mmol) in a similar manner to that described in a) gave **12a** (70.7 mg, 30%) and **11a** (80.9 mg, 39%) after separation by column chromatography ($C_6H_6$–EtOAc, 15:1). These compounds were shown to be identical with the authentic samples[16] by spectral (NMR) comparisons.

d) Table I Run 7: A solution of **11a** (192 mg, 0.93 mmol) in THF (6.0 ml) was added to a suspension of **7** (1.9 mmol) prepared from **3** (1.9 mmol), with stirring at −78 °C, and the mixture was stirred at the same temperature for 2 h. Treatments of the reaction mixture in a similar manner to that described in a) gave **12a** (174 mg, 81%) and **11a** (28 mg, 15%) after purification by column chromatography ($C_6H_6$–EtOAc 10:1). These samples were shown to be identical with an authentic sample[16] by spectral (NMR) comparisons.

e) Table I Run 8: When **11a** (101 mg, 0.49 mmol) was allowed to react with **7** (1.2 mmol), prepared from **4** (1.2 mmol), at −70——78 °C for 1 h, extractive isolation of the reaction mixture followed by separation by column

chromatography ($C_6H_6$–EtOAc, 15 : 1) gave **12a** (72.6 mg, 64%) and **11a** (17.9 mg, 18%). These compounds were shown to be identical with authentic samples[16] by spectral (NMR) comparisons.

f) Table I Run 11: A solution of **11a** (101 mg, 0.49 mmol) in THF (1.0 ml) was added to a suspension of **9** (0.32 mmol) prepared from **4** (1.2 mmol) and anhyd. cerium(III) chloride (0.32 mmol), with stirring at −78 °C, and the mixture was stirred at −55—−78 °C for 1 h. Extractive isolation of the reaction mixture followed by separation by column chromatography ($C_6H_6$–EtOAc, 15 : 1) gave **12a** (65.3 mg, 57%) and **11a** (16.6 mg, 16%). Identification of these samples were performed by comparing their NMR spectra with those of authentic samples.[16]

**5,8-Dimethoxy-2-(2-trimethylsilylethynyl)-1,2,3,4-tetrahydro-2-naphthol (13a)**——a) Table I Run 4: A solution of **11a** (309 mg, 1.5 mmol) in THF (2.0 ml) was added to a solution of **5** (3.3 mmol) in THF (11 ml) with stirring at −78 °C, and the mixture was stirred at the same temperature for 3 h. The reaction mixture was diluted with $H_2O$ (10 ml) at −78 °C and extracted with $Et_2O$. The ethereal extracts were combined and washed with $H_2O$. Filtration and concentration *in vacuo* gave a crude mixture of **13a** and **11a**. This was subjected to quantitative NMR spectral analysis using piperonal (126 mg) as an internal standard. Based on the NMR spectrum of the mixture and those of pure **13a** (see d) and **11a**,[7,16] this mixture was concluded to consist of **13a** (224 mg, 49%) and **11a** (136 mg, 44%).

b) Table I Run 5: A solution of **11a** (205 mg, 0.99 mmol) was added to a solution of **6** (2.3 mmol) in THF, and the mixture was stirred for 2.5 h in an ice bath, then overnight at room temperature. The reaction was quenched by the addition of 3 N HCl (10 ml), and extractive isolation followed by column chromatography ($C_6H_6$–EtOAc, 10 : 1) gave a mixture of **13a** and **11a**. This mixture was confirmed to contain **13a** (212 mg, 70%) and **11a** (21 mg, 10%) by examination of its NMR spectrum.

c) Table I Run 6: When **11a** (206 mg, 1.0 mmol) was allowed to react with **6** (2.3 mmol) at −78 °C for 1 h, a mixture of **13a** and **11a** was obtained after extractive isolation and purification by column chromatography ($C_6H_6$–EtOAc, 10 : 1). The amounts of **13a** and **11a** were determined as 55 mg (18%) and 160 mg (78%), respectively, by measuring the NMR spectrum of the mixture.

d) Table I Run 9: A solution of **11a** (205 mg, 1.0 mmol) in THF (6.0 ml) was added to a suspension of **8** (1.8 mmol) [prepared from **5** (1.8 mmol) and anhyd. cerium(III) chloride (516 mg, 2.1 mmol)] with stirring at −78 °C. The mixture was stirred at the same temperature for 1 h, then the reaction was quenched with $H_2O$ (10 ml) at −78 °C. The mixture was extracted with $Et_2O$, and the combined ethereal extracts were washed with $H_2O$. Filtration and concentration *in vacuo* gave an oily residue, which was purified by column chromatography ($C_6H_6$–EtOAc 10 : 1) to afford **13a** as a colorless solid (303 mg, 100%). Recrystallization from a mixture of $Et_2O$ and $C_6H_{14}$ gave an analytical sample of **13a** as colorless crystals, mp 91.5—92 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3500, 2970, 2175, 1485, 1255, 1110, 1100, 1040, 865, 845. NMR ($CDCl_3$) $\delta$: 0.08 (9H, s, $(C\underline{H}_3)_3Si$), 1.90 (1H, s, O$\underline{H}$), 1.98 (2H, t, $J$=6.8 Hz, $CH_2C\underline{H}_2C(OH)$), 2.79 (2H, t, $J$=6.8 Hz, $C\underline{H}_2CH_2C(OH)$), 2.98 (2H, br s, $ArC\underline{H}_2C(OH)$), 3.74 (6H, two s, $OC\underline{H}_3 \times 2$), 6.62 (2H, s, aromatic protons). *Anal.* Calcd for $C_{17}H_{24}O_3Si$: C, 67.06; H, 7.95. Found: C, 67.21; H, 7.96.

e) Table I Run 10: When **11a** (208 mg, 1.0 mmol) was allowed to react with **8** (2.0 mmol) [prepared from anhyd. cerium (III) chloride (529 mg, 2.1 mmol) and **6** (2.0 mmol)] at −78 °C for 1 h, a mixture of **13a** and **11a** was obtained after extractive isolation and purification by column chromatography. The amounts of **13a** and **11a** were calculated to be 221 mg (72%) and 28 mg (13%), respectively, from the NMR spectrum of this mixture.

f) Table I Run 12: A solution of **11a** (102 mg, 0.49 mmol) in THF (3.0 ml) was added to a suspension of **10** (0.33 mmol) [prepared from anhyd. cerium(III) chloride (96.5 mg, 0.39 mmol) and **5** (0.98 mmol)] with stirring at −78 °C. Stirring was continued at the same temperature for 1 h, then 3 N HCl (10 ml) was added to the reaction mixture to quench the reaction. The mixture was extracted with $CH_2Cl_2$, and the combined extracts were washed with $H_2O$. Filtration and concentration *in vacuo* followed by purification by column chromatography ($C_6H_6$–EtOAc, 10 : 1), gave **13a** (140 mg, 93%). This sample showed the same spectrum as that of **13a** obtained in d).

**2-(2-Trimethylsilylethynyl)-1,2,3,4-tetrahydro-2-naphthol (13b)**——Table I Run 13: The same treatments of **11b** (159 mg, 1.1 mmol) with **8** (2.1 mmol) as described for Table I run 9 gave **13b** (226 mg, 85%) after purification by column chromatography ($C_6H_6$–EtOAc, 15 : 1). Recrystallization from a mixture of $Et_2O$ and $C_6H_{14}$ gave an analytical sample of **13b** as colorless crystals, mp 125.5—126 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3250, 2175, 1250, 1050, 895, 870, 845, 760, 745. NMR ($CDCl_3$) $\delta$: 0.07 (9H, s, $(C\underline{H}_3)_3Si$), 1.97 (1H, s, O$\underline{H}$), 2.03 (2H, t, $J$=6.6 Hz, $CH_2C\underline{H}_2C(OH)$), 2.93 (2H, t, $J$=6.6 Hz, $C\underline{H}_2CH_2C(OH)$), 3.03 (1H, d, $J$=16.2 Hz, one of $ArC\underline{H}_2C(OH)$), 3.15 (1H, d, $J$=16.2 Hz, one of $ArC\underline{H}_2C(OH)$), 7.08 (4H, m, aromatic protons). *Anal.* Calcd for $C_{15}H_{20}OSi$: C, 73.71; H, 8.25. Found: C, 73.72; H, 8.16.

**2-Ethynyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (16)**——Table I Run 14: A suspension of **15** (10.6 g, 34 mmol) in THF (300 ml) was gradually added to a solution of **4** (0.86 mol) in THF (350 ml) with stirring at room temperature. After being stirred at the same temperature (41 h), the whole mixture was poured into 10% HCl (1 l), and extracted with EtOAc. The combined organic extracts were washed with satd. $NaHCO_3$ and $H_2O$. Filtration and concentration *in vacuo* gave a dark red solid (14.2 g). A part of this residue (500 mg) was purified by column chromatography ($C_6H_6$–EtOAc, 15 : 1—8 : 1) to give **16** (193 mg, 48%) and **15** (47.2 mg, 12%). Recrystallization from $C_6H_6$ gave an analytical sample of **16** as red crystals, mp 225—227 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3460, 3280, 1630, 1590, 1410, 1250. NMR ($CDCl_3$) $\delta$: 2.00—2.30 (2H, m, $CH_2C\underline{H}_2C(OH)$), 2.17 (1H, s, O$\underline{H}$), 2.49 (1H, s, C≡C$\underline{H}$), 2.90—3.50 (4H, m, $C\underline{H}_2CH_2C(OH)C\underline{H}_2$), 7.70—7.90, 8.20—8.50 (4H, two m, aromatic protons), 13.47 (2H, two s, phenolic O$\underline{H}$).

*Anal.* Calcd for $C_{20}H_{14}O_5$: C, 71.85; H, 4.22. Found: C, 71.62; H, 4.14.

**2,5,12-Trihydroxy-2-(2-trimethylsilylethynyl)-1,2,3,4-tetrahydronaphthacene-6,11-dione (17)**——a) Table I Run 15: A suspension of **15** (101 mg, 0.33 mmol) in THF (9.0 ml) was added to a suspension of **8** (2.0 mmol) [prepared from anhyd. cerium(III) chloride (571 mg, 2.3 mmol) and **5** (2.0 mmol)] with stirring at −78 °C. Stirring was continued at the same temperature for 3 h, then the mixture was diluted with 3 N HCl (10 ml), and extracted with EtOAc. The combined organic extracts were washed with $H_2O$ and satd. NaCl. Filtration and concentration *in vacuo* followed by purification by column chromatography ($C_6H_6$–EtOAc, 10:1) gave **17** as a red solid (82.8 mg, 62%). Recrystallization from a mixture of EtOAc and $Et_2O$ gave pure **17** as red crystals, mp 190—191 °C. IR $\nu_{max}^{KBr}$ $cm^{-1}$: 3600, 3475, 2960, 2175, 1625, 1590, 1440, 1410, 1260, 1250, 1220, 870, 850, 765. NMR ($CDCl_3$) $\delta$: 0.09 (9H, s, $(CH_3)_3Si$), 2.04 (1H, s, OH), 2.07 (2H, t, $J$=6.7 Hz, $CH_2CH_2C(OH)$), 2.97 (2H, t, $J$=6.7 Hz, $CH_2CH_2C(OH)$), 3.13 (2H, m, $ArCH_2C(OH)$), 7.70—7.90, 8.20—8.40 (4H, two m, aromatic protons), 13.44, 13.46 (2H, two s, phenolic OH). *Anal.* Calcd for $C_{23}H_{22}O_5Si \cdot 1/3H_2O$: C, 66.97; H, 5.54. Found: C, 67.08; H, 5.48.

b) Table I Run 16: A suspension of **15** (111 mg, 0.36 mmol) in THF (9.0 ml) was added to a suspension of **10** (0.73 mmol) [prepared from anhyd. cerium(III) chloride (203 mg, 0.82 mmol) and **5** (2.2 mmol)] with stirring at −78 °C, and the mixture was stirred at −78——65 °C for 5 h. The reaction mixture was worked up in a similar manner to that described in a) to give **17** as a red solid (81 mg, 55%) after purification by column chromatography ($C_6H_6$–EtOAc, 10:1). This sample showed the same NMR spectrum as that of **17** obtained in a).

**2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (14a)**——a) Table II Run 1: A solution of **12a** (4.84 g, 21 mmol) in THF (50 ml) was added to a mixture of HgO (2.60 g, 12 mmol) and 1.5 N $H_2SO_4$ (6.0 ml), and the mixture was stirred at room temperature for 15.5 h. Then 9 N $H_2SO_4$ (5.0 ml) and THF (20 ml) were added to the mixture, and stirring was continued for 3.5 h. THF was removed *in vacuo*, and the residual aqueous mixture was diluted with satd. NaCl (50 ml) and extracted with EtOAc. The combined organic extracts were washed with satd. $NaHCO_3$ and satd. NaCl. Filtration and concentration *in vacuo* followed by purification by column chromatography ($C_6H_6$–EtOAc, 6:1), gave pure **14a** as a pale brown crystalline solid (4.34 g, 83%). The IR and NMR spectra of this sample were identical with those reported.[9,16]

b) Table II Run 2: A mixture of **13a** (247 mg, 0.81 mmol), HgO (47 mg, 0.22 mmol), and 3 N $H_2SO_4$ (1.0 ml) in THF (5.0 ml) was stirred at room temperature for 16.5 h. The mixture was diluted with $H_2O$ (10 ml), and insoluble material that appeared was dissolved by adding a small amount of 3 N HCl. The aqueous mixture was extracted with $Et_2O$, and the combined ethereal extracts were washed with $H_2O$. Filtration and concentration *in vacuo* followed by purification by column chromatography ($C_6H_6$–EtOAc 10:1), gave **14a** as colorless crystals (203 mg, 100%), mp 104—105 °C (lit.,[9] mp 102—103 °C). The spectral (IR and NMR) properties of this sample were identical with those reported.[9,16]

**2-Acetyl-1,2,3,4-tetrahydro-2-naphthol (14b)**——Table II Run 3: Treatment of **13b** (196 mg, 0.80 mmol) in a similar manner to that described for **13a** (Table II run 2) gave pure **14b** as an oil (140 mg, 92%) after purification by column chromatography ($C_6H_6$–EtOAc, 10:1). The IR and NMR spectra of this sample were identical with those reported.[27]

**2-Acetyl-2,5,12-trihydroxy-1,2,3,4-tetrahydronaphthacene-6,11-dione (4-Dimethoxy-7-deoxydaunomycinone) (18)**——a) Table II Run 4: Crude **16** (13.7 g), which was prepared from **15** (10.6 g 34.5 mmol) and was presumed to contain **16** (5.48 g, 16.4 mmol) based on the chemical yield of pure **16**, was added to a mixture of HgO (4.91 g, 23 mmol), 9 N $H_2SO_4$ (12 ml), $H_2O$ (60 ml) in THF (400 ml). After being stirred at room temperature for 14 h, the mixture was diluted with 10% HCl, and extracted with EtOAc. The combined organic extracts were washed with satd. NaCl. Filtration and concentration *in vacuo* afforded a red solid, which was separated by column chromatography ($C_6H_6$–EtOAc, 7:1) to give **18** as red crystals (4.82 g, 83%, 40% based on **15**). The IR spectrum of this sample was identical with that reported.[9]

b) Table II Run 5: A mixture of **17** (72.7 mg, 0.18 mmol), HgO (21 mg, 0.097 mmol), 9 N $H_2SO_4$ (0.2 ml), and $H_2O$ (0.4 ml) in THF (2.0 ml) was stirred at room temperature for 12 h. The mixture was diluted with 3 N HCl (10 ml) and extracted with EtOAc. The combined organic extracts were washed with $H_2O$. Filtration and concentration *in vacuo* gave almost pure **18** as a red solid (60.0 mg, 95%). Recrystallization from $C_6H_6$ gave pure **18** as red crystals, mp 212.5—214.5 °C (lit.,[9] mp 214—216 °C). This sample showed the same IR spectrum as that reported.[9]

c) Table II Run 6: Crude **17** was prepared by treating **15** (92.8 mg, 0.30 mmol) with **8** (1.8 mmol) at −78 °C for 7 h. Mercury(II) oxide (31 mg, 0.14 mmol), THF (5.0 ml), 9 N $H_2SO_4$ (1.0 ml), and $H_2O$ (2.0 ml) were successively added to crude **17**, and the mixture was stirred at room temperature for 24 h. Extractive isolation followed by separation by column chromatography ($C_6H_6$–EtOAc, 12:1) in the same manner as described in a) afforded pure **18** as a red solid (65.3 mg, 62%). Recrystallization from $C_6H_6$ gave pure **18** as red crystals, mp 217—218 °C (lit.,[9] mp 214—216 °C). This sample showed the same spectral (IR and NMR) properties as an authentic sample.[9,16]

## References and Notes

1) Part of this report has been the subject of a preliminary communication: M. Suzuki, Y. Kimura, and S. Terashima, *Chem. Lett.*, **1984**, 1543.

2) *a*) F. Arcamone, *Lloydia*, **40**, 45 (1977); *b*) *Idem*, "Topics in Antibiotic Chemistry," Vol. 2, ed. by P. G. Sammes, Ellis Horwood, Chichester, England, 1978, pp. 99—239; *c*) *Idem*, "Anticancer Agents Based on Natural Product Models," ed. by J. M. Cassady and J. D. Douros, Academic Press, New York, 1980, pp. 1—41; *d*) *Idem*, "Doxorubicin Anticancer Antibiotics," Academic Press, New York, 1981.
3) 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.
4) *a*) T. Oki, *Hakko To Kogyo*, **37**, 1187 (1979); *b*) K. Ohta and K. Ohkuma, *Saisin Igaku*, **36**, 1060 (1981); *c*) T. Oki and T. Takeuchi, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 2 (1982).
5) *a*) F. Arcamone, L. Bernardi, P. Giardino, B. Patelli, A. DiMarco, A. M. Casazza, G. Pratesi, and P. Reggiani, *Cancer Treat. Rep.*, **60**, 829 (1976); *b*) F. Arcamone, L. Bernardi, B. Patelli, P. Giardino, A. DiMarco, A. M. Casazza, C. Soranzo, and G. Pratesi, *Experientia*, **34**, 1255 (1978).
6) *a*) T. R. Kelly, *Ann. Rep. Med. Chem.*, **14**, 288 (1979); *b*) S. Terashima, *Yuki Gosei Kagaku Kyokai Shi*, **40**, 20 (1982).
7) *a*) T. R. Lewis, W. B. Dickinson, and S. Archer, *J. Am. Chem. Soc.*, **74**, 5321 (1952); *b*) C. A. Grob and W. Jundt, *Helv. Chim. Acta*, **35**, 2111 (1952).
8) *a*) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, *Chem. Lett.*, **1984**, 473; *b*) *Idem, Bull. Chem. Soc. Jpn.*, **59**, 415 (1986).
9) K. Tamoto and S. Terashima, *Chem. Pharm. Bull.*, **32**, 4328 (1984).
10) K. Tamoto, M. Sugimori, and S. Terashima, *Tetrahedron*, **40**, 4617 (1984).
11) D. Dominguez, R. J. Ardecky, and M. P. Cava, *J. Am. Chem. Soc.*, **105**, 1608 (1983).
12) It has been reported that successive cyanohydrin formation, protection of the cyanohydrin with a tetrahydropyranyl group, addition of methylmagnesium iodide to the protected cyanohydrin, and acidic hydrolysis, could convert **11a** and 5,12-dihydroxy-7-methoxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione into the corresponding α-hydroxy methyl ketones.[13] When this method was examined using **15**, addition of methylmagnesium iodide to the protected cyanohydrin derived from **15** was found to afford a complex mixture of reaction products.
13) T. H. Smith, A. N. Fujiwara, W. W. Lee, H. Y. Wu, and D. W. Henry, *J. Org. Chem.*, **42**, 3653 (1977).
14) *a*) A. S. Kende, Y.-g. Tsay, and J. E. Mills, *J. Am. Chem. Soc.*, **98**, 1967 (1976); *b*) A. S. Kende, D. P. Curran, Y.-g. Tsay, and J. E. Mills, *Tetrahedron Lett.*, **1977**, 3537.
15) R. J. Blade and P. Hodge, *J. Chem. Soc., Chem. Commun.*, **1979**, 85.
16) N. Tanno and S. Terashima, *Chem. Pharm. Bull.*, **31**, 811 (1983).
17) After ethynylcerium(III) reagents had been explored as efficient tools for introducing the α-hydroxy ketone moiety into **15**, we succeeded in developing another synthetic route to **18** from **15**. Thus, cyanohydrin formation of **15** followed by hydrolysis gave the corresponding α-hydroxy acid. Successive treatments of the acylimidazole, derived from the α-hydroxy acid, with trimethylsilyl trifluoromethanesulfonate and methylmagnesium bromide were found to afford **18** in good overall yield.[18]
18) M. Suzuki, T. Matsumoto, R. Abe, Y. Kimura, and S. Terashima, *Chem. Lett.*, **1985**, 57.
19) *a*) T. Imamoto, T. Kusumoto, and M. Yokoyama, *J. Chem. Soc., Chem. Commun.*, **1982**, 1042; *b*) T. Imamoto, K. Kusumoto, Y. Tawaraya, Y. Sugiura, T. Mita, Y. Hatanaka, and M. Yokoyama, *J. Org. Chem.*, **49**, 3904 (1984).
20) T. Imamoto, Y. Tawaraya, T. Kusumoto, and M. Yokoyama, *Yuki Gosei Kagaku Kyokai Shi*, **42**, 143 (1984).
21) D. N. Gupta, P. Hoge, and N. Kahn, *J. Chem. Soc., Perkin Trans. 1*, **1981**, 689.
22) After completion of this work, we were informed by Dr. Imamoto that various ethynylcerium(III) reagents could cleanly react with easily enolizable ketones such as 1,3-diphenylpropan-2-one, 1-bromopropan-2-one, and 2-tetralone, to afford the addition products in excellent yields. We thank Dr. Imamoto for letting us see a copy of his paper in advance of publication. See, T. Imamoto, Y. Sugiura, and N. Takiyama, *Tetrahedron Lett.*, **25**, 4233 (1984).
23) Quite recently, it was reported that construction of the $C_9$-α-hydroxy methyl ketone moiety of 11-deoxyanthracyclinones could be accomplished using **8**. See, Y. Tamura, M. Sasho, H. Ohe, S. Akai, and Y. Kita, *Tetrahedron Lett.*, **26**, 1549 (1985).
24) All melting points were determined with a Yamato MP-21 melting point apparatus and are not corrected. Infrared (IR) spectral measurements were carried out with a JASCO A-202 diffraction grating infrared spectrometer. Nuclear magnetic resonance (NMR) spectra were taken with a Varian EM-390 spectrometer (90 MHz) and a Varian HA-100 spectrometer (100 MHz). The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br). All reactions were carried out using anhyd. solvents, and the combined organic extracts obtained in each experiment were dried over anhyd. $MgSO_4$ before filtration and concentration of the filtrate *in vacuo* with a rotary evaporator. Column chromatography was performed using silica gel (Wakogel C-200) as an adsorbent. The following abbreviations are used for solvents: benzene ($C_6H_6$); dichloromethane ($CH_2Cl_2$); ether ($Et_2O$); ethyl acetate (EtOAc); hexane ($C_6H_{14}$); tetrahydrofuran (THF).
25) Commercially available cerium(III) chloride heptahydrate was used after being dried *in vacuo* (*ca.* 100 °C, 1 h,

0.1 mmHg, then 140 °C, 2 h, 0.1 mmHg).

26) This operation seems to be necessary for preparing a complete suspension of cerium(III) chloride. The yields of the addition products decrease if this treatment is not done.

27) S.-s. Jew, S. Terashima, and K. Koga, *Chem. Pharm. Bull.*, **27**, 2351 (1971).