CHEMISTRY LETTERS, pp. 1543 - 1546, 1984.

A NOVEL SYNTHESIS OF THE α-HYDROXYKETONE MOIETY OF ANTHRACYCLINONES BY THE USE OF 2-TRIMETHYLSILYLETHYNYLCERIUM(III) REAGENTS

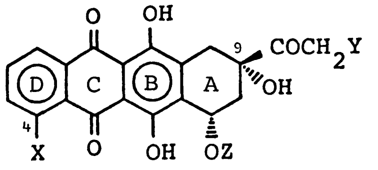
Michiyo SUZUKI, Yoshikazu KIMURA, and Shiro TERASHIMA*
Sagami Chemical Research Center, Nishi-Ohnuma, Sagamihara, Kanagawa 229

2-Trimethylsilylethynylcerium(III) reagents were found to efficiently react with 1,2,3,4-tetrahydronaphthalene-2-one derivatives, giving the corresponding adducts in high yields. Hydration of the adducts readily afforded the α-hydroxy methyl ketones which are versatile synthetic intermediates of natural and unnatural anthracyclinones.

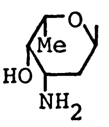
The anthracycline antibiotics, daunorubicin(1a) and adriamycin(1b), are clinically useful antineoplastic agents.$^{1)}$ For the past decade, numerous synthetic efforts have been devoted to anthracycline chemistry, especially to anthracyclinones, the aglycones of anthracyclines,$^{2)}$ culminating in the development of unnatural 4-demethoxyanthracyclines such as 4-demethoxydaunorubicin(1c) and 4-demethoxyadriamycin(1d), which show more improved therapeutic properties than natural 1a,b.$^{1,2)}$

In connection with our synthetic studies on optically active 4-demethoxyanthracyclinones(2c,d), the aglycones of 4-demethoxyanthracyclines (1c,d), we have recently reported the effective synthetic method of 5,12-dihydroxy-1,2,3,4-tetrahydronaphthacene-2,6,11-trione(3c).$^{3)}$ However, conversion of 3c to (±)-7-deoxy-4-demethoxydaunomycinone(6c) could only be achieved in 40% overall yield by sequential 1,2-addition with large excess (25 equiv.) of ethynylmagnesium bromide and hydration catalyzed by mercury(II) ion.$^{3)}$ Since 6c holds the pivotal position in the synthesis of optically active (+)-4-demethoxydaunomycinone (2c),$^{4,5)}$ an efficient reaction scheme was sought which would afford 6c from 3c more readily than the previous method.$^{3,6)}$

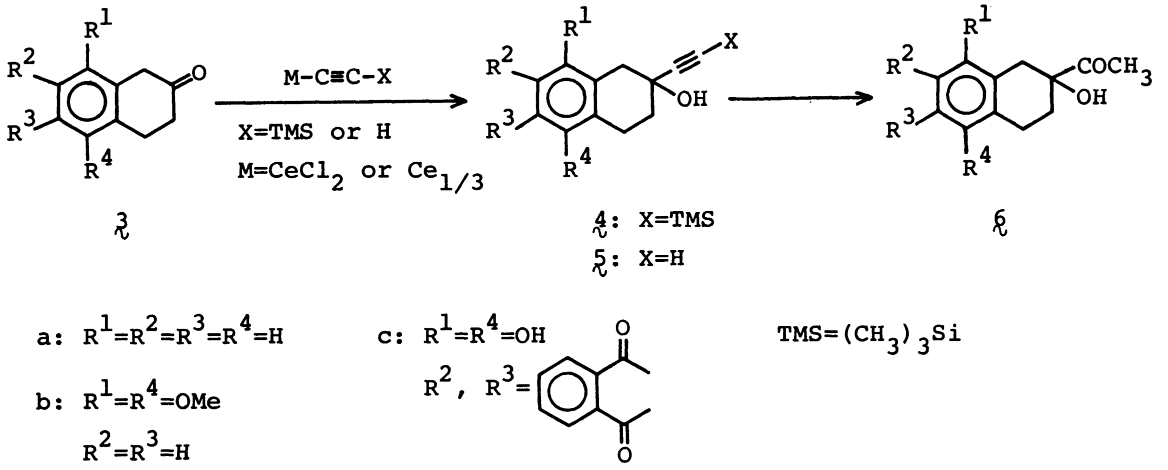
We have now found that 2-trimethylsilylethynylcerium(III) reagent, which can be produced from trimethylsilylethynyllithium and cerium(III) chloride, is quite



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

1: Z=


2: Z=H



3

4: X=TMS

5: X=H

6

a: $R^1=R^2=R^3=R^4=H$

b: $R^1=R^4=OMe$
$R^2=R^3=H$

c: $R^1=R^4=OH$
R^2, R^3=

TMS=$(CH_3)_3Si$

promising for transferring a 2-trimethylsilylethynyl moiety to 3c and that the adduct(4c) could readily be converted to 6c by simultaneous desilylation and hydration. While butylcerium(III) reagent prepared from butyllithium and cerium(III) chloride has been reported to react with various types of ketones to afford the corresponding adducts in excellent yields, 2-trimethylsilylethynylcerium(III) reagent has never been explored.[7]

Before subjecting the tetracyclic ketone(3c) to the addition reaction, efficacy of 2-trimethylsilylethynylcerium(III) reagent was studied by the use of 5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-2-one(3b), the AB ring synthon of 3c, since the addition of ethynylmagnesium bromide to 3b could afford 5b in ca. 80% yield when more than 10 equiv. of the Grignard reagent was used.[8] (±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol(6b) derived from 5b, has been utilized in the syntheses of racemic and optically active anthracyclinones including unnatural 2c,d.[2,4,5,8]

After examining the addition reactions under various conditions, the following standard procedure was established (Table 1, run 2). Thus, anhyd. cerium(III) chloride[9] (516 mg, 2.09 mmol, 2.1 equiv. to 3b) was suspended in anhyd. tetrahydrofuran(THF) (4 ml) and the suspension was stirred overnight at room temperature under an argon atmosphere.[10] A solution of 2-trimethylsilylethynyllithium, which was prepared by adding butyllithium (1.63 mol $\mathrm{dm^{-3}}$ solution in hexane, 1.1 ml, 1.79 mmol, 1.8 equiv. to 3b) to a solution of trimethylsilylacetylene (217 mg, 2.21 mmol, 2.23 equiv. to 3b) in THF (3 ml) at -78 °C, was added to the suspension of cerium(III) chloride at -78 °C. The whole mixture was stirred at -78 °C for 1 h, giving a solution of 2-trimethylsilylethynylcerium (III) chloride. A solution of 3b[8] (205 mg, 0.99 mmol) in THF (6 ml) was added to the solution of 2-trimethylsilylethynylcerium(III) chloride at -78 °C. The mixture was stirred at the same temperature for 1 h, then the reaction was quenched by the addition of water (10 ml). Usual extractive isolation followed by concentration and purification by column chromatography (SiO_2, benzene: ethyl acetate = 10:1), gave pure 4b as a colorless solid (303 mg, 100%), mp 91.5-92 °C (from ether-hexane).

When trimethylsilylethynyllithium was allowed to react with 3b at -78 °C

Table 1. Addition reaction of 2-trimethylsilylethynyl- and ethynylcerium(III) reagents to the ketones(3) and hydration of the adducts(4,5).

	Addition reaction to the ketones(3)a)							Hydration of the adducts(4,5)a)		
Run	3	X	M	Ratio of X-C≡C-M/3	Time h	Product	Yield of 4 or 5/%b)	Time h	Ratio of HgO/4 or 5	Yield of 6/%c)
1	3a	TMS	$CeCl_2$	1.9	1	4a	85(0)	31	0.29	92
2	3b	TMS	$CeCl_2$	1.8	1	4b	100(0)	16.5	0.27	100
3	3b	TMS	$Ce_{1/3}$	2.0	1	4b	93(0)			
4	3b	TMS	$CeCl_2$d)	2.0	1	4b	72(13)			
5	3b	H	$CeCl_2$	2.0	2	5b	81(15)	19	0.57	83
6	3b	H	$Ce_{1/3}$	2.4	1	5b	57(16)			
7	3b	H	$CeCl_2$d)	2.4	1	5b	64(18)			
8	3c	TMS	$CeCl_2$	5.9	3	4c	62	12	0.54	95
9	3c	TMS	$Ce_{1/3}$	6.1	5	4c	55			

a) All reactions were performed at -78 °C (for addition reaction) or at room temperature (for hydration) in the same manner as that for run 2. (See the text) b) Isolated yields based on 3. Numbers in parentheses refer to recovery yield of 3. c) Isolated yields based on 4 or 5. d) 2-Trimethylsilylethynylmagnesium bromide or ethynylmagnesium bromide was used for preparing 2-trimethylsilylethynylcerium(III) or ethynylcerium(III) chloride in place of 2-trimethylsilylethynyllithium or ethynyllithium.

without metal exchange with cerium(III) chloride, only 49% of 4b could be obtained with 44% recovery of 3b. This control experiment obviously shows enhanced reactivity of the explored cerium(III) reagent for the addition of 3b.

We have also found that tris(2-trimethylsilylethynyl)cerium(III), which may be produced by reacting trimethylsilylethynyllithium with 0.33 equiv. of cerium (III) chloride, can react with 3b, giving 4b in 93% yield without a recovery of 3b (Table 1, run 3).

While Grignard reagent has been reported to be less effective for producing alkylcerium(III) reagent,[7] 2-trimethylsilylethynylmagnesium bromide prepared from trimethylsilylacetylene and ethylmagnesium bromide seems to afford 2-trimethylsilylethynylcerium(III) chloride in a similar manner to the corresponding lithium reagent. Thus, the reaction of 2-trimethylsilylethynylcerium(III) chloride produced from the corresponding Grignard reagent gave 72% of 4b (Table 1, run 4). The experiment performed by using 2-trimethylsilylethynylmagnesium bromide afforded 4b in 18% yield with 78% recovery of 3b.

Although it was found that ethynylcerium(III) reagents can be also produced by using inexpensive acetylene gas in place of trimethylsilylacetylene(Table1, runs 5-7), 2-trimethylsilylethynylcerium(III) reagents seems to be superior to ethynylcerium(III) reagents by taking account of chemical yields (compare runs 2 and 5, runs 3 and 6, and runs 4 and 7) and operational simplicity.

The best reaction condition established with 3b was applied to β-tetralone (3a),giving the adduct(4a), mp 125.5-126 °C(from ether-hexane), in 85% yield (Table 1,run 1). Treatments of 3c with two types of 2-trimethylsilylethynylcerium(III) reagents (5.9 and 6.1 equiv. to 3c) furnished the adduct(4c) in 62% and 55% yields, respectively.

With three types of the adducts(4a-c) in hand, direct transformation of 4a-c into the corresponding α-hydroxy ketones(6a-c) was next examined. This was found to be readily achieved by treating 4a-c with a catalytic amount of mercury(II) ion, similarly to the transformation of 5b to 6b.[4,11] Treatment of 4b(247 mg, 0.81 mmol) with mercury(II) oxide (47 mg, 0.22 mmol, 0.27 equiv.) in a mixture of H_2SO_4 (3 mol dm^{-3}, 3 ml) and THF (5 ml) at room temperature for 16.5 h, readily afforded 6b (203 mg, 100%), mp 104-105 °C (lit.,[4] mp 102-103 °C), after extraction and purification by column chromatography (SiO_2, benzene-ethyl acetate 10:1) (Table 1, run 2). The same reaction condition also gave 6b from 5b in 83% yield (Table 1, run 5). Similarly, 4a,c were converted to 6a,[12] oil, and 6c, mp 212.5-214.5 °C (from benzene)(lit.,[8] mp 214-216 °C), in 92% and 95% yields, respectively (Table 1, runs 1 and 8).

Since numerous synthetic approaches to anthracyclinones hitherto reported terminate at or proceed through 1,2,3,4-tetrahydronaphthacene-2,6,11-trione derivatives,[2] our reagent should be promising to add the C_9-α-hydroxy ketone moiety (anthracycline numbering) to those tetracyclic systems.

References

1) F. Arcamone, "Topics in Antibiotic Chemistry," ed by P.G. Sammes, Ellis Horwood, Chichester, England(1978), Vol. 2, pp. 98-239.

2) S. Terashima, Yuki Gosei Kagaku Kyokai Shi, 40, 20(1982).

3) Y. Kimura, M. Suzuki, T. Matsumoto, R. Abe, and S. Terashima, Chem. Lett., 1984, 473.

4) S. Terashima and K. Tamoto, Tetrahedron Lett., 23, 3715(1982).

5) S. Terashima, K. Tamoto, and M. Sugimori, Tetrahedron Lett., 23, 4107(1982).

6) Successive cyanohydrin formation, protection of the cyanohydrin with tetrahydropyranyl group, addition of methylmagnesium iodide to the protected cyanohydrin, and acidic hydrolysis were anticipated to be another possible reaction scheme which could convert 3c to 6c (T.H. Smith, A.N. Fujiwara, W.W. Lee, H.Y. Wu, and D.W. Henry, J. Org. Chem., 42, 3653(1977).). While this reaction scheme was examined on 3c, addition of methylmagnesium iodide to the protected cyanohydrin derived from 3c was found to yield a complex mixture of the reaction products.

7) T. Imamoto, Y. Tawarayama, T. Kusumoto, and M. Yokoyama, Yuki Gosei Kagaku Kyokai Shi, 42, 143(1984). After completion of this work, Dr. Imamoto informed us that he had also developed ethynylcerium(III) reagent. We thank Dr. Imamoto for letting us know his results in advance of publication.

8) N. Tanno and S. Terashima, Chem. Pharm. Bull., 31, 811(1983).

9) Commercial cerium(III) chloride heptahydrate was used after dried in vacuo (140 °C, 2 h, 13.3 Pa).

10) This procedure seems to be necessary for preparing a complete suspension of cerium(III) chloride. Without this treatment, the yield of 4b decreased to ca. 60%.

11) R.J. Blade and P. Hodge, J. Chem. Soc., Chem. Commun., 1979, 85.

12) S-s. Jew, S. Terashima, and K. Koga, Chem. Pharm. Bull., 27, 2351(1979).

(Received June 27, 1984)