Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5059-5062, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00923-X

Stereochemistry and Total Synthesis of Dolastatin E

Masayuki Nakamura, Takunobu Shibata, Kimitoshi Nakane, Takayuki Nemoto, Makoto Ojika, and Kiyoyuki Yamada*

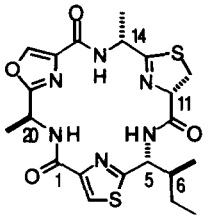
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464, Japan

Abstract: The absolute stereochemistry of dolastatin E (**1**), a cyclic hexapeptide isolated from the sea hare *Dolabella auricularia*, has been determined by a combination of the degradation experiments and total synthesis.

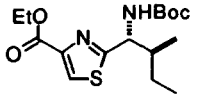
We have recently reported the isolation and gross structure of a new cyclic hexapeptide, dolastatin E (**1**), from the Japanese sea hare *Dolabella auricularia*.[1] Dolastatin E (**1**) is a novel peptide consisting of three kinds of modified amino acid residues that contain oxazole, thiazole, and thiazoline rings, and exhibits weak cytotoxicity against a tumor cell line. Although a number of cyclic peptides possessing such heterocycles have been isolated primarily from tunicates of the genus *Lissoclinum*[2] and several total syntheses reported,[3] it has been difficult to determine the stereochemistry of a thiazoline amino acid moiety (especially at the chiral center adjacent to the thiazoline ring)[4] because of its liability to racemization.[5] In this communication we report the complete stereostructure of **1**, which has unambiguously been determined by the syntheses of **1** and its possible seven stereoisomers coupled with the chiral HPLC analysis of the amino acids derived from **1**.

We first examined the degradation reactions of dolastatin E (**1**). Acid hydrolysis of **1** (6 M HCl, 110 °C, 20 h) gave a mixture of amino acids, the HPLC analysis (column: CHIRALPAK MA(+)) of which revealed that the hydrolysate contained DL-alanine (L:D = 2:1) and DL-cystine (L:meso:D = 1:4:5), which were derived from oxazole and thiazoline amino acids. On the other hand, the ozonolysis-acid hydrolysis sequence, which was developed for determining the stereochemistry of thiazole amino acids,[6] provided enantiomerically pure allo-D-isoleucine as well as DL-alanine (L:D = 1:2). These results indicated that both the thiazoline and oxazole moieties of **1** tend to racemize under the degradation conditions and it was difficult to determine the stereochemistry of these moieties.[7] The partial stereochemistry of **1** was thus determined to be 5*R*,6*S*.

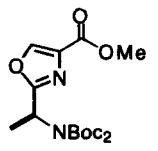
To determine the complete stereostructure of dolastatin E (**1**), we decided to synthesize the eight possible stereoisomers of **1**. Since thiazoline amino acids easily undergo racemization and hydrolysis under acidic and



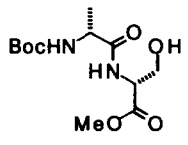
dolastatin E (**1**)



2

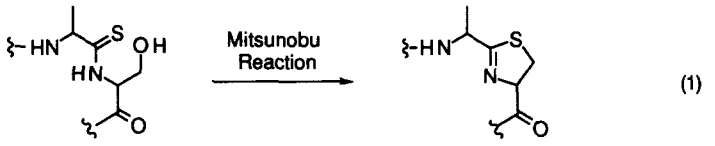


3



4

basic conditions,[5] an efficient method for constructing a thiazoline moiety under neutral conditions would be required for the successful total synthesis of **1**. Although several methods have been developed for preparing thiazoline-containing amino acid derivatives,[5a-c,8] the synthetic procedures applicable to a wide range of thiazoline-containing peptides are quite limited and the total synthesis of such compounds is scarcely known.[9] For this purpose we chose cyclodehydration of a serine-containing thiopeptide under Mitsunobu conditions in the last step of our synthesis, which was reported by Galéotti[8e] and Wipf[8f] (Eq. 1). Thus, **1** was retrosynthetically disconnected at the amide bonds into the three units, thiazole **2**, oxazole **3**, and the alanylserine derivative **4** (as a thiazoline precursor).

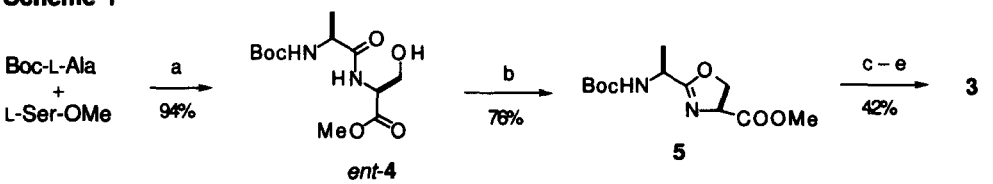


(1)

Thiazole **2** {colorless oil, $[\alpha]^{25}_D$ +12.9° (*c* 1.2, MeOH)} was readily prepared in four steps and 69% overall yield from *N*-Boc-allo-D-isoleucine[10] by a modified Hantzsch synthesis.[11] HPLC analysis (column: CHIRALCEL OD) of **2** indicated that only a small degree of racemization (*R*:*S* = 98:2) occurred.

The synthesis of oxazole **3** started with the coupling reaction of *N*-Boc-L-alanine and L-serine methyl ester hydrochloride by using diphenylphosphoryl azide (DPPA)[12] to afford dipeptide *ent*-**4**, which was cyclized to oxazoline **5** under Mitsunobu conditions (Scheme 1).[8e,f,13] Since the oxidative aromatization of **5** with nickel peroxide[14] provided the corresponding oxazole derivative in low yields (6–22%), we used the method reported by Evans[15] for constructing the oxazole ring. Oxazoline **5**, after *N*-*t*-butoxycarbonylation, led to the ester enolate, which on reaction with phenylselenenyl chloride afforded a diastereomeric mixture of selenides. The mixture was oxidized with hydrogen peroxide to provide the desired oxazole **3** {mp 111–112 °C (hexane-ether), $[\alpha]^{28}_D$ –24.3° (*c* 0.89, MeOH)} in 42% overall yield from **5**.

Scheme 1[a]

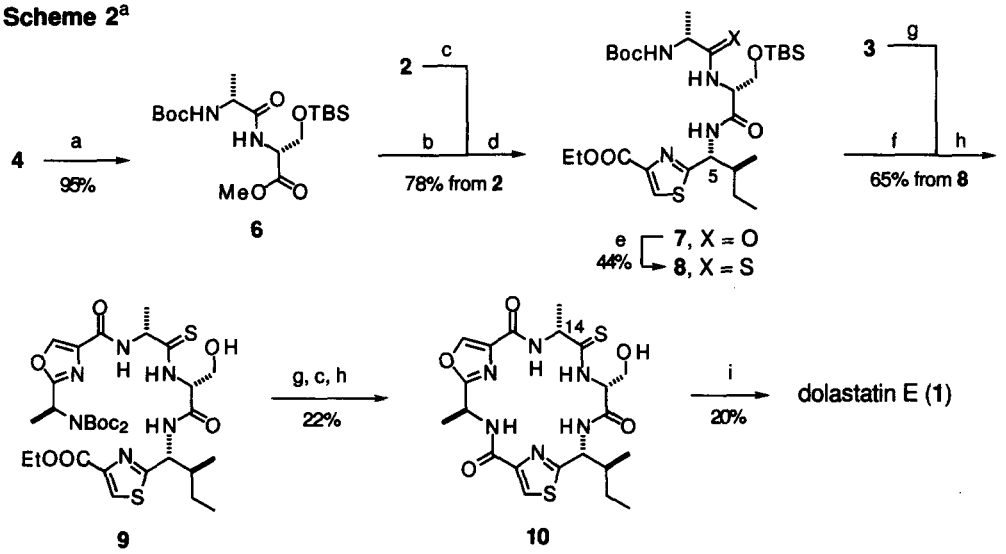


[a] (a) DPPA, Et_3N, DMF, 0 °C. (b) diisopropyl azodicarboxylate, Ph_3P, THF, 0 °C. (c) Boc_2O, DMAP, MeCN, rt . (d) $KN(TMS)_2$, THF-toluene, –78 °C, then PhSeCl, –78 → 0 °C. (e) 30% H_2O_2, CH_2Cl_2, 0 °C.

With thiazole **2** and oxazole **3** in hand, the synthesis of dolastatin E (**1**) itself was accomplished as shown in Scheme 2. Dipeptide **4** was first converted to silyl ether **6**, which, after basic hydrolysis, was coupled using diethyl phosphorocyanidate (DEPC)[16] with the amine obtained by deprotection of the *N*-Boc group of thiazole **2** to afford tetrapeptide **7** {mp 166–167 °C (hexane-EtOAc), $[\alpha]^{29}_D$ +40.4° (*c* 0.75, MeOH)}.[17] Regioselective thionation of **7** was carried out by using a modified Lawesson's reagent (2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide)[18] to provide the desired thiopeptide **8** {colorless oil, $[\alpha]^{26}_D$ +32.5° (*c* 1.08,

MeOH)} in 44% yield along with trace amounts of additional thionation products (3–5% yield). Deprotection of the *N*-Boc group of **8** with trifluoroacetic acid provided a mixture of amines in which the silyl ether was partially deprotected. Addition of water to the reaction mixture induced complete deprotection of the silyl group to afford the corresponding amino alcohol, which was coupled using DPPA with the carboxylic acid obtained by basic hydrolysis of oxazole **3** to provide hexapeptide **9** {colorless oil, $[\alpha]^{29}_D$ +8.9° (*c* 1.2, MeOH)}. After deprotection of the *N*-Boc group and hydrolysis of the ester group of **9**, the cyclization was achieved using DPPA to provide cyclic peptide **10** in 22% overall yield.[19] The cyclodehydration of **10** to construct the thiazoline ring, which was the final and most crucial step in this synthesis, was performed under Mitsunobu conditions as described previously to provide dolastatin E (**1**) in 20% yield.[20] Other seven stereoisomers of **1** have also been synthesized in the same manner. The yields of the final thiazoline formation reaction varied (10–76% yields) with stereoisomers, being very sensitive to the stereochemistry of the cyclic peptides.[21] Interestingly, no epimerization (>95% de) at the C14 position was observed during the cyclodehydration in all cases, although it has recently been reported that the Mitsunobu conditions caused extensive epimerization at the chiral center adjacent to the thiazoline ring (ref. 8g).

Scheme 2[a]



[a] (a) TBSCl, imidazole, DMF, rt. (b) NaOH, H_2O-MeOH, 0 °C. (c) CF_3COOH, CH_2Cl_2, 0 °C. (d) DEPC, Et_3N, DMF, 0 °C. (e) 2,4-bis(4-phenoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide, THF, rt. (f) CF_3COOH, CH_2Cl_2, 0 °C, then H_2O, rt. (g) NaOH, H_2O-MeOH, rt. (h) DPPA, Et_3N, DMF, 0 °C. (i) diisopropyl azodicarboxylate, Ph_3P, THF, 0 °C.

The synthetic material {$[\alpha]^{30}_D$ –24° (*c* 0.03, MeOH), IC_{50} = 31 μg/mL (HeLa-S_3 cells)} was identical with the natural one {$[\alpha]^{27}_D$ –22° (*c* 0.22, MeOH), IC_{50} = 22–40 μg/mL (HeLa-S_3 cells)}[1] in all respects including the spectroscopic[22] and chromatographic properties (IR, ^{1}H NMR, MS, $[\alpha]_D$, TLC, HPLC) and cytotoxic activity. These findings have established the absolute stereostructure of dolastatin E (**1**), which consists of one L-alanine, one D-alanine, one D-cysteine, one allo-D-isoleucine, one serine, and one cysteine, the chirality of the latter two amino acids being lost owing to the formation of two aromatic heterocycles.

Acknowledgement. This work was supported in part by Grants-in-Aid for Scientific Research (Nos. 04403009 and 06680557) and for Scientific Research on Priority Areas (Natural Supramolecules No. 06240103) from the Ministry of Education, Science, and Culture, Japan.

REFERENCES AND NOTES

1. Nemoto, T.; Nakamura, M.; Ojika, M.; Yamada, K. *Tetrahedron Lett.* preceding paper in this issue.
2. (a) Kobayashi, J.; Ishibashi, M.: Marine Alkaloids II. In *The Alkaloids*; Brossi, A.; Cordell, G. A. Eds.; Academic Press; New York, 1992; Vol. 41, pp 41–124. (b) Davidson, B. S. *Chem. Rev.* **1993**, *93*, 1771–1791.
3. (a) Albizati, K. F.; Martin, V. A.; Agharahimi, M. R.; Stolze, D. A.: Synthesis of Marine Natural Products. In *Bioorganic Marine Chemistry*; Scheuer, P. J. Ed.; Springer-Verlag; Berlin, 1992; Vol. 6, pp. 24–68. (b) A recent report: Boden, C.; Pattenden, G. *Tetrahedron Lett.* **1994**, *35*, 8271–8274.
4. The following papers reported that the stereochemistry of thiazoline moieties of several peptides could not be (or could only be tentatively) determined: (a) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; van den Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1349–1354. (b) Degnan, B. M.; Hawkins, C. J.; Lavin, M. F.; McCaffrey, E. J.; Parry, D. L.; Watters, D. J. *J. Med. Chem.* **1989**, *32*, 1354–1359. (c) Hawkins, C. J.; Lavin, M. F.; Marshall, K. A.; van der Brenk, A. L.; Watters, D. J. *J. Med. Chem.* **1990**, *33*, 1634–1638.
5. (a) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2945–2949. (b) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2950–2954. (c) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1870–1873. (d) Yonetani, K.; Hirotsu, Y.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3302–3305.
6. McDonald, L. A.; Ireland, C. M. *J. Nat. Prod.* **1992**, *55*, 376–379.
7. It was reported that racemization at the chiral center adjacent to thiazoline ring was avoided by using the ozonolysis-acid hydrolysis sequence: McDonald, L. A.; Foster, M. P.; Phillips, D. R.; Ireland, C. M.; Lee, A. Y.; Clardy, J. *J. Org. Chem.* **1992**, *57*, 4616–4624. However, this method could not be applied to dolastatin E (**1**), because alanine was produced from both the oxazole amino acid part and the thiazoline amino acid moiety in **1**.
8. (a) Hirotsu, Y.; Shiba, T.; Kaneko, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1564–1567. (b) Minster, D. K.; Jordis, U.; Evans, D. L.; Hecht, S. M. *J. Org. Chem.* **1978**, *43*, 1624–1626. (c) Inami, K.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 352–360. (d) North, M.; Pattenden, G. *Tetrahedron*, **1990**, *46*, 8267–8290. (e) Galéotti, N.; Montagne, C.; Poncet, J.; Jouin, P. *Tetrahedron Lett.* **1992**, *33*, 2807–2810. (f) Wipf, P.; Miller, C. P. *Tetrahedron Lett.* **1992**, *33*, 6267–6270. (g) Wipf, P.; Fritch, P. C. *Tetrahedron Lett.* **1994**, *32*, 5397–5400.
9. A non-stereoselective synthesis of a thiazoline-containing natural peptide was reported (ref. 8c).
10. Flouret, G.; Nakagawa, S. H. *J. Org. Chem.* **1975**, *40*, 2635–2637.
11. (a) Schmidt, U.; Gleich, P.; Griesser, H.; Utz, R. *Synthesis*, **1986**, 992–998. (b) Recently the experimental conditions to obtain optically pure thiazoline amino acid derivatives have been reported: Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473–2476, and references cited therein.
12. Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
13. Nakajima, K.; Sasaki, H.; Neya, M.; Morishita, M.; Sasaki, S.; Okawa, K. *Peptide Chemistry*, **1982**, *20*, 19–24.
14. Evans, D. L.; Minster, D. K.; Jordis, U.; Hecht, S. M.; Mazzu, A. L. Jr.; Meyers, A. I. *J. Org. Chem.* **1979**, *44*, 497–501.
15. Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434–9453.
16. Shioiri, T.; Yokoyama, Y.; Kasai, Y; Yamada, S. *Tetrahedron*, **1976**, *32*, 2211–2217.
17. Pure **7** was obtained by recrystallization.
18. Lajoie, G.; Lépine, F.; Maziak, L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 3815–3818.
19. During this cyclization, polymerization seemed to occur as a side reaction to produce insoluble materials (*ca.* 50% yield). The cyclization proceeded in the moderate yields in the case of C14,C20-*diepi*-**10** (46%) and C11,C14,C20-*triepi*-**10** (47%).
20. Elimination of the β-hydroxy amide moiety in **10** predominantly occurred to produce an *exo* olefin (32%).
21. For example, 11-*epi*-dolastatin E was obtained in 76% yield and 20-*epi*-dolastatin E in 10% yield under the same conditions.
22. Synthetic **1** was distinguished from other seven stereoisomers by ^{1}H NMR spectroscopy.

(*Received in Japan* 25 *March* 1995; *revised* 3 *May* 1995; *accepted* 17 *May* 1995)

Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5063-5064, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00924-8

An Efficient Chemo-Enzymatic Synthesis of α-Amino-β-Hydroxy-γ-Butyrolactone

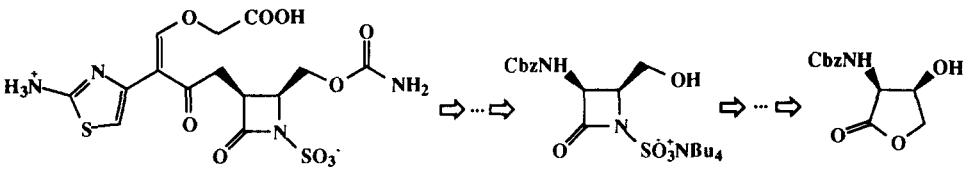
Vassil P. Vassilev[a], Taketo Uchiyama[a], Tetsuya Kajimoto*[a], Chi-Huey Wong*[a,b]

[a] Frontier Research Program, The Institute of Physical and Chemical Research, 2-1 Hirosawa, Wako City, 351-01, Japan.

[b] Department of Chemistry, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA.

Abstract: The synthesis of *(2S,3R)*-2-amino-3-hydroxybutyrolactone, a precursor of the monobactam antibiotic Carunoman, has been accomplished in three steps involving the use of L-threonine aldolase.

Monobactams are monocyclic β-lactams having a sulfonic acid group on the nitrogen of the β-lactam ring[1]. The synthetic analogs of this class of compounds (Carunoman) **1** (Scheme 1) show strong antibacterial activity against gram-negative bacteria and high stability to β-lactamases from various bacterial spesies[1,2]. Different approaches had been developed [3,4] for the synthesis of the key precursor **2**, including the use of L-ascorbic acid[4] and *(2S,3R)*-2-amino-3-hydroxy-butyrolactone **3** derived from L-threonate[5,6] as starting materials.

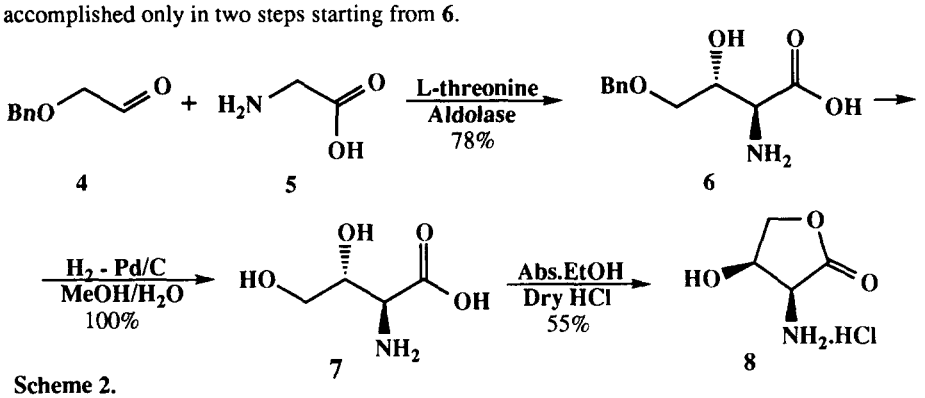


1 **2** **3**

Scheme 1.

We report here a highly efficient synthesis of *(2S,3R)*-2-amino-3-hydroxybutyrolactone **3** by using L-threonine aldolase as a catalyst for the synthesis of a β-hydroxy-α-amino acid with desired stereochemistry of both chiral centers found in **3** (Scheme 2). This achievement is based on our discovery [7] that an oxygen at the β-position of an aldehyde is very important for obtaining a high diastereoisomeric *erythro/threo* ratio in the enzymatic aldol addition reaction. Simple recrystallizatiom of the enzyme product with 92:8 *erythro/threo* ratio, for example, affords pure benzyloxyprotected hydroxy amino acid **6**. Compound **8** was readily converted to **3** for use in the

synthesis of **1** and analogs. The synthesis of aminolactone **8** was straightforward[8] and accomplished only in two steps starting from **6**.



Scheme 2.

References

1. Wei, C.C., De Bernardo, S., Tengi, J.P., Borgese, J., Weigele, M., *J. Org. Chem.*, **1985**, *50*, 3462.
2. Kishimoto, S., Sendai, M., Hashiguchi, S., Tomimoto, M., Satoh, Y., Matsuo, T., Kondo, M., Ochiai, M., *J. Antibiot.*, **1983**, *36*, 1421.
3. Sendai, M., Hasiguchi, S., Tomimoto, M., Kishimoto, S., Matsuo, T., Ochiai, M., *Chem. Pharm. Bul.* **1985**, *33*, 3798.
4. Cooper, R.D.G., Daugherty, B.W., Boyd, D.B., *Pure & Appl. Chem..*, **1987**, *59*, 485.
5. Manchand, P. S., Luk, K.-C., Belica, P. S., Choundry, S. C., Wei, C. C., *J.Org. Chem.*, **1988**, *53*, 5507 and references therein.
6. Bols, M., Lundt, I., *Acta Chem.Scand.* **1988**, *B42*, 67.
7. Vassilev, V. P., Uchiyama, T., Kajimoto, T., Wong, C.-H., *Tetrahedron Lett.* in press.
8. Procedures for the enzyme preparation and the enzymatic synthesis are as reported previously[7]. Compound **6**: ^{1}H NMR, CD_3OD/D_2O ~ 3/1) δ 7.29-7.38 (m, 5H), 4.55 (s, 2H), 4.24-4.29 (dd, 1H *J* = 4 .0 and 4.3 Hz), 3.84 (d, 1H *J* = 4.3 Hz), 3.70 (d, 2H, *J* = 4.0 Hz); m.p. 201-202 °C (dec) H_2O/EtOH; $[\alpha]_D$=+20.1 (c=0.88 1N HCl); TOFMS $[M+H]^+$ calc. 226.1 found. 226.
7 : The reduction was carried out at atmospheric pressure in 50% MeOH/H_2O untill deprotection was completed (TLC). Yield 100%. M.p. 194 °C (dec) H_2O/MeOH, (ref.[9] 194-195 °C); $[\alpha]_D$ = - 11.6 (c, 1.06 H_2O), (ref.[9] $[\alpha]_D$ =-11.3). ^{13}C NMR (D_2O, acetone as int. stand. $(CH_3)_2$ - 30.3 ppm) ; d 58.0 ($CHNH_2$), 62.8 (CH_2OH), 69.0 (CHOH), 171.5 (C=O). TOFMS $(M+H)^+$, calc. 136.0, found 136.0. **8** : The procedure follows the one previously described [10]. Yield 55%. M.p. 178-179 °C, lit.[9] 176 °C ; $[\alpha]_D$ =+59.7 (c, 1.06, H_2O), lit.[9] +55.6. ^{13}C NMR data are in good agreement with reported[6].
9. Okawa, K., Hori, K., Hirose, K., Nakagawa, Y., *Bull. Chem. Soc. Jpn.*, **1969**, *42*, 2720.
10. Hamel, E. E., Painter, E. P., *J. Am. Chem. Soc.*, **1953**, *75*, 1362.

(*Received in Japan* 28 *March* 1995; *revised* 6 *May* 1995; *accepted* 18 *May* 1995)

Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5065-5068, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00940-X

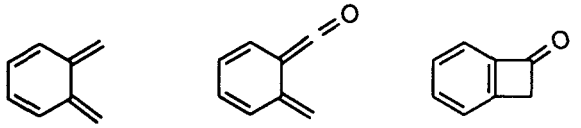
Synthesis of Pyrido[b]cyclobuten-5-one and 1-Azafulvenallene by Flash Vacuum Pyrolysis of 3-Chloroformyl-2-methylpyridine

Chin-Hsing Chou*, Cheng-Chang Wu and Wey-Kao Chen

Department of Chemistry, National Sun Yat-Sen University
Kaohsiung, Taiwan, 80424, China

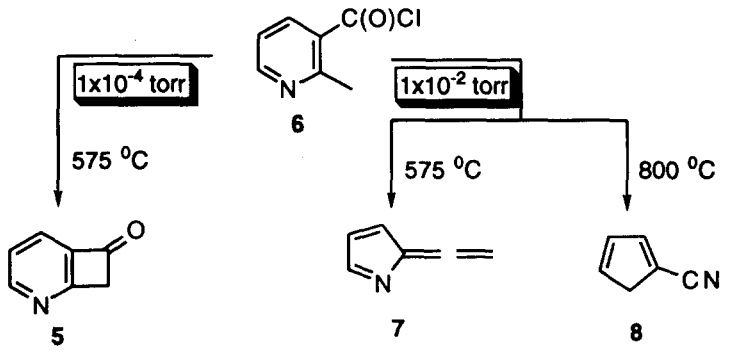
Abstract: The temperature and pressure dependence of products formed on pyrolysis of 3-chloroformyl-2-methylpyridine (**6**) have been studied. Pyrolysis of **6** at 575 ^{0}C and ca. 1x10^{-4} torr gives pyrido[b]cyclobuten-5-one (**5**) in 20% yield. Pyrolysis of **6** at 575 and 800 ^{0}C and under the pressure of ca. 1x10^{-2} torr give 1-azafulvenallene (**7**, 46%) and 1-cyanocyclopentadiene (**8**, 42%), respectively. Irradiation of **5** (λ > 300 nm) in methanol affords 2-methoxy-3-acetylpyridine (**9**) quantitatively.

o-Quinodimethane (**1**) has been shown to be a transient intermediate in many reactions[1] and has been used extensively as a diene in several organic syntheses.[1b-f, i] The development of the chemistry of **1** has led to the study of its ketene derivative, α-oxo-*o*-quinodimethane (**2**). Although **2** has never been isolated successfully, the closed form of **2**, benzocyclobutenone (**3**), has been prepared by several methods.[2] One of the methods is pyrolysis of *o*-toluoyl chloride (**4**) to give **3** as the main product, presumably, involving **2** as the key intermediate.[2h] Based on the same approach, we have synthesized the previously unknown pyridine analogue of **3**, pyrido[b]cyclobuten-5-one (**5**), by the flash vacuum pyrolysis (FVP) of 3-chloroformyl-2-methylpyridine (**6**). We have also studied the chemistry of **5** thermally and photochemically and the results are presented herein.



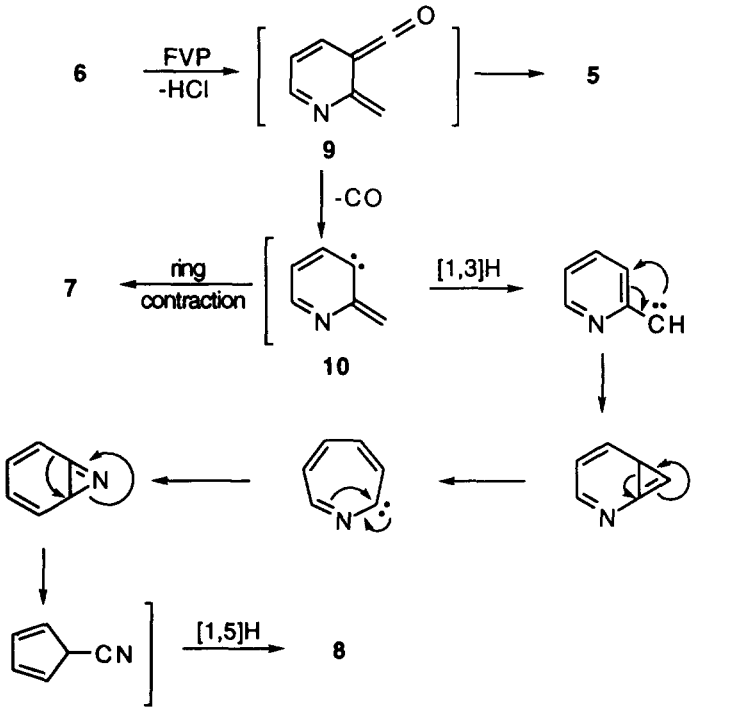
1 **2** **3**

FVP of **6**[3] at 575 ^{0}C and ca. 1x10^{-4} torr by the previously described procedure[4] gave **5** as the only identifiable product along with substantial amounts of polymers. Purification of the product mixture by flash column chromatography on silica gel (EtOAc-hexane, 1:2) afforded **5** in 20% yield.[5] When the pressure was raised to ca. 1x10 $^{-2}$ torr, FVP of **6** at 575 ^{0}C gave 1-azafulvenallene (**7**) as the main pyrolysis product in 46% yield,[6] whereas at 800 ^{0}C FVP of **6** gave 1-cyanocyclopentadiene (**8**) in 42% yield.[7]



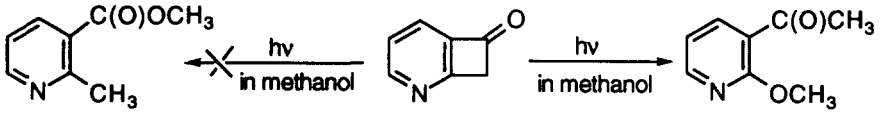
FVP of **6** is expected to give 3-carbonyl-2-methylene-2,3-dihydropyridine (**9**) as the primary pyrolysis product by 1,4-elimination of HCl from **6**. Under high vacuum condition, i.e. at ca. $1x10^{-4}$ torr and 575 °C, **9**, due to short contact time in the hot zone, survives under the reaction condition and cyclizes to give the more stable product **5**. When the pyrolysis is performed under lower vacuum condition, i.e. at ca. $1x10^{-2}$ torr, **9** eliminates a CO molecule to give the carbene intermediate **10**, which, at 575 °C, undergoes ring contraction to give **7**, or, at 800 °C, proceeds through a series of rearrangement to give **8**. A possible reaction mechanism for the formation of **8** from **6** is proposed as shown in Scheme 1.

Scheme 1



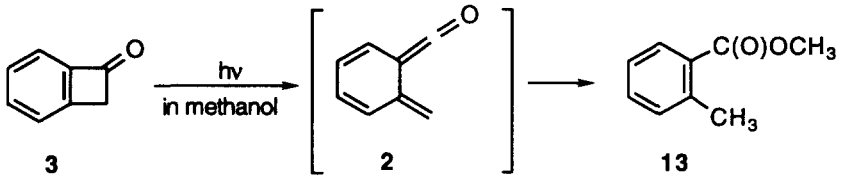
It is noteworthy that FVP of the isolated **7** at 800 °C and ca. $1x10^{-2}$ torr does not give **8**. A result indicates that **7** is not an intermediate leading to the formation of **8**, and supports the mechanism shown above.

Irradiation of **5** ($\lambda > 300$ nm) in methanol afforded 3-acetyl-2-methoxypyridine (**11**) quantitatively, whereas irradiation of **5** ($\lambda > 300$ nm) in benzene only resulted in complete decomposition of **5**. The formation of **11** instead of the expected methyl 2-methylnicotinate (**12**), from irradiation of **5** in methanol, might result from an attack of a methanol molecule at the bridgehead carbon atom adjacent to the nitrogen atom in the pyridine ring of **5** and suggests that no open form of **5**, i.e. compound **9**, is involved.



12 **5** **11**

A result that is different from irradiation of benzene analogue, **3**, in methanol, from which methyl 2-methylbenzoate (**13**) is obtained as the major product, presumably, involve **2** as the intermediate.[2e] The structure of **11** was confirmed by comparing NMR spectral data of **11**[8] with that of **12**, prepared from an reaction of **6** wih methanol.[9]



3 **2** **13**

We are currently applying this approach to the preparation of other heterocyclic analogues of α-oxo-*o*-quinodimethanes.

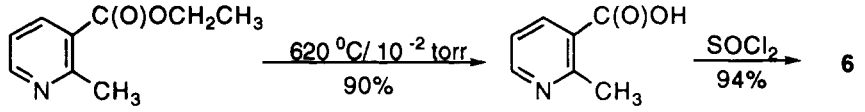
Acknowledgment: We thank the National Science Council of the Republic of China for financial support.

References and Notes

1. (a) McCullough, J. J. *Acc. Chem. Res.* **1980**, *13*, 270-276, and references cited. (b) Oppolzer, W.; Roberts, D. A.; Bird, T. G. *Helv. Chim. Acta* **1979**, *62*, 2017-2021. (c) Oppolzer, W.; Roberts, D. A. *Helv. Chim. Acta* **1980**, *63*, 1703-1705. (d) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 863-865. (e) Nicolaou, K. C.; Barnette, W. E.; Ma, P. *J. Org. Chem.* **1980**, *45*, 1463-1470. (f) Ito, Y.; Nakatsuka, M.; Saegusa, T. *J. Am. Chem. Soc.* **1981**, *103*, 476-477. (g) Trahanovsky, W. S.; Macias, J. R. *J. Am. Chem. Soc.* **1986**, *108*, 6820-6821. (h) Trahanovsky, W. S.; Chou, C. H.; Fischer, D. R.; Gerstein, B. C. *J. Am. Chem. Soc.* **1988**, *110*, 6579-6581. (i) Sato, H.; Isono, N.; Okamura, K.; Date, T.; Mori, M.*Tetrahedron Lett.* **1994**, 2035-2038.
2. (a) Cava, M. P.; Muth, K. *J. Am. Chem. Soc.* **1960**, *83*, 652-654. (b) Bertelli, D. J.; Crews, P. *J. Am. Chem. Soc.* **1968**, *90*, 3889-3890. (c) Hedaya, E.; Kent. M. E. *J. Am. Chem. Soc.* **1970**, *92*, 2149-2151. (d) Spangler, R. J.; Kim, J. H. *Tetrahedron Lett.* **1972**, 1249-1251. (e) Arnold, D. R.; Hedaya, E.; Marritt, V. Y.; Karnischky, L. A.; Kent, M. E. *Tetrahedron Lett.* **1972**, 3917-3920. (f) Arnold, B. J.; Sammes, P.

G.; Wallace, T. W. *J. Chem. Soc., Perkin Trans. 1* **1974**, 415-420. (g) Kitahara, Y.; Oda, M.; Miyakoshi, S.; Nakanishi, S. *Tetrahedron Lett.* **1976**, 2149-2152. (h) Schiess P.; Heitzmann, M. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 469-470. (i) Adam, G.; Andrieux, J.; Plat, M. *Tetrahedron Lett.* **1981**, 3181-3184. (j) Chenard, B. L.; Slapak, C.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1981**, 179-180. (k) Stevens, R. V.; Bisacchi, G. S. *J. Org. Chem.* **1982**, *47*, 2393-2396. (l) South, M. S.; Liebeskind, L. S. *J. Org. Chem.* **1982**, *47*, 3816-3821. (m) Spangler, L.A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800-1806. (n) Schiess, P.; Eberle, M.; Huys-Francotte, M.; Wirz, J. *Tetrahedron Lett.* **1984**, 2201-2204. (o) Wey, H. G.; Butenschon, H, *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 880-881. (p) Yoshioka, M.; Momose, S.; Nishizawa, K.; Hasegawa, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 499-503. (q) Aidhen, I. S.; Ahuja, J. R. *Tetrahedron Lett.* **1992**, 5431-5432. (r) Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Venugopal, D. *J. Org. Chem.* **1992**, *57*, 6716-6720. (s) Frimer, A. A.; Weiss, J. *J. Org. Chem.* **1993**, *58*, 3660-3667.

3. Compound **6** was prepared as follows.



4. Chou, C. H.; Trahanovsky, W. S. *J. Am. Chem. Soc.***1986**, *108*, 4138-4144.
5. **5**: pale yellow solid, m.p. 54-56 °C; IR ($CDCl_3$, cm^{-1}) 1796, 1768, 1572, 1472, 1394; ^1H NMR ($CDCl_3$) δ 8.69 (dd, *j* = 5.1, 1.2 Hz, 1H), 7.62 (dd, *j* = 7.5, 1.2 Hz, 1H), 7.37 (dd, *j* = 7.5, 5.1 Hz, 1H), 4.17 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 186.10 (C), 170.24 (C), 156.38 (CH), 141.46 (C), 128.85 (CH), 124.53 (CH), 55.69 (CH_2); HRMS Calcd for C_7H_5NO: 119.0371. Found: 119.0376.
6. **7**: IR ($CDCl_3$, cm^{-1}) 1928, 1717, 1607, 1457, 1378; ^1H NMR ($CDCl_3$) δ 6.75 (m, 1H), 6.35 (m, 1H), 5.15 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 215.83 (C) 146.59 (CH), 116.30 (C), 96.57 (CH), 91.86 (CH), 77.62 (CH_2); MS, m/z (rel intensity) 92 (9), 91 (M^+, 100), 65 (14), 64 (43), 63 (32), 62 (13), 61 (10).
7. (a) **8**: IR ($CDCl_3$, cm^{-1}) 2928, 2905, 2220, 1620, 1395, 1198; ^1H NMR ($CDCl_3$) δ 7.32 (t, *j* = 1.5 Hz, 1H), 6.69 (m, 1H), 6.61 (m, 1H), 3.33 (dd, *j* = 2.7, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 147.18 (CH), 139.23 (CH), 132.22 (CH), 116.81 (C), 114.35 (C), 44.24 (CH_2); MS, m/z (rel intensity) 92 (7), 91 (m^+, 100), 65 (13), 64 (61), 63 (26), 62 (10), 52 (21), 50 (10), 41 (10), 40 (11).(b) Wentrup, C.; Crow, W. D. *Tetrahedron* **1970**, *26*, 4375-4386.
8. **11**: ^1H NMR ($CDCl_3$) δ 8.77 (br s, 1H), 8.54 (br s, 1H), 7.56 (br s, 1H), 3.99 (s, 3H), 3.04 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.91 (C), 158.20 (C), 147.86 (CH), 142.27 (CH), 127.14 (C), 122.53 (CH), 52.87 (CH_3), 22.33 (CH_3).
9. **12**: ^1H NMR ($CDCl_3$) δ 8.62 (dd, *j* = 4.8, 1.8 Hz, 1H), 8.20 (dd, *j* = 8.1, 1.8 Hz, 1H), 7.22 (dd, *j* = 8.1, 4.8 Hz, 1H), 3.93 (s, 3H), 2.85 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 166.94 (C), 159.86 (C), 151.77 (CH), 138.39 (CH), 125.34 (C), 120.84 (CH), 52.21 (CH_3), 24.74 (CH_3).

(*Received in China* 6 *March* 1995; *accepted* 12 *May* 1995)

Pergamon

Tetrahedron Letters, Vol. 36, No. 28, pp. 5069-5070, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00941-8

Formation of Quasi-racemic Diastereoisomeric Salts as a Structural Cause for Efficient Optical Resolutions

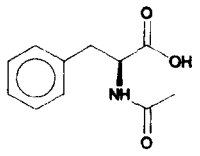
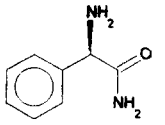
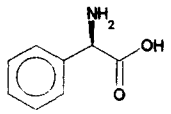
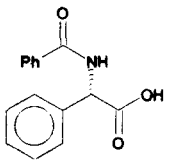
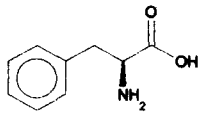
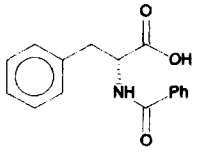
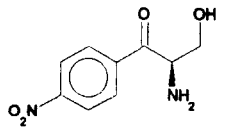
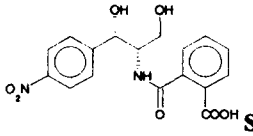
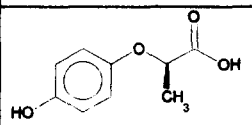
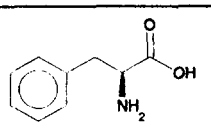
Elemér Fogassy* and Dávid Kozma

a) Department of Organic Chemical Technology ,Technical University of Budapest, Budapest POB 91, H-1521, Hungary

***Abstract**: During optical resolutions, when the resolving agent is structurally similar to the racemate, very efficient resolution can be achieved, because of the formation of quasi-racemic diastereoisomeric salts, in which the enantiomers have opposite configuration.*

The optical isomers can crystallize in homochiral and in heterochiral form.[1] The heterochiral packing (racemic molecular compound), when the two mirror image enantiomer crystallize together, usually result the more stable packing, it is assumed that at least 90% of the enantiomers crystallize in this form.[2-4]

Table 1. Structural drawings of the molecules and a summary of the experimental results of the resolutions

	Enantiomer in the precipitated salt	Resolving agent	OP %	Y %	S[5]
1.	 **S-I**	 **R-II**	100	86.1	0.86[6]
2.	 **R-III**	 **S-IV**	95.4	90.0	0.86[7]
3.	 **S-V**	 **R-VI**	100	80.0	0.80[8]
4.	 **R-VII**	 **S,S-VII**	81.0	95.0	0.77[9]
5.	 **R-IX**	 **S-V**	48.8	90.4	0.44[7]

The optical resolution of racemates via quasi-racemates formation is also based on the preferred formation of the heterochiral packing.[1] For example the racemic malic acid can be resolved by R,R-tartaric acid,[10] since the

heterochiral crystal of tartaric acid and malic acid are more stable, than either the heterochiral racemic malic acid or the homochiral tartaric acid.

An analysis on 12 effective optical resolutions[11] performed by our group via diastereoisomeric salt formation, led us to the recognition that when the resolving agents are structurally similar to the racemate, the formation of quasi-racemate type diastereoisomeric salts is possible and as a result of it a very efficient resolution can be achieved. In the Table 1. the results of five optical resolutions are summarised. The structural similarity can be seen from the structural drawings. At the resolution of III, V and VII the resolving agent is an acidic derivative of the enantiomer. It seems that there are some relationships between the efficiency of the resolution and the structural similarity. The lower efficiency is achieved at the resolution of IX when the structural difference is larger. Since the structurally similar enantiomers in the precipitated diastereoisomeric salts always have opposite configuration, it can be assumed that the formation of a quasi racemate type, heterochiral crystal is preferred. That quasi racemates is differ from the others described in the literature, since here salt formation takes place between the racemate forming enantiomers.

The selection of the resolving agent is the key step of the optical resolutions which is still accomplished by trial and error method.[12] As a practical conclusion of this study, we can suggest the use of structurally similar resolving agent, because if the quasi racemic packing is possible, a very efficient resolution can be expected.

Acknowledgements: The authors are grateful the OTKA foundation (Grant no.:F7386(D.K.), T4183(E.F.)) for financial support.

References and Notes

1.) Jacques,J.; Collet,A.; Willen,S.H. Enantiomers, Racemates and Resolutions, Wiley and Sons, New York, 1981

2.) C.P.Brock, W.B. Schweizer and J.D.Dunitz, *J.Am.Chem.Soc.*, 1991, **113**, 9811

3.) A. Collet, *in " Problems and Wonders of Chiral Molecules"* Ed. by M.Simonyi, Akadémiai Kiadó, Budapest, 1990, p.91

4.) Kozma,D., Böcskei,Zs., Simon,K., Fogassy,E., J.Chem.Soc.Perkin Trans.2.,1994,1883

5.)The efficiency (0<S<1) of the optical resolution has been defined as the product of the optical purity (0<OP<1) and the yield (0<Y<1) of the precipitated salt: S= OPxY, in Fogassy,E.; Lopata,A.; Faigl,F.; Darvas,F.; Ács,M; Tőke,L. Tetrahedron Lett., 1980,**21**, 647

6.) 193201. Hungarian Patent (1986)

7.) unpublished results

8.) 193199. Hungarian Patent (1986)

9.) 195174. Hungarian Patent (1989)

10.) Arsenijevic,V.A., C.R.Acad.Sci., 1957, **245**,317

11.) The mean value of OP= 91 %, Y= 82 % and S= 0.74 were in the whole dataset containing the 12 analysed resolution. The estimated error of S (calculated from the experimental data) ± 2 %.

12.) Kozma,D., Pokol,Gy., Ács,M., J.Chem.Soc.Perkin Trans.2.,1992,435

(*Received in UK* 21 *December* 1994; *accepted* 26 *May* 1995)