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2-AZABICYCLO[3.2.0]HEPTANE-3,4-DIONES (6)

A NOVEL METHOD OF REGIO-CONTROLLED SYNTHESIS OF FUNCTIONALIZED HYDROINDOLES AND ERYTHRINAN DERIVATIVES[1]

Takehiro Sano*, Jun Toda, Yoshie Horiguchi, and Kazue Imafuku
Showa College of Pharmaceutical Sciences, Setagaya-Ku, Tokyo 154, Japan
Yoshisuke Tsuda
Faculty of Pharmaceutical Sciences, Kanazawa University, Kanazawa 920, Japan

A regio-controlled synthesis of functionalized hydroindoles from a Δ^2-pyrrolinedione and its application to the synthesis of erythrinan skeleton were described. The method is to construct with [2+2] photocycloaddition of a trimethylsilyloxybutadiene to a Δ^2-pyrrolinedione followed by thermal [1,3]-rearrangement to yield a hydroindole silyl enol ether, which is isomeric with the hydroindole silyl enol ether obtained by Diels-Alder cyclization between the same substrates.

During the investigation of thermolysis of 2-azabicyclo[3.2.0]heptane-3,4-diones,[2~4] we have found that the 7-*exo*-vinyl derivative (1, R=H) undergoes thermal [1,3]-rearrangement to yield hydroindole (3) via homolytic cleavage of C_1-C_7 bond.[4] A stabilizing effect of C_7-substituent on the radical (2) wherein formed and the known fact that the electron donating substituent such as trimethylsilyloxy group at a migrating center (C_7) accelerates a thermal [1,3]-shift[5], directly leads to the idea that a vinyl oxycyclobutane derivative (1, R=OTMS) may be a potential precursor for synthesis of functionalized hydroindoles.

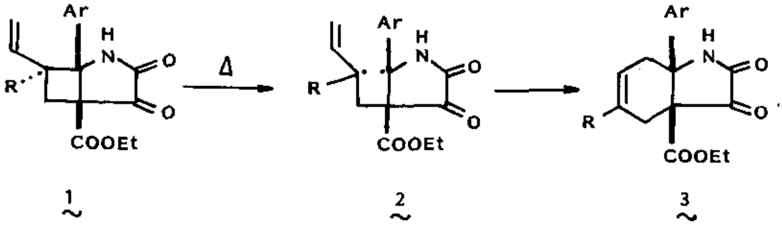

Chart 1

The desired 7-vinyl-7-trimethylsilyloxy derivatives (5a~c) were readily prepared by photocycloaddition (>300 nm)[6] of 2-trimethylsilyloxybutadiene (2 molar equiv.) to 1-aryl-Δ^2-pyrroline-4,5-diones (4a~c). The reaction proceeded in regio- and stereoselective manner in every case to give the product (5) homogeneously. The structures of 5a~c were assigned from the results of analogous photocycloaddition[7] and their NMR spectra (Table 1) except for stereochemistry at C_7 which is still to be established.[8]

On heating the adducts (5a~c) in boiling toluene for 3 hr, an facile [1,3]-shift occurred as expected to give the hydroindole (6a~c) in the yields shown in Table 2. The presence of the silyl enol ether moiety in 6 was easily recognized by their NMR and IR spectra. On hydrolysis with 5%HCl-THF (1:1) at room temp. for 30 min., 6 afforded the corresponding diketone (7) in quantitative yield, while on treatment with potassium fluoride (in THF, r.t., overnight), it gave the ketol (8) exclusively, as a result of an intramolecular aldol condensation of 7. They were easily distinguishable by IR spectra (Table 3) and their structures were confirmed by the following spectral evidence. In ^{13}C-NMR spectrum the ketol (8a) exhibited three $-\overset{|}{\underset{|}{C}}-$ (δ 67.6, 68.0, 88.1), one $-\overset{|}{\underset{|}{C}}H$ (δ 53.4) and one ketonic carbon (δ 207.4), while the diketone (7a) showed two $-\overset{|}{\underset{|}{C}}-$ (δ 60.2, 62.9), and two ketonic carbons (δ 204.8, 196.1), but no signal of $-\overset{|}{\underset{|}{C}}H$. The structure (8a) was further verified by the following chemical transformation.

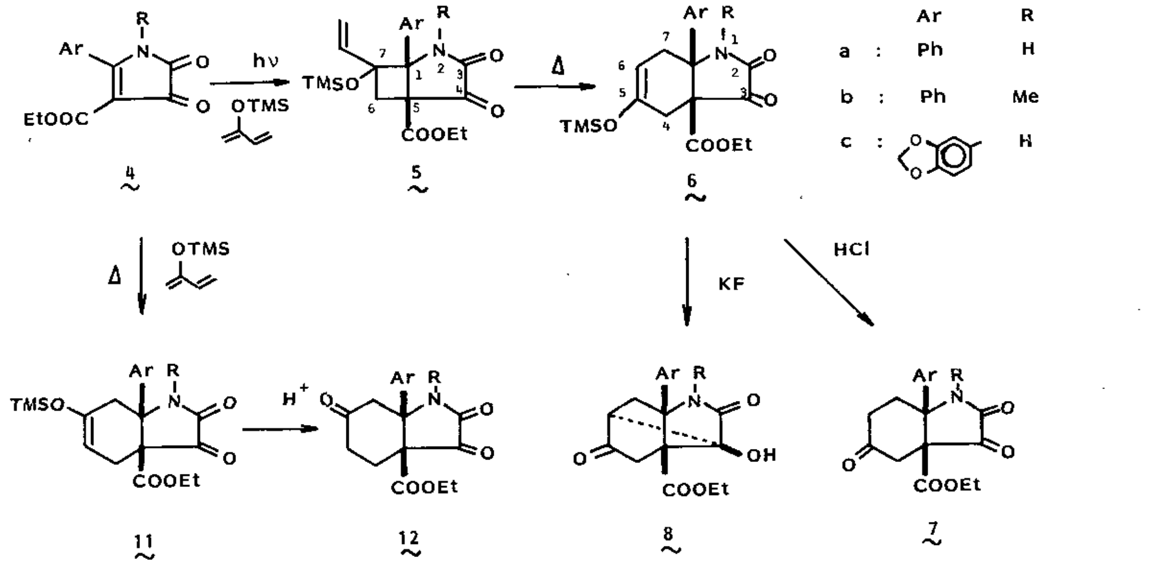

Chart 2

Table 1. Photocycloaddition[6] of 2-Trimethylsilyloxybutadiene to **4**.

1,2-Adduct			NMR(δ, $CDCl_3$)		IR(Nujol, cm^{-1})
	mp	yield(%)	vinyl protons*1	C_6-H(J, Hz)*2	
5a:	176-178°,	70	5.05-5.57(3H)	2.37, 3.53(14)	1780, 1760, 1730
5b:	141-143°,	60	5.32-6.37(3H)	2.33, 3.38(13)	1760, 1720
5c:	169-171°,	50	5.03-5.53(3H)	2.29, 3.41(13)	1780, 1730

*1 Signals appeared as a typical ABM pattern.

*2 Each signal appeared as a doublet.

Table 2. Pyrolysis of The 1,2-Adduct (**5**)

Product			NMR(δ, $CDCl_3$)		IR(Nujol, cm^{-1})
	mp	yield(%)	OTMS*1	-CH=*2	
6a:	——*3,	58*4			
6b:	144-146°,	51	0.18	4.75	1765, 1720, 1645
6c:	172-178°,	58	0.18	4.66	1775, 1750, 1730, 1650

*1 The signal appeared as a 9H singlet.

*2 The signal appeared as a 1H multiplet.

*3 The silyl enol ether of **6a** was cleaved on trituration with ether to give **8a**.

*4 Yield was calculated from the weight of **8a**.

Table 3. Physical Data of The Diketones (**7**) and The Ketols (**8**)

Diketone (**7**)			Ketol (**8**)		
	mp	IR(Nujol, cm^{-1})		mp	IR(Nujol, cm^{-1})
7a:	150-152°	1770, 1740, 1720, 1710	**8a**:	195-196°	3200, 1770, 1725
7b:	141-142°	1765, 1740, 1720, 1710	**8b**:	175-176°	3200, 1760, 1725, 1695
7c:	152-155°	1770, 1745, 1725, 1700	**8c**:	222-226°	3480, 3330, 1755, 1730 1700

Sodium borohydride reduction of 8a in ethanol gave a mixture of isomeric alcohols (9) which, without separation, were mesylated in pyridine with methansulfonyl chloride and the product was treated with DBU to give a compound (10), mp 229-231°, which was identical with the Diels-Alder adduct of 4a and butadiene.[9]

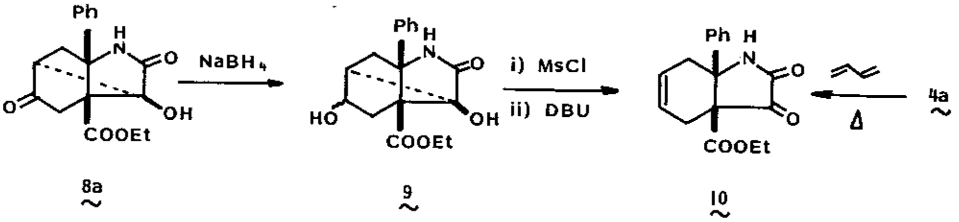

Chart 3

It is worth noting that the silyl enol ether (6) (hence the diketone 7) obtained in this reaction is isomeric with the silyl enol ether (11) (hence the diketone 12) prepared by the Diels-Alder reaction between the same substrates (4 and 2-trimethylsilyloxybutadiene).[10]

The above method was applied to the isoquinolinopyrrolinedione (13)[10] which was expected to lead to erythrinan derivative. The photocycloaddition[6] of 2-trimethylsilyloxybutadiene to 13 also proceeded in regio- and stereoselective manner to give a single 1,2-adduct (14)[11] in 90% yield, which underwent thermal [1,3]-shift in boiling toluene (3 hr) to give the erythrinan derivative (15)[11] in 64% yield. Hydrolysis of 15 with 5%HCl-THF (1:1) or KF in THF yielded the ketone (16), mp 283-284°, in 90% yield, identity of which with the known trioxo compound (16)[12] was confirmed by their direct comparisons (mp , TLC, IR and NMR). Again the ketone (16) was isomeric with the ketone (17) in the position of the carbonyl moiety in ring D of the erythrinan skeleton; the latter being prepared *via* the Diels-Alder reaction of 13 and 2-trimethylsilyloxybutadiene.[10] 1-Methoxy-3-trimethylsilyloxybutadiene underwent cycloaddition (72%) to 13 giving the product (18)[13] which was then rearranged in boiling toluene (3 hr) into the erythrinan (19)[14] in the similar manner as above. Hydrolysis of 19 with boiling 5%HCl-THF (1:1) under reflux (1 hr) afforded the conjugated enone (20)[13] (38% from 18) and treatment of 19 with KF in THF (r.t., overnight) gave the ketol (21)[13] (48% from 18), respectively.

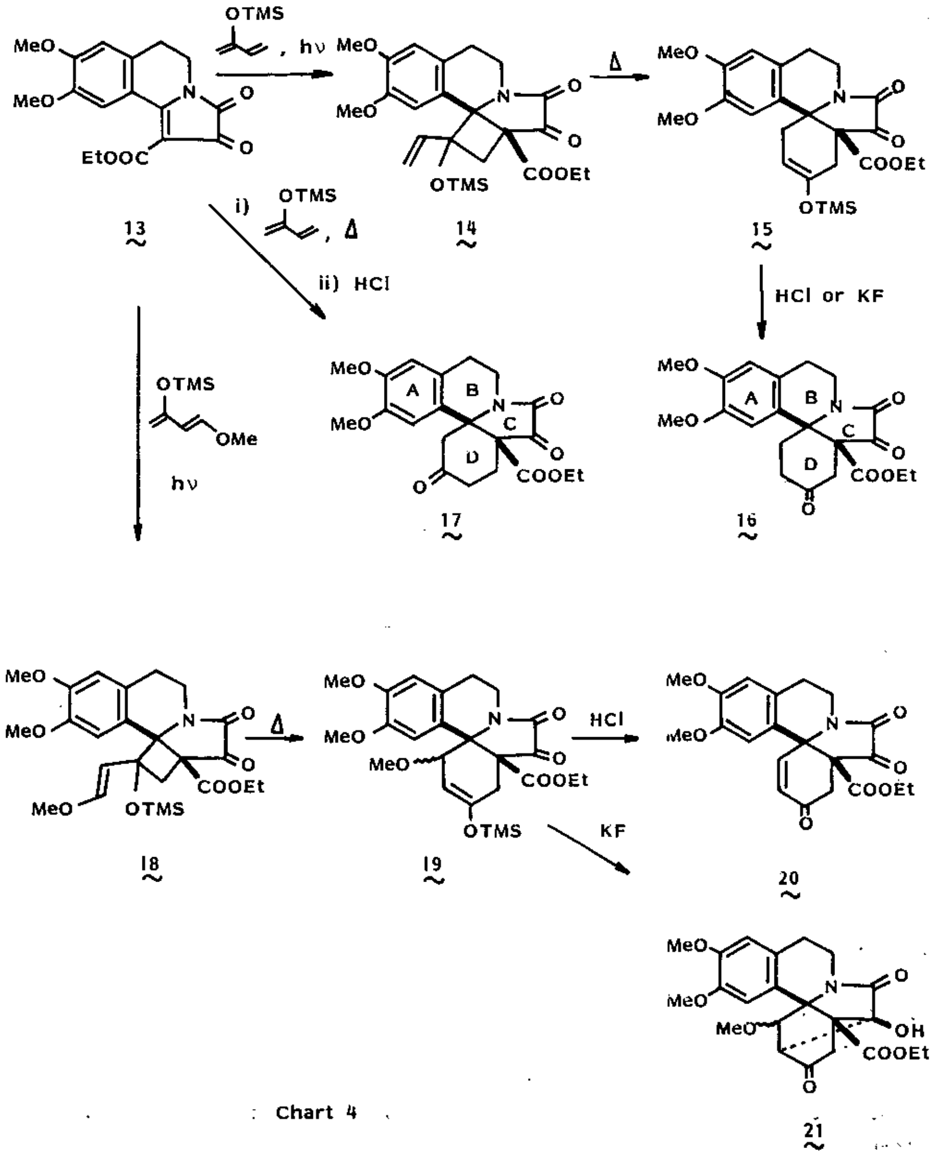

Chart 4

The present method for the preparation of functionalized hydroindoles and erythrinan derivatives has a great synthetic value in the points that it shows a reverse regioselectivity to Diels-Alder reaction and that the silyl enol ether whereon produced is appropriate to further manipulation.

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Reference and Note

1. Dioxopyrrolines XXII. This paper also constitutes Part (5) of Syntheses of Erythrina and Related Alkaloids. Part XXI: T. Sano, J. Toda, N. Kashiwaba, Y. Tsuda, and Y. Iitaka, *Heterocycles*, 1981, **16**, 1151.
2. T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, 1981, **16**, 355.
3. T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, 1981, **16**, 889.
4. T. Sano, Y. Horiguchi, S. Kambe, J. Toda, J. Taga, and Y. Tsuda, *Heterocycles*, 1981, **16**, 893.
5. a) B. M. Trost and M. J. Bogdonowicz, *J. Am. Chem. Soc.*, 1973, **95**, 289.
   b) R. W. Thies and J. E. Billigmeier, *J. Am. Chem. Soc.*, 1974, **96**, 200.
6. Irradiated in dimethoxyethane with high pressure mercury lamp (300w, pyrex filtered) at 0°C for 30 min.
7. T. Sano, Y. Horiguchi, and Y. Tsuda, *Heterocycles*, 1981, **16**, 359.
8. The result of the thermal reaction described here is compatible with that of the *exo*-vinyl derivative (**1**, R=H), thus suggesting C_7-*exo*-vinyl and *endo*-OTMS configuration. However, the fact does not necessarily confirm the stereochemistry since the possibility of the thermal epimerization of C_7-substituents *via* the biradical intermediate (**2**, R=OTMS) prior to the [1,3]-shift can not be eliminated.
9. T. Sano and Y. Tsuda, *Heterocycles*, 1976, **4**, 1361.
10. See Part XXI.
11. **14**: mp 120-122°. IR(Nujol); 1770, 1720 cm^{-1}. ^1H-NMR($CDCl_3$); δ 0.12(9H, s, Me_3Si-), 0.83(3H, t, J=7 Hz, $-COOCH_2\underline{CH_3}$), 2.27 and 3.53(each 1H, d, J=14 Hz, $-CH_2-$ on cyclobutane), 3.82 and 3.88(each 3H, s, OMe), 3.93(2H, q, J=7 Hz), 5.05-5.55(3H, m, $-CH=CH_2$), 6.50 and 6.63(each 1H, s, Ar-H).
    15: mp 158-160°. IR(Nujol); 1765, 1740, 1705, 1650 cm^{-1}. ^1H-NMR($CDCl_3$); δ 0.20(9H, s, Me_3Si-), 0.67(3H, t, J=7 Hz, $-COOCH_2\underline{CH_3}$), 2.68(2H, d, J=5 Hz, C_4-H), 3.00(2H, bs, C_1-H), 3.61(2H, q, J=7 Hz, $-COO\underline{CH_2}CH_3$), 3.87(6H, s, 2×OMe), 4.64(1H, d, J=5 Hz, olefinic H), 6.58 and 6.63(each 1H, s, Ar-H).
12. Y. Tsuda, Y. Sakai, and T. Sano, *Heterocycles*, 1981, **15**, 1097.
13. **18**: mp 127-128°. IR(Nujol); 1760, 1730, 1710, 1660 cm^{-1}. ^1H-NMR($CDCl_3$); δ 0.06(9H, s, $-SiMe_3$), 0.77(3H, t, J=7 Hz, $-COOCH_2\underline{CH_3}$), 2.26 and 3.37(each 1H, d, J=14 Hz, $-CH_2-$ on cyclobutane), 3.34, 3.80 and 3.87(each 3H, s, -OMe), 4.35 and 6.47(each 1H, d, J=14 Hz, -CH=CH-), 6.47 and 6.58(each 1H, s, Ar-H).
    20: mp 170-172°. IR(Nujol); 1765, 1730, 1710, 1680 cm^{-1}. ^1H-NMR($CDCl_3$); δ 0.77(3H, t, J=8 Hz, $-COOCH_2\underline{CH_3}$), 3.94(2H, bs, C_1-H), 3.82 and 3.88(each 3H, s, -OMe), 6.06 and 6.80(each 1H, d, J=12 Hz, -COCH=CH-), 6.53 and 6.67 (each 1H, s, Ar-H).
    21: mp 196-198°. IR(Nujol); 3200, 1760, 1710, 1685 cm^{-1}. ^1H-NMR($CDCl_3$); δ 1.05(3H, t, J=8 Hz, $-COOCH_2\underline{CH_3}$), 3.31(3H, s, -OMe), 3.90(6H, s, 2×OMe), 6.69 and 6.78(each 1H, s, Ar-H).
14. The silyl enol ether was too labile to be isolated in pure form and changed into **21** on direct trituration with ether.

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