Communications to the Editor

[Chem. Pharm. Bull. 34(7)3058—3060(1986)]

USING MICROBIAL REDUCTION TO SYNTHESIZE CARBACYCLIN

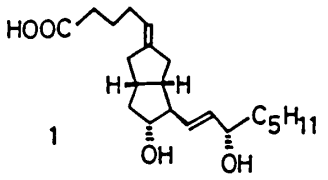
Zhuo-Feng Xie,[a] Kazuhisa Funakoshi,[a] Hiroshi Suemune,[a] Takeshi Oishi,[b] Hiroyuki Akita,[b] and Kiyoshi Sakai*,[a]
Faculty of Pharmaceutical Sciences, Kyushu University,[a] 3-1-1, Maidashi, Fukuoka 812, Japan and The Institute of Physical and Chemical Research (Riken),[b] Wako-shi, Saitama 351-01, Japan

Microbial reduction of 7-methoxycarbonyl bicyclo[4.3.0]non-3-en-8-one ((±)-**3**) afforded the optically active (-)-**3**, which was efficiently converted by ring contraction using thallium (III) nitrate to the intermediate (**11**) used to synthesize carbacyclin (**1**).

KEYWORDS —— carbacyclin; microbial reduction; ring contraction; thallium (III) nitrate

As part of our research on the synthesis of biologically active compounds using microbial procedures,[1] we synthesized a key intermediate (**11**) for carbacyclin (**1**)[2] via the microbial reduction of (±)-**3**.

The kinetical resolution of (±)-**3**, which was readily prepared from commercially available cis-1,2,3,6-tetrahydrophthalic anhydride (**2**),[3] was screened by microbial reduction using forty species of yeast. The results are summarized in Table I. Among these, Kloeckera saturnus (Entry 1) and Pichia farinosa (Entry 2) afforded the optically active (-)-**3** as a recovered substrate with the desired absolute stereochemistry[4,5] in 17% (96% ee) and 27% (93% ee) yields. Reduction products (Entry 1∿4) were obtained as an inseparable mixture of **4** and **5**[6] with high optical purity (>99% ee). These were converted into the optically pure (+)-**3** by PCC oxidation. Saccharomyces cerevisiae (Baker's yeast) (Entry 5) afforded **4** (>99% ee) as a sole reduction product, but the optical purity of the recovered substrate ((-)-**3**) was 27% ee.



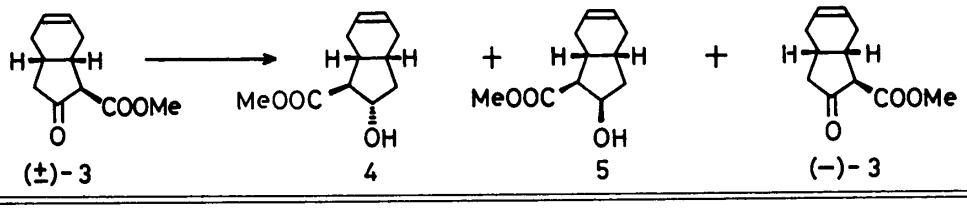
1

The chemical conversion of (-)-**3** into the key intermediate (**11**) for carbacyclin (**1**) was achieved as shown in Chart 1. Stereoselective reduction of the ketone function in (-)-**3** with $NaBH_4$, and subsequent acetylation in the usual manner afforded the acetate (**6**, 90% yield, $[\alpha]_D^{22}$ -20.3°(c=0.70, $CHCl_3$)). Compound **6** was treated with $Tl(NO_3)_3$ (1.5 eq) in trimethyl orthoformate to give the ring-contracted product (**7**,[7] 73% yield, IR (neat): 1740, 1735 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.34 (6H,s,CH_3O×2), 3.64 (3H,s,$COOCH_3$), 4.15 (1H,m,$CH(OCH_3)_2$), 5.24 (1H,m,C_7-H). MS m/z: 300 (M^+), 268.). By deprotection of the acetal function with 88% formic acid followed by treatment with acetic anhydride in the presence of N,N-dimethylaminopyridine (0.1 eq) in THF, **7** was converted into enol acetate (**9**)[7] in 65% yield. Ozonolysis of **9** afforded the keto-acetate (**10**,

45% yield, $[\alpha]_D^{20}$ -16.4°(c=0.55, $CHCl_3$)), which was converted into the desired intermediate (11, 80% yield, $[\alpha]_D^{18}$ +29.0°(c=2.30, $CHCl_3$))[2d] by the conventional method.

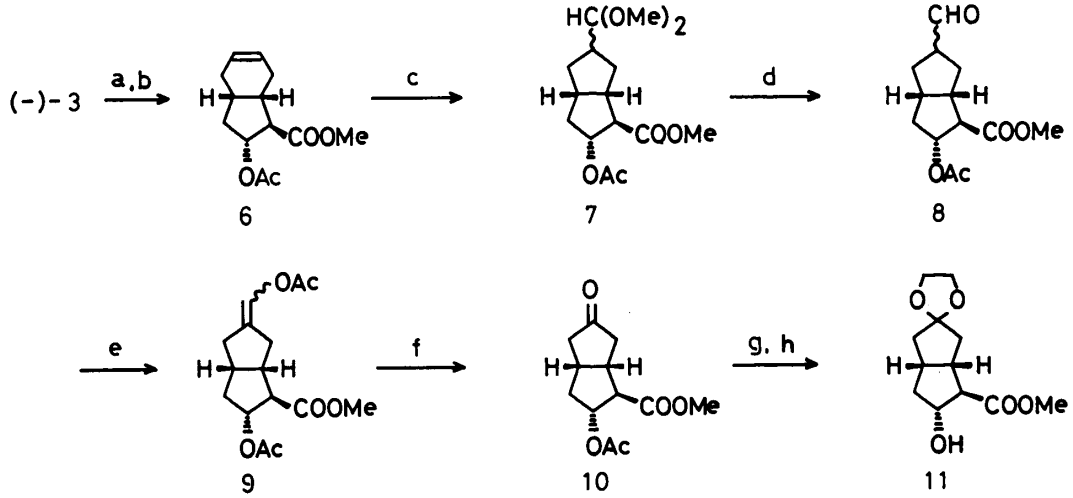
The aldehyde (8) is also considered to be an advantageous intermediate for the synthesis of carbacyclin analog.[8]

Table I. Microbial Reduction of (±)-3



(±)-3 4 5 (−)-3

Entry	Microorganisms	Reduction products[6] Chemical yield (%) as MTPA ester	4/5	Optical purity (% ee)	Recovered (−)-3[4] Chemical yield (%)	Optical purity (% ee)
1	Kloeckera saturnus	48	73/27	4 ; >99 5 ; >99	17	96
2	Pichia farinosa	25	96/ 4	4 ; >99 5 ; >99	27	93
3	Saccharomyces acidifaciens	38	49/51	4 ; >99 5 ; >99	—	—
4	Hansenula anomala Jyozo Kyokai 2019	39	59/41	4 ; >99 5 ; >99	—	—
5	Saccharomyces cerevisiae (Baker's yeast)	17	99/ 0	4 ; >99	40	27



a) $NaBH_4$. b) Ac_2O, Py. c) $Tl(NO_3)_3$, $HC(OMe)_3$. d) HCOOH. e) Ac_2O, DMAP. f) i) O_3; ii) Zn, AcOH. g) $HOCH_2CH_2OH$, BF_3-Et_2O. h) K_2CO_3, MeOH.

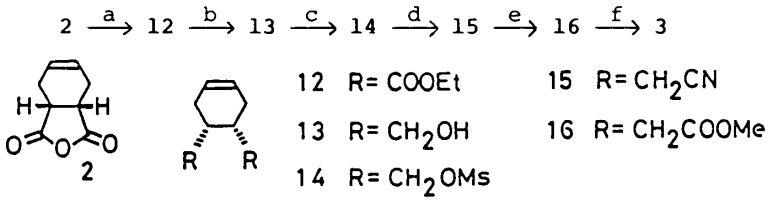
Chart 1

REFERENCES AND NOTES

1) H. Suemune, N. Hayashi, K. Funakoshi, H. Akita, T. Oishi, and K. Sakai, Chem. Pharm. Bull., 33, 2168 (1985).

2) a) W. Bartmann and G. Beck, Angew. Chem. Int. Ed. Engl., 21, 751 (1982); b) N. Mongelli, A. Andreoni, L. Zuliani, and C. A. Gandolfi, Tetrahedron Lett., 24, 3527 (1983); c) K. Ueno, H. Suemune, and K. Sakai, Chem. Pharm. Bull., 32, 3768 (1984); d) K. Kojima, K. Amemiya, K. Koyama, and K. Sakai, ibid, 33, 2688 (1985); e) R. J. Ferrier and P. C. Tyler, J. Chem. Soc. Perkin Trans. 1, 1985, 295; f) K. Mori and M. Tsuji, Tetrahedron, 42, 435 (1986).

3) (±)-3 was synthesized from 2 via 12∿16 in 40% overall yield.



a) EtOH, p-TsOH. b) $LiAlH_4$. c) MsCl, Py. d) NaCN, DMSO. e) MeOH, HCl. f) tert-BuOK, benzene.

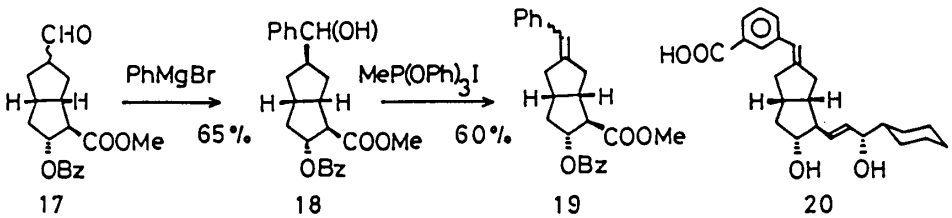
4) The absolute stereochemistry of the recovered (-)-3 was determined by comparison with the known compound ($[\alpha]_D^{30}$ -160.9°(c=0.21, $CHCl_3$)).[5] Optical purity was determined by 400 MHz ^{1}H-NMR spectra after stereoselective reduction of the ketone function with $NaBH_4$ followed by esterification with (+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) chloride.

5) Y. Nagao, T. Nakamura, M. Kume, M. Ochiai, K. Fuji, and E. Fujita, Symposium Papers of The 14th Symposium on Organic Sulfur and Phosphorous Chemistry (Urawa), p. 125, 1986.

6) The optical purity and stereochemistry of 4 and 5 were also determined by comparing the 400 MHz ^{1}H-NMR spectra after conversion to MTPA esters with those of (±)-4 and (±)-5, which was obtained from (±)-4 by the Mistunobu method. The absolute stereochemistry of 4 and 5 was indicated by the fact that the PCC oxidation of the 1:1 mixture of 4 and 5 (reduction products of Entry 3) afforded the optically pure (+)-3 ($[\alpha]_D^{25}$ +153.7°(c=0.20, $CHCl_3$)).

7) Compounds 7, 8 and 9 were obtained as stereoisomeric or geometric mixtures.

8) By the reaction of 17 with phenylmagnesium bromide (1.1 eq), followed by dehydration, 19 was obtained as a geometric mixture. This way to introduce the double bond suggests a new way to synthesize 20, a strong inhibitor of arachidonic acid-induced platelet aggregation.[9]



9) L. Flohe, H. Bohlke, E. Frankus, S.-M. A. Kim, W. Lintz, G. Loschen, G. Michel, B. Muller, J. Schneider, U. Seipp, W. Vollenberg, and K. Wilsmann, Arzneim.-Forsch./Drug Res., 33(II), 1240 (1983).

(Received April 28, 1986)

Communications to the Editor

Chem. Pharm. Bull. 34(7)3061—3063(1986)

PHOTOCHEMISTRY OF CONJUGATED NITROGEN-THIOCARBONYL SYSTEMS. III[1a] PHOTOADDITION OF OLEFINS TO 3(2H)-PYRIDAZINETHIONES[1b,c]

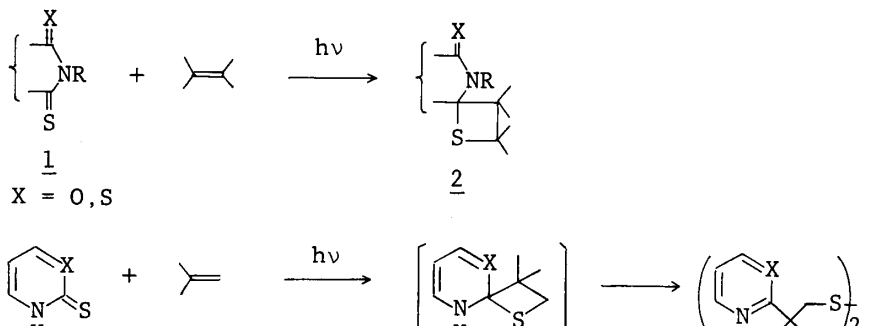
Eisuke Sato, Masato Hasebe[2] and Yuichi Kanaoka*
Faculty of Pharmaceutical Sciences, Hokkaido University
Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan

Photoaddition of olefins to 3(2H)-pyridazinethiones takes dual pathways producing both thieno[2,3-c]pyridazines and 3-substituted pyridazine disulfides, probably by way of thietanes.

KEYWORDS —— photoaddition; 3(2H)-pyridazinethione; thietane; thieno[3,2,c]pyridazine; olefin

Whereas cyclic thioimides 1 undergo [2+2]photocycloadditon with olefins giving thietanes 2,[3] heteroaromatic thiones such as 3, a conjugated nitrogen-thiocarbonyl system, afford 2-substituted products 5 apparently as a result of subsequent aromatization of the intermediate conjugated thietanes 4,[1a] which are less stable than the normal non-conjugated imidethietanes 2. We have examined a similar reaction of 3(2H)-pyridazinethiones 6, and here we report that the photoaddition takes dual-pathways in this pyridazine system.

Chart 1

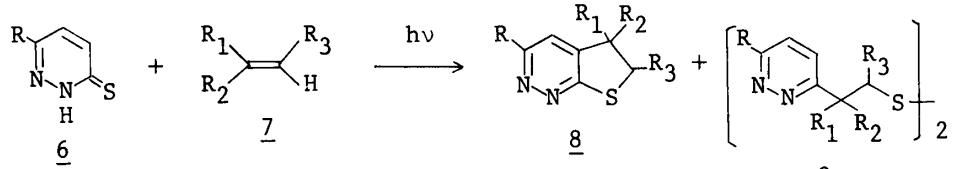


A solution of 3(2H)-pyridazinethione 6 in acetonitrile was irradiated in the presence of olefin 7 with a 100 W high-pressure mercury lamp with a Pyrex filter, and the products were purified by thin-layer chromatography (Table I, Chart 2).[4] As in the case of 3, 3-substituted disulfides 9 were isolated. Unexpectedly the second and major products were sulfur-containing bicyclic compounds 8. The fact that desulfurization of the bicyclic product obtained from 6a and 7a with Raney Ni afforded 3-methyl-5-t-butylpyridazine 10 indicates a thieno[2,3-c]-pyridazine structure for 8. Thus, the reaction provides a new carbon-carbon bond formation at the 4-position of the pyridazine ring.

Table I. Yields of Photoproducts

Heterocycles (mmol)	Olefins (mmol)	Time (h)	Yield (%) 8	9
6a (3.2)	7a (89)	4	52	19
6a (3.2)	7b (64)	11	49	16
6b (3.6)	7a (71)	3	39	7
6b (3.6)	7b (71)	6	50	7
6a (3.2)	7d (83)	7	21(8c)	-
6a (3.2)	7e (70)	22	25(8c)	-

Chart 2



6

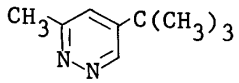
a: R=CH_3
b: R=H

7

a: R_1=R_2=CH_3, R_3=H
b: R_1=R_2=R_3=CH_3
c: R_1=R_2=R_3=H
d: R_1=EtO, R_2=R_3=H
e: R_1=AcO, R_2=R_3=H

8

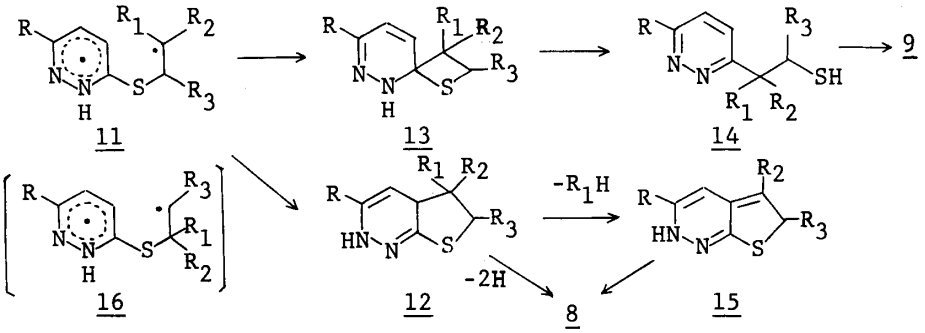
9



10

These reactions may be explained in terms of the dual possibilities in the collapsing mode of the intermediate diradical 11, formed by the photoaddition of the olefin 7 in preference to the less stable regioisomer 16 (Chart 3). The sites cyclizing towards the side chain radical are dispersed over the pyridazine ring leading to bicyclic products 12 and thietanes 13. 12 aromatizes to dihydrothieno-pyridazines 8 by (air) oxidation, while the disulfides 9 arise through oxidative dimerization of sulfide 14 formed from 13. In agreement with this assumption, olefins with a good leaving group such as 7d and 7e gave the same product 8c, probably by way of 15. These results reveal that the photoaddition of certain nitrogen-aromatic thiones such as 6 may afford not only the substituted products 9 but also the bicyclic system 8 depending on the ambident reactivities of the relevant heteroaromatics which determine the collapsing course of the intermediate diradical 11. This suggests new synthetic possibilities in heterocyclic systems.

Chart 3



11 13 14 9

16 12 8 15

ACKNOWLEDGMENTS This work was supported in part by grants from the Ministry of Education, Science and Culture, and The Foundation of Promotion on Research for Medicinal Resources.

REFERENCES AND NOTES

1) a) Part II: Y. Kanaoka, M. Hasebe, T. Nishio, Y. Ikeda and E. Sato, submitted.
b) Photoinduced Reactions. 88. Part 87: M. Machida, K. Oda, E. Yoshida and Y. Kanaoka, submitted.
c) A preliminary report of this work was presented at 12th Congress of Heterocyclic Chemistry, Tokyo, October, 1979. Abstracts of papers, p. 156.
2) Present address: Hokuriku College of Pharmacy, Kanazawa.
3) M. Machida, K. Oda, E. Yoshida and Y. Kanaoka, J. Org. Chem., 50, 1681 (1985).
4) All new compounds gave satisfactory elemental analyses and showed reasonable spectral data. Physical and spectral data of some typical products, 8aa: colorless leaflets, mp 85-86°C. NMR ($CDCl_3$) δ: 1.43 (6H, s, $-CH_3$), 2.63 (3H, s, $-CH_3$), 3.20 (2H, s, $-CH_2-$), 6.96 (1H, s, aromatic). MS m/z: 180 (M^+). 9aa: colorless oil, bp 160°C (bath temp.)/3.0 mmHg. NMR ($CDCl_3$) δ: 1.48 (12H, s, $C(CH_3)_2$), 2.70 (6H, s, $-CH_3$), 3.07 (4H, s, $-CH_2-$), 7.30 (2H, d, J=9 Hz, aromatic), 7.50 (2H, d, J=9 Hz, aromatic). 10: colorless oil, bp 140°C (bath temp.)/20 mmHg. NMR ($CDCl_3$) δ: 1.36 (9H, s, t-butyl), 2.64 (3H, s, $-CH_3$), 7.13 (1H, d, J=3 Hz, C_5-H), 8.98 (1H, d, J=3 Hz, C_3-H). MS m/z: 150 (M^+).

(Received May 12, 1986)