HETEROCYCLES, Vol. 54, No. 1, 2001, pp. 81 - 86, Received, 26th May, 2000

EFFICIENT AND STEREOSELECTIVE β-EPOXIDATION OF THE 16(17)-DOUBLE BOND OF GIBBERELLIC ACID DERIVATIVES WITH AN ACYLPEROXY RADICAL GENERATED BY IRRADIATION OF α-DIKETONES AND OXYGEN

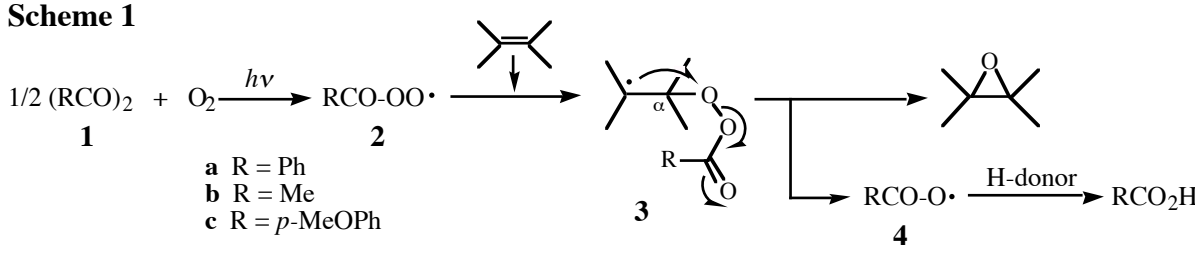
Hideharu Seto,* Mikio Hoshino, Shozo Fujioka, Toshiro Suenaga,
Takeshi Shimizu, and Shigeo Yoshida

RIKEN (The Institute of Physical and Chemical Research), Wako-shi, Saitama 351-0198, Japan

Abstract - Irradiation of gibberellic acid derivatives in the presence of α-diketones in an oxygen saturated solution led to efficient epoxidation of the 16(17)-double bond to give the 16β,17-epoxides predominantly. The observed stereoselectivity of α- to β-epoxidation ranging from 0:100 on 3,13-di-*O*-acetylgibberellic acid methyl ester (**7**) through 11:89 on its 3,13-di-*O*-methoxymethyl congener, *i.e.*, β-selectivity, was in contrast to the α-selectivity of 74:26 resulted from a peracid epoxidation on **7**. This clearly illustrates the radical reaction mechanism involving an acylperoxy radical as a one-oxygen transfer species, in which the stability of the diastereomeric transition states of the intermediary α-acylperoxy carbon radical determines the stereochemical course.

Since the first observation by Shimizu and Bartlett in 1976,[1] photo-epoxydation of olefins with α-diketone (**1**) and oxygen has been extensively studied mechanistically.[2-8] As proposed by Sawaki and Ogata in 1984,[6] the reactive oxidant involved in this reaction is an acylperoxy radical (**2**) generated by photochemical reaction of **1** and oxygen; the oxidation proceeds *via* attack of **2** to olefins, followed by leaving of the acyloxy radical (**4**) from the resulting adduct (**3**), leading to the formation of epoxides (Scheme 1). From a synthetic point of view, this epoxidation is attractive, because the stereochemical course is controlled by a

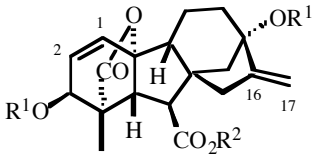
Scheme 1



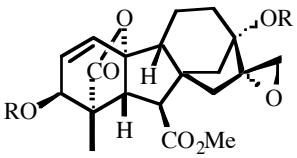
This paper is dedicated to Professor Shô Itô on the occasion of his 77th birthday

factor different from that of epoxidation with common reagents such as organic peracids which proceeds *via* a concerted process. Namely, it has been well documented that the photo-epoxidation of acyclic olefins resulted in the predominant formation of *trans*-epoxides independently of their starting geometry, *cis* or *trans*; this is accounted for by the free rotation around the $C_{radical}$-C_{α} bond of intermediary alkyl radical (**3**) that is much faster than the cyclization to epoxides, thus the resulting *cis*/*trans* ratio reflecting an energy difference between the two rotational conformers of **3**.[2] However, except for the case of acyclic simple olefins, only one example illustrating the stereochemical course characteristic of this radical epoxidation has been reported so far.[9]

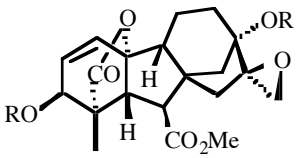
In a continuation of our study on the reactivity and synthetic utility of acylperoxy radicals,[7,8,10] and in conjunction with our synthetic study on phytohormone gibberellins, we examined the reactivities of gibberellic acid (GA_3) derivatives (**6-9**) with an acylperoxy radical, and found that the 16(17)-double bond of **7-9** was epoxidized in efficient and stereoselective manner to give 16β,17-epoxides (**15-17**) predominantly. Since the observed stereoselectivity, the so-called β-selectivity, in contrast to the α-selectivity of the conventional peracid epoxidation, apparently attests to the radical mechanism of this reaction, we herein report the results, along with a plausible explanation for the stereoselectivity based on the stability of the diastereomeric transition states of the intermediary α-acylperoxy carbon radical.



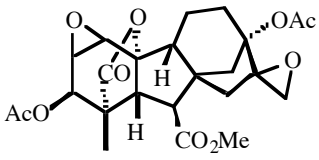
5 R^1=R^2=H
6 R^1=H, R^2=Me
7 R^1=Ac, R^2=Me
8 R^1=R^2=Me
9 R^1=MOM, R^2=Me



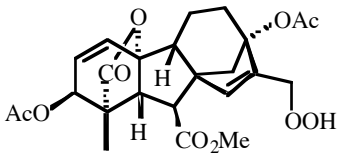
10 R=H
11 R=Ac
12 R=Me
13 R=MOM



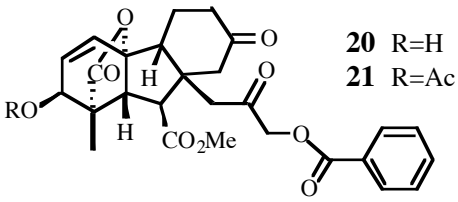
14 R=H
15 R=Ac
16 R=Me
17 R=MOM



18



19



20 R=H
21 R=Ac

In a typical experiment, a 5.0 x 10^{-2} mol solution of 3,13-di-*O*-acetylGA_3 methyl ester (**7**)[11] in benzene was irradiated in the presence of 1.0 equiv. of benzil (**1a**) in a Pyrex tube with a 300 W medium-pressure mercury lamp at 5–10 °C; oxygen was continuously bubbled through the solution during irradiation. The starting material was completely consumed in 1 h (monitored by thin layer chromatography). The reaction mixture was directly subjected to flash chromatography on silica gel to give 16β,17-epoxide (**15**) as the sole product in 94% isolated yield (Entry 2 in Table 1). The ^{1}H NMR (300 MHz) spectrum of the crude mixture showed that neither 16α,17-epoxide (**11**) nor di-epoxide (**18**) was formed under the conditions at all. Furthermore, almost the same results were obtained, either when the solvent was replaced by

acetonitrile or ethyl acetate or when the acylperoxy radical source was replaced by biacetyl (**1b**),[7] *p*-anisil (**1c**),[3] dibenzoyldiazene[8] or benzoin.[2]

Avent *et al.*[12] reported that when **7** was treated with *m*-chloroperbenzoic acid (*m*-CPBA) in chloroform at room temperature overnight, the reaction occurs both regio- and stereo-selectively at the 16(17)-double bond to yield mono-epoxides (**11**) and (**15**) in 69 and 24% yields, respectively. Such highly regioselective epoxidation of the 16(17)-double bond in the presence of the 1(2)-double bond is usually observed in gibberellins. Although a reasonable explanation has not been reported so far, the regioselectivity may be accounted for by the electron-deficient and steric hindered nature of the 1(2)-double bond compared with the 16(17)-double bond, *i.e.*, the two allylic oxygens of the 1(2)-double bond retard epoxidation there. On the other hand, the predominant formation of α-epoxide (**11**) is well explained by the less hindered α-face attack of *m*-CPBA to the 16(17)-double bond of **7** and its concerted reaction mechanism.[13] Thus, the result obtained from photo-epoxidation of **7** shows that the steric and electronic requirements of the acylperoxy radical for the addition to olefins are parallel to those of *m*-CPBA, while the stereochemical outcome is the reverse to that of peracid epoxidation due to its radical reaction mechanism as described later.[14]

Table 1 Photo-epoxidation of GA_3 derivatives with benzil (**1a**) and oxygen[a]

Entry	Substrate	Product Yield (%)[b]	Ratio of α- and β-epoxides
1	**6**[c]	**10** (31), **14** (29), **20** (9.3)	52 : 48
2	**7**	**15** (94)	0 : 100 (74 : 26)[d]
3	**8**	**12** (8.5), **16** (87)	10 : 90
4	**9**	**13** (10), **17** (85)	11 : 89

[a]Unless otherwise indicated, the reaction conditions identical to those for **7** were used. See Text.
[b]Isolated yields.
[c]Due to the low solubility of the substrate, ethyl acetate was used as a solvent, and for separation of products, aqueous work-up was required.
[d]The ratio in parenthesis results from epoxidation with *m*-chloroperbenzoic acid; see ref. 12.

Photo-epoxidation of the protecting group variants of **7**, 3,13-di-*O*-methylGA_3 methyl ester (**8**)[15] and 3,13-di-*O*-methoxymethylGA_3 methyl ester (**9**),[16] also proceeded efficiently with high β-stereoselectivity, but a small amount of α-epoxide formed: **8** gave the corresponding α-epoxide (**12**) and β-epoxide (**16**) in 8.5 and 87% isolated yields, respectively (Entry 3), and **9** gave α-epoxide (**13**) and β-epoxide (**17**) in 10 and 85 % isolated yields, respectively (Entry 4). In contrast, reaction of GA_3 methyl ester (**6**) possessing non-protected 3,13-dihydroxyl groups led to a somewhat confused result. The reaction was carried out in an ethyl acetate solution due to its poor solubility to benzene, giving α-epoxide (**10**)[17] and β-epoxide (**14**) in 31 and 29% isolated yields along with 9.3% of 13,16-secogibberellin (**20**) (Entry 1).

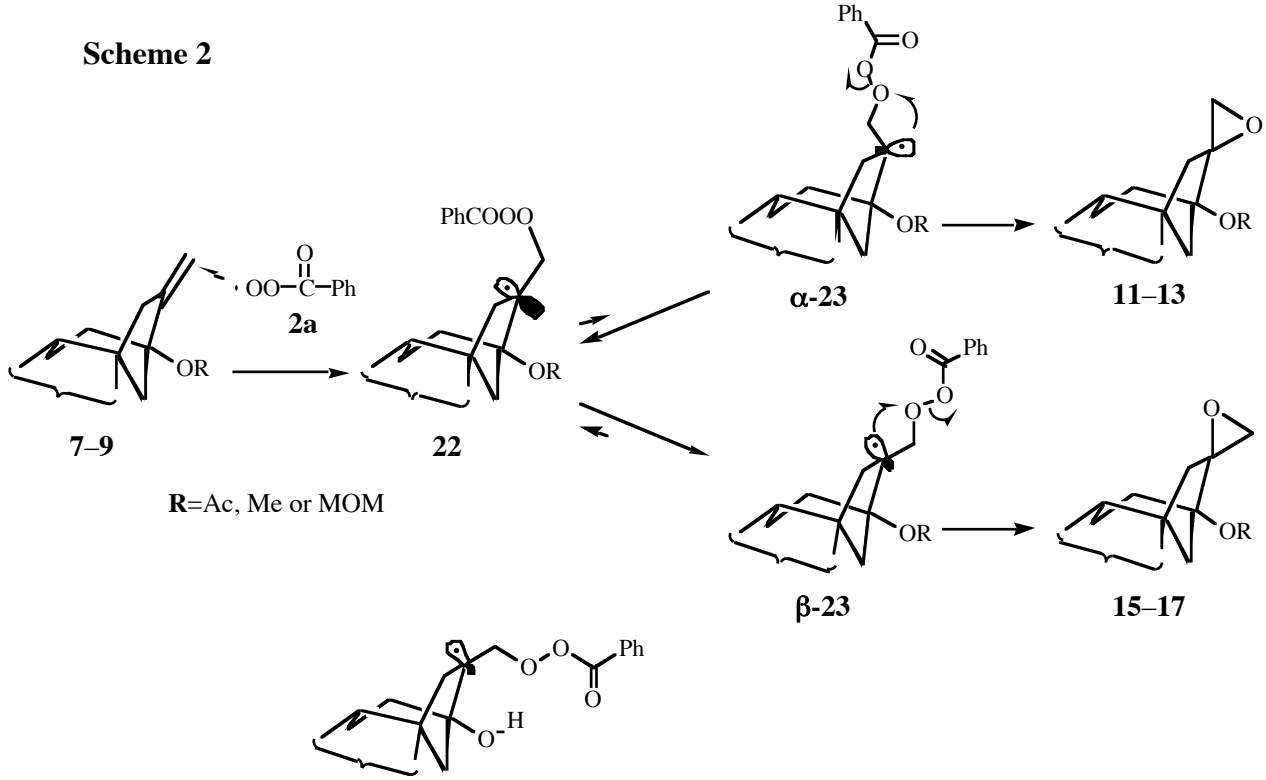
The new compounds (**12**, **13**, **14**, **16**, **17** and **20**) gave correct high-resolution MS spectrum, and satisfactory NMR and MS spectra.[18] The stereochemistries at C-16 of the epoxides were confirmed by comparison of their ^{1}H NMR spectra with those of known α-epoxide (**11**) and β-epoxide (**15**).[12] Table 2 shows the resonances based on 17-H_2 of **10**-**17** and 15β-H of **14**-**17** in their ^{1}H NMR spectra: doublet doublet resonances due to 15β-H observed at δ 1.38-1.49 are characteristic for β-epoxides (**14**-**17**), while those of α-epoxides (**10**-**13**) overlap with others at lower field than δ 2.00.

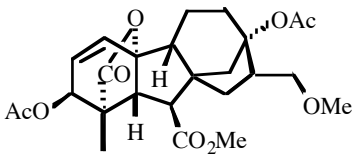
Table 2 Resonances of 17-H_2 and 15β-H on epoxides in 300 MHz ^{1}H NMR ($CDCl_3$, TMS; δ: multiplicity, *J* in Hz)

α-epoxides	17-H_2	β-epoxides	17-H_2	15β-H
10	2.73 and 2.86: ABq, 4.8	**14**	2.62 and 2.98: ABq, 5.8	1.38: dd, 13.6 and 3.3
11	2.75 and 3.12: ABq, 5.3	**15**	2.81 and 3.04: ABq, 5.0	1.46: dd, 13.3 and 3.3
12	2.78 and 2.82: ABq, 5.0	**16**	2.74 and 3.07: ABq, 5.6	1.47: dd, 13.6 and 3.3
13	2.80: s	**17**	2.75 and 3.10: ABq, 5.6	1.49: dd, 13.6 and 3.3

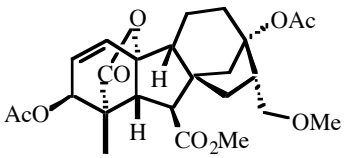
The β-selectivity may plausibly be explained by assuming that it reflects the stable geometry of the radical intermediate. As illustrated in Scheme 2, benzoylperoxy radical (**2a**) generated by irradiation of **1a** and oxygen attacks the 17-position of **7**-**9** from the less-hindered α-side to form tertiary carbon radical (**22**). Since carbon radicals, except for a methyl radical, are considered to be pyramidal with a low energy barrier to inversion,[19] the radical intermediate may exist as an equilibrium mixture of α- and β-radicals (α**–23** and β**–23**). It is speculated that β**–23** with a 16-*exo*-substituent would have lower energy than α**–23** with a 16-*endo*-substituent, because the energy difference between global minimum conformers of model compounds (**25** and **26**), calculated by a Low-Mode conformational search,[20,21] is in favor of **26**, ΔE = 1.6 kcal/mol. Thus, β−epoxides (**15–17**) *via* β**–23** predominantly form. In the reaction of **6**, a hydrogen bonding between the 13-hydroxyl and 17-benzoylperoxyl groups on the intermediary β-radical (**24**) appears to be responsible for the low stereoselectivity and formation of by-product (**20**), although the reaction mechanism of the formation of **20** can not be explained reasonably at this moment. The arrangement of benzoylperoxyl group and carbon radical on **24** is not suitable for cyclization to β-epoxide (**14**).

Scheme 2





25



26

As described, irradiation of GA_3 derivatives (**11**-**13**) in the presence of α-diketones in an oxygen saturated solution led to predominant formation of 16β,17-epoxides (**15**-**17**) in high yields. This well illustrated the stereochemical course characteristic of the radical epoxidation by acylperoxy radical generated by irradiation of α-diketones and oxygen. We are currently investigating the reactivity and synthetic utility of 16β(17)-epoxides (**15**-**17**) derived from gibberellic acid (**5**, GA_3), the cheapest and most plentiful starting material in the gibberellin field,[22] for further manipulation of the D-ring.

REFERENCES AND NOTES

1. N. Shimizu and P. D. Bartlett, *J. Am. Chem. Soc.*, 1976, **98**, 4193.
2. Y. Sawaki and Y. Ogata, *J. Am. Chem. Soc.*, 1981, **103**, 2049.
3. E. C. Clennan, D. R. Speth, and P. D. Bartlett, *J. Org. Chem.*, 1983, **48**, 1246.
4. J. P. Shepherd, *J. Org. Chem.*, 1983, **48**, 337.
5. Y. Sawaki and C. S. Foote, *J. Org. Chem.*, 1983, **48**, 4934.
6. Y. Sawaki and Y. Ogata, *J. Org. Chem.*, 1984, **49**, 3344.
7. M. Hoshino, M. Kagata, H. Seki, and H. Seto, *J. Am. Chem. Soc.*, 1996, **118**, 2160.
8. M. Hoshino, R. Konishi, H. Seto, H. Seki, T. Yokoyama, and H. Shimamori, *Res. Chem. Intermed.,* in press.
9. T. Muto, J. Umehara, H. Masumori, T. Miura, and M. Kimura, *Chem. Pharm. Bull.,* 1985, **33**, 4749.
10. H. Seto, K. Yoshida, S. Yoshida, T. Shimizu, H. Seki, and M. Hoshino, *Tetrahedron Lett.*, 1996, **37**, 4179.
11. J. MacMilan and C. L. Willis, *J. Chem. Soc., Perkin Trans. 1*, **1986**, 309.
12. A. G. Avent, M. K. Baynham, J. R. Hanson, P. B. Hitchcock, and B. H. de Oliveira, *J. Chem. Soc., Perkin Trans. 1*, **1989**, 627.
13. A. Azman, B. Borstnik, and B. Plesnicar, *J. Org. Chem.*, 1969, **34**, 971; R. Kavcic and B. Plesnicar, *ibid.*, 1970, **35**, 2033.
14. It should be also noted that no formation of any allylic hydrogenperoxide like compound (**19**) attests to the extremely inactive nature of the 16(17)-double bond on gibberellin toward singlet oxygen, because the photo-epoxidation of aliphatic olefins possessing allylic hydrogen atoms with **1a** and oxygen usually competes with the reaction with singlet oxygen generated by photosensitization with photo-exited triplet **1a**, which accompanies the formation of a considerable amount of allylic hydrogenperoxides.[1]
15. P. S. Kirkwood, J. MacMillan, and M. L. Sinnott, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2117.
16. H. Seto, H. Hayasaka, H. Koshino, S. Fujioka, and S. Yoshida, *Heterocycles*, 2000, **52**, 897.
17. K. Schreiber, G. Schneider, and G. Sembdner, *Tetrahedron*, 1966, **22**, 1437.

18. The structure of **20** was eventually confirmed by full assignment of ^{1}H and ^{13}C NMR spectra of the acetylated derivative (**21**) [Ac_2O, pyridine, room temperature, 2 h] by using HMBC, HMQC and SELROESY techniques. **21**: ^{1}H NMR ($CDCl_3$, 600 MHz): δ 1.13 (s, 18-H_3), 2.13 (s, -$OCOCH_3$), 2.26 and 2.29 (each m, 11-H_2), 2.30 and 2.59 (each m, 12-H_2), 2.45 and 2.78 (ABq, J_{gem}=18.1 Hz, 15-H_2), 2.60 (d, $J_{6,5}$=11.5 Hz, 6-H), 2.64 and 2.82 (ABq, J_{gem}=15.1 Hz, 14-H_2), 2.75 (t, $J_{9,11}$=7.1 Hz, 9-H), 3.43 (d, $J_{5,6}$=11.5 Hz, 5-H), 3.72 (s, -CO_2CH_3), 4.75 and 4.79 ((ABq, J_{gem}=16.6 Hz, 17-H_2), 5.34 (d, $J_{3,2}$=3.9 Hz, 3-H), 5.90 (dd, $J_{2,1}$=9.3 Hz and $J_{2,3}$=3.9 Hz, 2-H), 6.50 (d, $J_{1,2}$=9.3 Hz, 1-H), 7.43 (dd, J=8.3 and 7.4 Hz, aromatic 3- and 5-H_2), 7.61 (tt, J=7.4 and 1.5 Hz, aromatic 4-H), 8.07 (dd, J=8.3 and 1.5 Hz, aromatic 2- and 6-H_2); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 14.4 (C-18), 19.8 (C-11), 20.8 (-OCO$\underline{C}H_3$), 36.0 (C-12), 45.8 (C-9), 45.8 (C-15), 48.2 (C-8), 49.5 (C-14), 51.9 (C-4), 52.5 (-$CO_2\underline{C}H_3$), 53.1 (C-5), 54.8 (C-6), 68.6 (C-17), 70.2 (C-3), 90.9 (C-10), 128.6 (aromatic C-3 and C-5), 128.8 (aromatic C-1), 129.4 (C-2), 129.9 (aromatic C-2 and C-6), 133.7 (aromatic C-4), 134.5 (C-1), 165.8 (-O$\underline{C}$OPh), 170.0 (-O$\underline{C}OCH_3$), 171.7 (C-7), 176.3 (C-19), 202.0 (C-16), 210.2 (C-13).
19. N. S. Issacs, *Reaction Intermediates in Organic Chemistry*, John Wiley and Sons, Inc., New York, **1974**, p. 294; D. P. Curran, in *Comprehensive Organic Syntheses,* ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford, **1991**, Vol. 4, p. 715, and references cited therein.
20. I. Kolossváry and W. C. Guida, *J. Am. Chem. Soc*., 1996, **118**, 5011.
21. The conformational search for each isomer was carried out using MM2* force field in the Macromodel 6.0.
22. L. N. Mander, *Natural Product Reports*, 1988, **7**, 541; J. R. Hanson, *Natural Product Reports*, 1990, **9**, 41: L. N. Mander, *Chem. Rev*., 1992, **92**, 573.