and the assistance of Daniel L. Severance with molecular modeling and computer graphics. We especially wish to thank Dr. Robert C. Kelly and Dr. Martha A. Warpehoski of the Upjohn Company for a sample of natural (+)-CC-1065, for many helpful discussions, for comparative optical rotations of intermediates, and for preprints of their work (ref 18, 19, 40, and 47).

**Supplementary Material Available:** Synthetic procedures and full spectral and physical characterizations of **5-10**, **14**, **17** and **18**, figures 2 and 3 (footnote 12), and preliminary, comparative B-DNA binding properties of CC-1065 and CPI-CDPI$_2$ ($\Delta T_m$, poly[dA]·poly[dT]) are provided (11 pages). Ordering information is given on any current masthead page.

# Acromelic Acids A and B. Potent Neuroexcitatory Amino Acids Isolated from *Clitocybe acromelalga*†

**Katsuhiro Konno,‡ Kimiko Hashimoto,‡ Yasufumi Ohfune,§ Haruhisa Shirahama,*,‡ and Takeshi Matsumoto‡**

*Contribution from the Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan, and Suntory Institute for Bioorganic Research, Shimamoto-cho, Mishima-gun, Osaka 618, Japan.* *Received February 2, 1988*

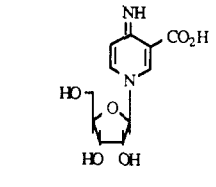
**Abstract:** The minute amount of toxic principles, acromelic acids A (ca. 110 μg) and B (ca. 40 μg), was isolated from a poisonous mushroom *Clitocybe acromelalga*. Spectral analyses and biogenetic consideration led to the structures **1** and **2** for acromelic acids A and B, respectively. The syntheses of **1** and **2** starting from L-α-kainic acid **3** established the proposed structures. Both amino acids show extremely potent neuroexcitatory action.

The poisonous mushroom *Clitocybe acromelalga* Ichimura (Japanese name, Dokusasako), found only in Japan, has been known for many years to exhibit unique symptoms similar to acromelalgia and erythromelalgia. Ingestion of the mushroom causes a sharp pain and a marked reddish edema in hand and foot (after several days), and it continues for about a month.

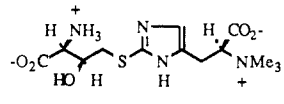
These characteristic properties prompted us to study the chemical constituents of the fungus. Fractionation monitored by lethal effect in mice led to the isolation of four new compounds: clitidine, a toxic nucleoside;[1] clithioneine, an unusual nontoxic betaine;[2] and acromelic acids A (**1**) and B (**2**), powerful neuroexcitatory amino acids. We describe here the isolation, characterization, and syntheses of acromelic acids A and B in detail.[3]

**Isolation and Structure.** From the water extract of fresh fruiting bodies (16.2 kg), pure acids A and B (ca. 110 and 40 μg, respectively) were isolated. Both compounds showed yellow coloration with a ninhydrin test and the behavior of a strong acid on ion-exchange chromatography and paper electrophoresis.

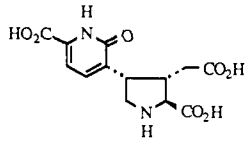
Due to the scarcity of the samples, spectral data available were limited. For example, no $^{13}C$ NMR signals could be observed even after 35912 transients (25.0 MHz), and all attempts to measure the mass spectrum (FD-MS, SIMS) were unsuccessful. Thus, the data obtained were only those of $^1H$ NMR (360 MHz), UV, and CD spectra. The formulas **1** and **2**, however, could be inferred from the data comparing with those of related compounds.



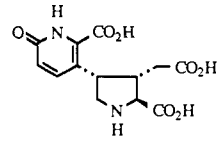
clitidine



clithioneine



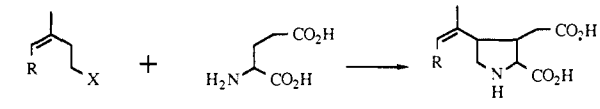
acromelic acid A (1)



acromelic acid B (2)

† Dedicated to Professor E. J. Corey on the occasion of his 60th birthday.
‡ Hokkaido University.
§ Suntory Institute for Bioorganic Research.

**Scheme I.** Biogenesis of Kainic Acid and Domoic Acid



isoprene unit glutamic acid kainic acid , domoic acid

The $^1H$ NMR spectra of both **1** and **2** consisted of the signals of two aromatic protons, three methine, and two methylene groups. The sequence of the methine and methylene groups was a readily suggested presence of a partial structure (**A**) in both compounds by the decoupling experiments (Figure 1). The terminal methine proton was thought to be an α-proton of amino acid,[4] judging from chemical shift values (4.13 in **1** and 4.16 in **2**). On the other hand, one of the methylene groups was indicated to be α to the carbonyl group because of its chemical shifts (2.01, 2.54 in **1** and 2.23 in **2**) and a large $J$ value (hertz) between geminal protons (16.5 Hz). These analyses led to a partial structure (**B**) possessing a glutamic acid moiety, which was in accord with the strongly acidic nature of **1** and **2** on chromatography. Another partial structure (C) (including the proline moiety) was suggested from the facts that both **1** and **2** gave a yellow coloration with a ninhydrin test and the chemical shifts of the other methylene (3.73, 3.76 in **1** and 3.67, 3.78 in **2**) were assignable to a methylene α to an ammonium nitrogen. Taking all these evidence into consideration, a structure of 4-substituted 2-carboxy-3-(carboxymethyl)pyrrolidine (D) was inferred for each of **1** and **2**. Indeed, as shown in Table I, the $^1H$ NMR spectral data (360 MHz) of **1** and **2** closely resembled those of domoic acid (**4**)[5] and kainic acid (**3**),[6] respectively, except

(1) (a) Konno, K.; Hayano, K.; Shirahama, H.; Saito, H.; Matsumoto, T. *Tetrahedron Lett.* **1977**, 481-482. (b) Konno, K.; Hayano, K.; Shirahama, H.; Saito, H.; Matsumoto, T. *Tetrahedron* **1982**, *38*, 3281-3284.
(2) (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1981**, *22*, 1617-1618. (b) Konno, K.; Shirahama, H.; Matsumoto, T. *Phytochemistry* **1984**, *23*, 1003-1006.
(3) Preliminary accounts of this work: (a) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939-942. (b) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1986**, *27*, 607-610. (c) Hashimoto, K.; Konno, K.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1986**, 1399-1400.
(4) Roberts, G. C. K.; Jardetzky, O. *Adv. Protein Chem.* **1970**, *24*, 447-545.
(5) (a) Isolation and structure: Takemoto, T.; Daigo, K.; Kondo, Y.; Kondo, K. *J. Pharm. Soc. Jpn.* **1966**, *86*, 874-877. (b) Total synthesis: Ohfune, Y.; Tomita, M. *J. Am. Chem. Soc.* **1982**, *104*, 3511-3513.
(6) For review see: McGeer, E. G.; Olney, J. W.; McGeer, P. L. *Kainic Acid as a Tool in Neurobiology*; Raven: New York, 1978.

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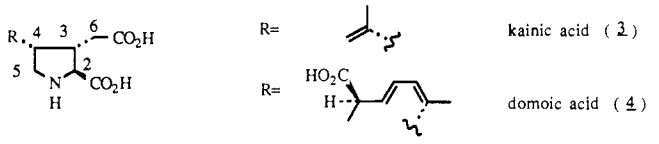
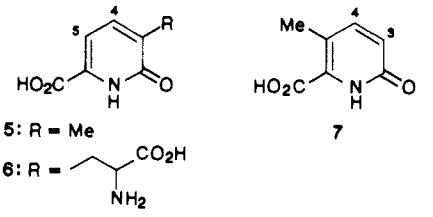
**Table I.** Comparison of NMR Spectral Data of Acromelic Acid A with That of Domoic Acid and That of Acromelic Acid B with That of Kainic Acid




| | $H_2$ | $H_3$ | $H_4$ | $H_5$ | $H_{5'}$ | $H_6$ | $H_{6'}$ |
|---|---|---|---|---|---|---|---|
| acromelic acid A | 4.13, d (8.1) | 3.12, dddd (5.4, 7.1, 8.1, 10.8) | 3.82, q (7.1) | 3.73, dd (7.1, 12.0) | 3.76, dd (7.1, 12.0) | 2.01, dd (10.8, 16.5) | 2.54, dd (5.4, 16.5) |
| domoic acid | 3.98, d (8.2) | 3.05, dddd (5.8, 7.6, 8.2, 9.1) | 3.83, q (7.6) | 3.49, dd (7.6, 12.3) | 3.70, dd (7.6, 12.3) | 2.50, dd (9.1, 16.8) | 2.75, dd (5.8, 16.8) |
| acromelic acid B | 4.46, d (3.6) | 3.15, ddd (3.6, 7.2, 7.7) | 4.47, dt (7.2, 11.7) | 3.67, t (11.7) | 3.78, dd (7.2, 11.7) | 2.23, d (7.7) | |
| kainic acid | 4.12, d (3.6) | 3.10, dddd (3.6, 6.3, 7.2, 8.3) | 3.03, dt (7.2, 11.7) | 3.45, t (11.7) | 3.65, dd (7.2, 11.7) | 2.40, dd (8.3, 16.6) | 2.49, dd (6.3, 16.6) |

**Table II.** Comparison of NMR and UV Data of Acromelic Acid A and B with Those of Their Model Compounds




| | $^1$H NMR | | | $\lambda_{max}$ | | |
|---|---|---|---|---|---|---|
| | $\delta_4$ | $\delta_{5(3)}$ | $J_{4\text{-}5(3)}$ | pH 2 | pH 7 | pH 12 |
| acromelic acid A | 7.54 | 6.98 | 7.2 | 240, 313 | 242, 317 | 241, 312 |
| **5** | 7.62 | 6.96 | 7.0 | 241, 306 | 242, 310 | 245, 307 |
| **6** | 7.66 | 7.08 | 7.0 | 239, 311 | 241, 315 | 244, 311 |
| acromelic acid B | 7.63 | 6.68 | 9.3 | 231, 308 | 227, 300 | 241, 311 |
| **7** | 7.69 | 6.68 | 9.0 | 239, 310 | 235, 302 | 242, 313 |

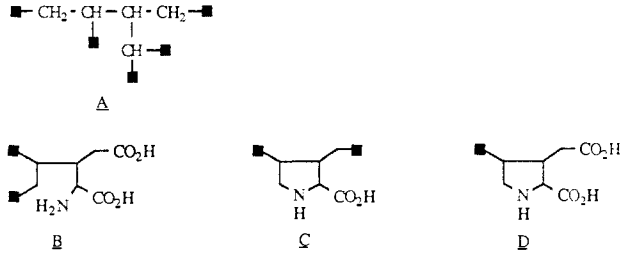



**Figure 1.** Partial structures assigned by NMR data, including decoupling experiments, chromatographic behavior, and coloring test.

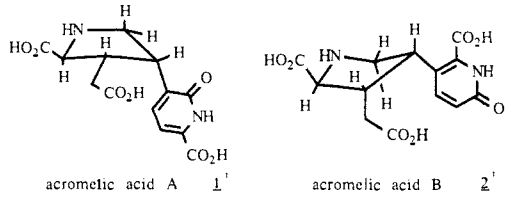
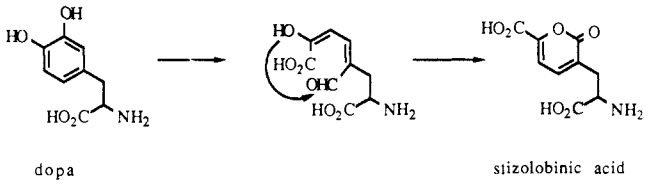



**Figure 2.** Conformations of acromelic acids A and B deduced by the NMR data.

**Scheme II.** Biosynthetic Route of Stizolobinic Acid




for the signals of C-4 protons.

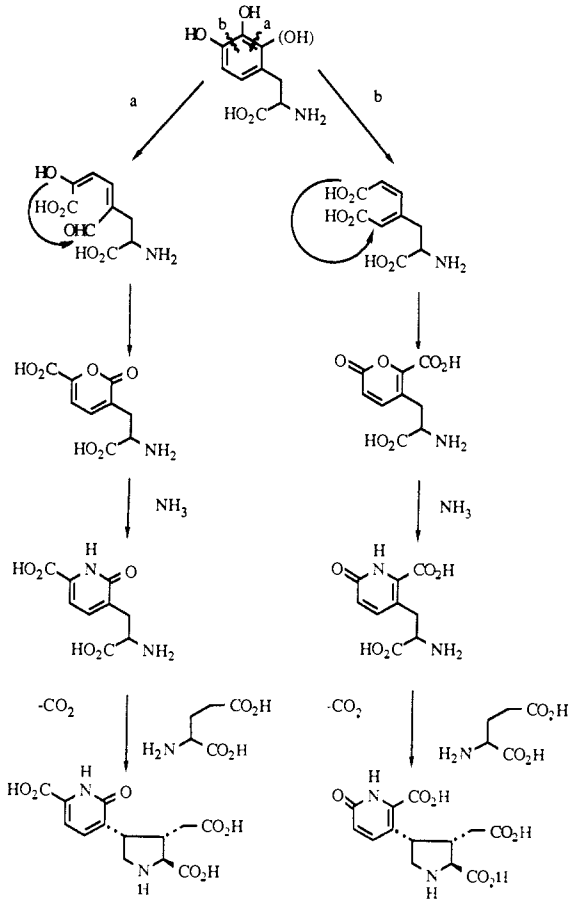
The structure of the aromatic portion was deduced by UV and NMR analyses. The UV spectra of both compounds exhibited two, pH-independent maxima around at 240 and 310 nm, characteristic of 2-pyridone, in particular, of 2-pyridone-6-carboxylic acid derivatives.[7] Moreover, in the $^1$H NMR spectrum, coupling constants of 9 and 7 Hz are known to be indicative of $J_{3\text{-}4}$ and $J_{4\text{-}5}$, respectively, in 2-pyridone-6-carboxylic acid derivatives.[8] Therefore, 3- and 5-substituted 2-pyridone-6-carboxylic acids were suggested as the structure of aromatic portion of **1** and **2**, respectively.

In order to verify the above argument, appropriate model compounds such as **5**–**7** were prepared and their spectral data were compared with those of **1** and **2**. As shown in Table II, the $^1$H NMR and UV data of the aromatic portion of natural products were almost identical with those of the corresponding model compounds, supporting the deduced structures.

The conclusion that the pyrrolidine and pyridone thus far deduced were linked directly at C-4 of the former to the 3- or 5-position of the latter was reached as described below. A biogenetic consideration suggested the directly linked formulas **1** and **2**. For the biogenesis of kainic acid and domoic acid, condensation of an isoprene unit with glutamic acid followed by cyclization to form pyrrolidine ring as shown in Scheme I is most likely. Consequently, it was supposed that the pyrrolidine moiety of **1** and **2** arose from glutamic acid. For the origin of the aromatic portion, DOPA was suggested since the fission of catechol ring and subsequent recyclization to pyrone ring have been established biosynthetically in the case of stizolobinic acid (Scheme II).[9,10] Accordingly, the extradiol cleavage (Scheme III, path a) followed by cyclization with ammonia would give pyridone carboxylic acid, which then condensed with glutamic acid to afford **1** along with

(7) Rateb, L.; Mina, G. A.; Soliman, G. *J. Chem. Soc. C* **1968**, 2140–2144.
(8) Weber, H. *Arch. Pharm.* **1976**, *309*, 664–669.
(9) Saeki, Y.; Nozaki, M.; Senoh, S. *J. Biol. Chem.* **1980**, *255*, 8465–8471.
(10) Musso, H. *Tetrahedron* **1979**, *35*, 2843–2853.
(11) Nakamori, R. *J. Pharm. Soc. Jpn.* **1956**, *76*, 275–300.

**Scheme III.** Biogenesis of Acromelic Acids A and B




deamination and decarboxylation. In a similar way, the intradiol cleavage (path b) would lead to **2**.

$^1$H NMR analyses gave support for the formulas **1** and **2**. In both compounds the doublet signals assigned to $H_4$ of pyridone (7.54 in **1** and 7.63 in **2**) appeared in lower height and broader width than the other pyridone proton (6.98 in **1** and 6.68 in **2**), indicating a small long-range coupling between the C-4 proton of pyridone and $H_4$ of pyrrolidine. In fact, in the case of model compounds **5** and **7**, clear long-range couplings were observed.

Conformational analyses further supported the above argument. As main conformations, **1′** and **2′**, shown in Figure 2, were deduced from $J$ values and inspection of molecular models; anomalous down-field shifts of pyrrolidine $H_4$ peaks (3.82 in **1** and 4.47 in **2**) were well rationalized from these models, since in **1′** and **2′** the carbonyl and carboxyl groups can approach close to $H_4$, respectively, giving the anisotropy effect. This implies the direct linkage of the pyrrolidine and pyridone rings.

Relative stereochemistry of three asymmetric centers on pyrrolidine ring in both **1** and **2** was indicated to be the same as kainic acid (**3**) and domoic acid (**4**), respectively, 2,3-trans and 3,4-cis, since the corresponding $J$ values of the ring protons of **1** and **2** were almost the same as **4** and **3**, respectively, as shown in Table I.

Furthermore, the 2,3-trans structure was suggested by the chemical shifts of $\alpha$-protons. In all the kainoids ever found, when the 2,3-substituents (carboxyl and carboxymethyl) were trans oriented, the signals of $\alpha$-proton appear at a higher field than 4.2 ppm. On the other hand, in the cis compounds, they appear lower than 4.2 ppm, irrespective of the substituent at C-4. These data were shown in Figure 3. The chemical shift values of $\alpha$-protons of **1** and **2** (4.13 and 4.16) were consistent with this empirical rule. Thus, acromelic acids A and B are best expressed by **1** and **2**, respectively, except for absolute configuration.

**Syntheses.** Acromelic acids A (**1**) and B (**2**) were synthesized in order to corroborate the proposed structures and to provide the

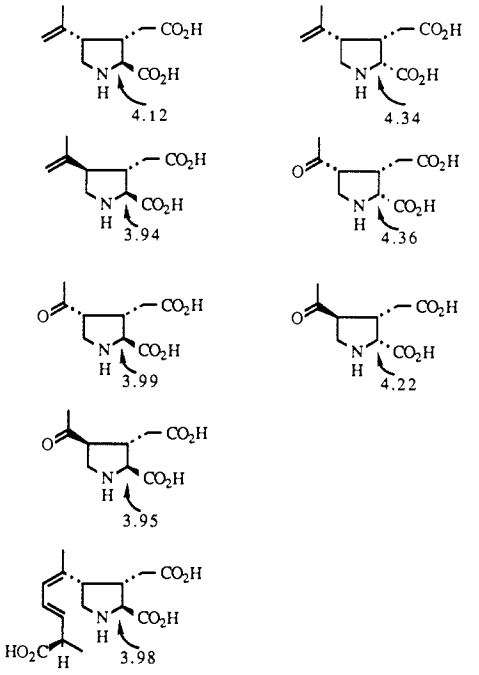
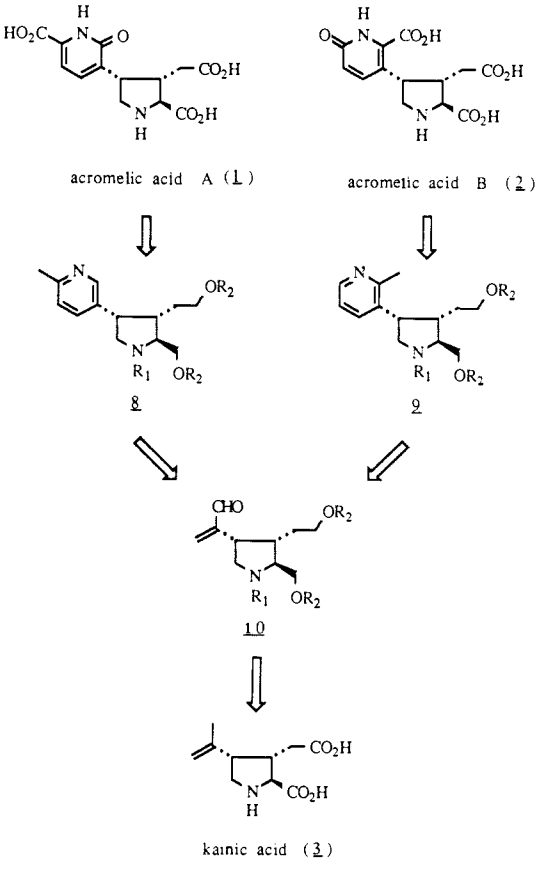



**Figure 3.** Chemical shifts of $\alpha$-protons in kainoids. All these kainoids except for kainic acid and domoic acid were prepared from kainic acid by known methods.[11]

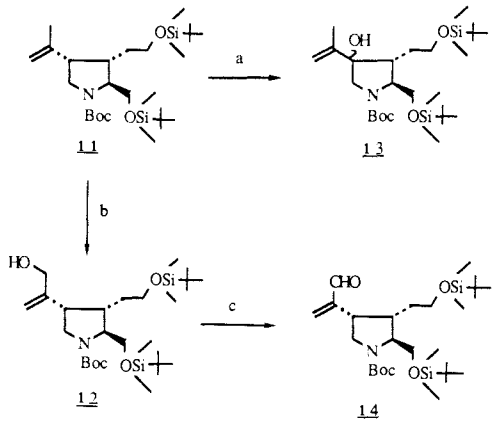
**Scheme IV.** Retrosynthesis of Acromelic Acids A and B




samples for the biological assays.

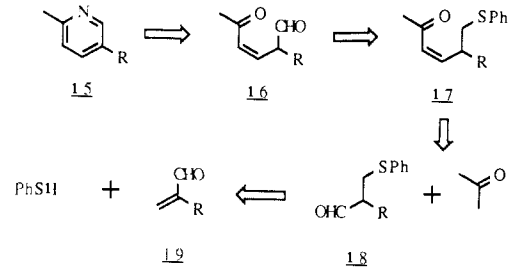
The synthetic plan is outlined in Scheme IV. We chose L-$\alpha$-kainic acid (**3**), which is commercially available in optically pure form, as the starting material because it has identical stereochemistry with the target molecules. The key intermediates methylpyridines **8** and **9** would lead to **1** and **2**, respectively, through the sequential oxidation of methyl group to carboxylic acid and pyridine to pyridone. The $\alpha,\beta$-unsaturated aldehyde **10** can be a precursor of the key intermediates **8** and **9** since it is

**Scheme V.** Oxidation of the Methyl Group of Kainic Acid[a]



[a] (a) $SeO_2$; (b) mCPBA–$CH_2Cl_2$ (2) lithium tetramethylpiperidide-ether, 0–25 °C (60%); (c) $MnO_2$ (86%).

**Scheme VI.** Synthetic Scheme for 2,5-Disubstituted Pyridine from an $\alpha,\beta$-Unsaturated Aldehyde

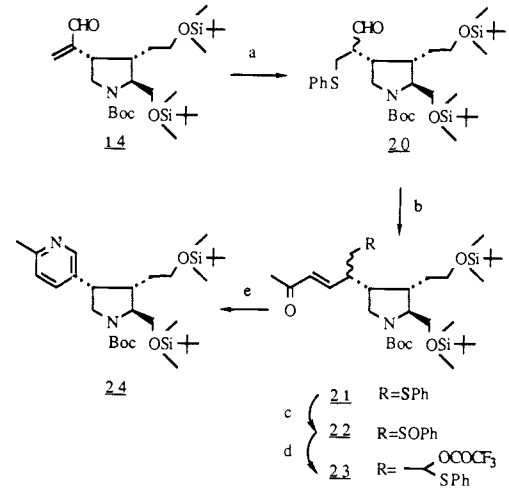


convertible to the pyridines. Allylic oxidation of kainic acid should afford the aldehyde **10**.

The imino and carboxyl groups were successively protected by the conventional way [(1) 2-[[(*tert*-butoxycarbonyl)oxy]imino]-2-phenylacetonitrile (Boc-ON), (2) $CH_2N_2$] to afford dimethyl *N*-Boc-kainate in quantitative yield. In order to avoid the racemization at the $\alpha$-position,[5b] the ester groups were reduced to alcohols ($LiAlH_4$) and then protected by silyl groups (TBDMSCl) to provide **11** in 70% yield. The use of selenium dioxide for the allylic oxidation of **11** afforded an undesired alcohol **13** instead of the desired material **12** as the main product (Scheme V). So the stepwise procedure that involved epoxidation and subsequent isomerization of the epoxide to allylic alcohol was examined. Epoxidation of **11** with mCPBA gave a corresponding epoxide in 97% yield, which was exposed to various reagents under various conditions. The best result was obtained by using LiTMP (4 equiv) in ether (0 °C, 1 h → room temperature, 1 h), by which allylic alcohol **12** was obtained in 60% yield. Protective groups other than TBDMS (Me, MOM, MEM, and Bzl) resulted in decrease of the yield. No epimerization of C-4 on the pyrrolidine ring was demonstrated by the conversion of **12** back to **11** [(1) TsCl, LiCl–MeLi; (2) Zn]. Further oxidation of **12** with $MnO_2$ produced aldehyde **14** in 86% yield.

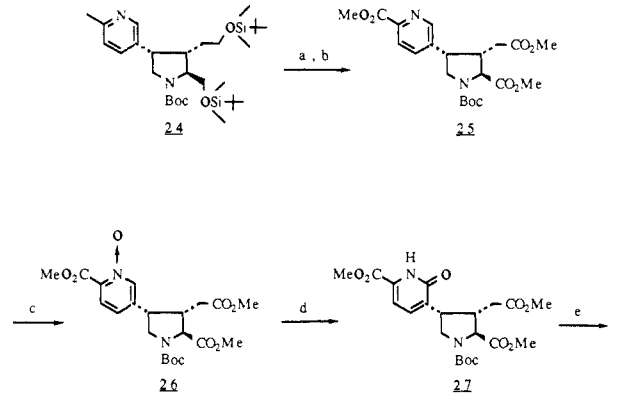
Construction of the pyridine ring is the most crucial stage of this synthesis. After numerous model studies, we found a mild and efficient method of pyridine synthesis that started from $\alpha,\beta$-unsaturated carbonyl compound.[12] Cyclization of an unsaturated 1,5-dicarbonyl compound with a variety of ammonia sources is a facile process for pyridine ring formation.[13] However, difficulties encountered in preparation of an unsaturated 1,5-dicarbonyl system made it of limited use in synthesis. In our method the problem was solved by the use of the Pummerer reaction. As shown in Scheme VI, keto sulfide **17** can be regarded as a synthetic equivalent to keto aldehyde **16** since the (phenylthio)methyl group is convertible to aldehyde by the Pummerer reaction. The keto sulfide **17** is readily accessible because the reaction sequence **19** → **18** → **17** is a feasible and conventional process.

**Scheme VII.** Assembling a Pyridine Nucleus with an $\alpha,\beta$-Unsaturated Aldehyde Moiety on Kainic Acid[a]



[a] (a) PhSH–$Et_3N$, 0 °C (93%); (b) $CH_3COCH_2PO(OEt)_2$, NaH-THF, 0 °C (79%); (c) $NaIO_4$, $Na_2HPO_4$; (d) TFAA, py–$CH_2Cl_2$, 0 °C; (e) $NH_3$–MeOH (64%, three steps).

**Scheme VIII.** Oxidation of Methylpyridine Moiety to $\alpha$-Pyridonecarboxylic Acid[a]



[a] (a) $SeO_2$–py, 120 °C, (2) $CH_2N_2$, (3) *n*-$Bu_4NF$ (43%); (b) (1) PDC–DMF, (2) $CH_2N_2$ (48%); (c) mCPBA–$CH_2Cl_2$ (77%); (d) TFAA–DMF (68%); (e) (1) KOH, (2) TFA (71%).

Treatment of **14** with thiophenol afforded adduct **20** as a mixture of diastereoisomers in 93% yield, which was then converted to ketone **21** by the Horner–Emmons reaction. For oxidation of sulfide **21** into sulfoxide **22**, $Na_2HPO_4$ was added to bufferize the reaction mixture, otherwise the silyl protecting groups were partially removed. The Pummerer reaction of **22** smoothly proceeded under mild and neutral condition[14] (TFAA–py, 0 °C, 1 h) to furnish a rearranged product **23** in quantitative yield. The Pummerer product **23** was rather unstable, so that it was immediately cyclized by methanolic ammonia, in one pot operation, to afford key intermediate **24** in good yield (Scheme VII).

The stage was set to complete the synthesis. Oxidation of methyl group in **24** by $SeO_2$[15] gave the corresponding carboxylic acid, which was immediately esterified with $CH_2N_2$ and then desilylated with *n*-$Bu_4NF$. Treatment of the resulting diol successively with PDC–DMF and $CH_2N_2$ afforded triester **25** in 20%

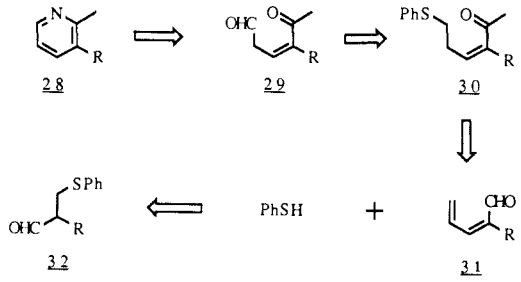
(12) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 3865–3868.

(13) Klinsberg, E. *The Chemistry of Heterocyclic Compounds. Vol. 14, Pyridine and Its Derivatives*; Interscience: New York, 1960.

(14) (a) T. Matsumoto and H. Shirahama et al. found improved conditions for Pummerer reactions by using pyridine as additive to acetic anhydride during their studies on the total syntheses of illudin S and M.[14b,c] A slight modification of their conditions led to good results. (b) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Matsumoto, S. Nishida, S. *J. Am. Chem. Soc.* **1968**, *90*, 3280. (c) Matsumoto, T.; Shirahama, H.; Sakan, F.; Takigawa, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 325–326.

(15) Jerchel, D.; Bauer, E.; Hippchen, H. *Chem. Ber.* **1955**, *88*, 156–163.

**Scheme IX.** Synthetic Scheme for 2,3-Disubstituted Pyridine from an $\alpha,\beta$-Unsaturated Aldehyde



overall yield, which in turn was led to *N*-oxide **26** by mCPBA in 77% yield.

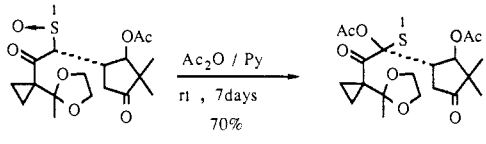
The conversion of pyridine *N*-oxide into 2-pyridone in acetic anhydride is a well-known procedure developed by Ochiai and colleagues.[16] However, application of this procedure to picolinic acid derivatives resulted in low yield.[17] In addition, the condition seemed to be too vigorous for our compound. After some model studies, we found a superior condition with which the reaction proceeded rapidly and mildly enough, namely, with trifluoroacetic anhydride instead of acetic anhydride in dimethylformamide at room temperature.[18] Exposure of *N*-oxide **26** to our modified condition gave pyridone **27** in good yield. Finally, acromelic acid A (**1**) was obtained from pyridone **27** by removal of the protective groups in a usual manner (Scheme VIII).

For the synthesis of acromelic acid B (**2**), methylpyridine **28** is the key intermediate. Again it can be prepared by our newly developed pyridine synthesis with only slight modification. In this case, the keto sulfide **30** is a precursor for pyridine **28** (Scheme IX). This can be obtained by 1,6-conjugate addition of thiophenol to $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde **31**. Two carbon extension and subsequent Pummerer reaction would lead the sulfide **32** to the aldehyde **31** (Scheme IX).

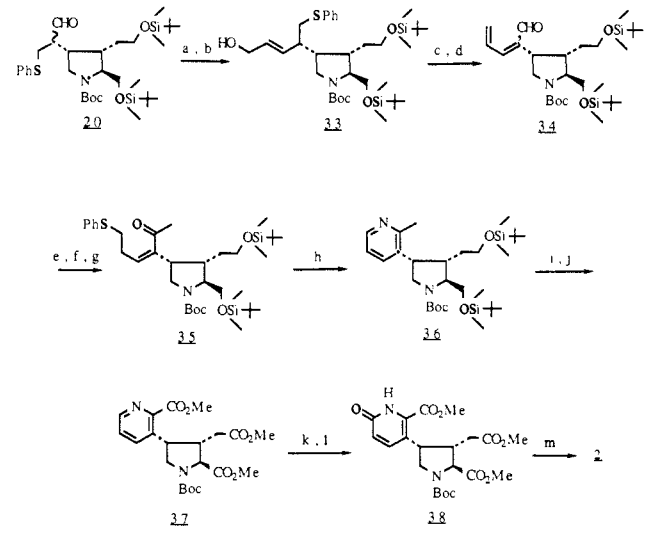
The sulfide **20** was subjected successively to the Horner–Emmons reaction and DIBAH reduction to afford allylic alcohol **33** as a mixture of diastereoisomers in high yield. The alcohol **33** was then led to $\alpha,\beta,\gamma,\delta$-unsaturated aldehyde in good yield by the Pummerer reaction and subsequent dehydration. Selective 1,6-conjugate addition of thiophenol to aldehyde **34** proceeded smoothly, and the resulting adduct was successively treated with MeLi and PDC to yield ketone **35**. In a similar manner to the conversion of **21** → **24**, methylpyridine **36** was obtained from **35** in modest yield. Acromelic acid B (**2**) was synthesized from methylpyridine **36** through **37** and **38** in a similar procedure as before (Scheme X see the Experimental Section).

The synthetic materials were identical with natural products in all respects ($^1$H NMR, UV, and TLC analyses, PEP mobilities), confirming the inferred structures of acromelic acids A (**1**), and B (**2**). The absolute configurations of both compounds were determined to be L, namely all three configurations were *S*, by the CD spectral comparison. Thus, the structures of acromelic acids A and B were established to be **1** and **2**, respectively, including absolute configuration.

In the preliminary test with crayfish neuromuscular preparation, both acromelic acids A (**1**) and B (**2**) showed the most potent depolarizing action among the compounds related to L-glutamic acid ever known. The action was also proved in rat central neurons. Thus, acromellic acids A (**1**) and B (**2**) were found to be powerful neutroexcitants and may be very useful tool in the field of the neuroscience research.[19]



**Scheme X.** Synthetic Route of Acromelic Acid B[a]



[a] (a) $EtO_2CCH_2PO(OEt)_2$, NaH–THF, 0 °C (98%); (b) DIBAH–toluene, 0 °C (99%); (c) (1) $NaIO_4$, $Na_2HPO_4$, (2) TFAA, py–$CH_2Cl_2$, 0–25 °C, (3) $Na_2CO_3$(aq) 0–25 °C; (d) MsCl, $Et_3N$–$CN_3CN$, 0 °C; (e) PhSH, $Et_3N$–DMF, 0 °C (48% three steps); (f) MeLi–THF, −15 °C (87%); (g) PDC–DMF (83%); (h) (1) $NaIO_4$, $Na_2HPO_4$, (2) TFAA, py–$CH_2Cl_2$, 0 °C, (3) $NH_3$(aq) (62%); (i) (1) $SeO_2$–py, 100 °C, (2) $CH_2N_2$, (3) *p*-TsOH–MeOH (25%); (j) (1) PDC–DMF, 40 °C, (2) $CH_2N_2$ (48%); (k) mCPBA–$CH_2Cl_2$ (75%); (l) TFAA–DMF (62%); (m) (1) KOH, (2) TFA (73%).

## Experimental Section

Active charcoal for chromatography was purchased from Wako Pure Chemical Ltd. The silica gel used was Wako C-200. Paper electrophoresis (PEP) was performed on Whatman 3MM filter paper with a Model 20-TR apparatus (MS-kiki Co. Ltd.). Separation was effected at pH 4.6, py–AcOH–$H_2O$ (3:3:994 by volume), 600 V, 2 h, unless otherwise stated. Cellulose TLC was carried out with use of Avicel SF cellulose TLC plates with appropriate solvent systems and visualized by a UV lamp (254 nm) or ninhydrin.

Fruiting bodies of *C. acromelalga* were collected at Nagaoka city, Niigata-ken, Japan, frozen upon collection, and stored at −20 °C.

**Isolation of Acromelic Acids A and B.** Frozen fruiting bodies (5.4 kg) were extracted with water (3 × 10 L) at 4 °C overnight. The combined extracts were concentrated to ca. 2 L. To this turbid solution was added acetone (8 L), the mixture was left at 0–4 °C overnight, the supernatant was decanted, and the precipitate was dissolved in water (1 L) and dialyzed against water (3 × 6 L) at 4 °C overnight. The combined dialyzate was evaporated, and the residue (82 g) was applied to a column of charcoal (82 g, packed with water). After the residue was washed with water, stepwise elution with aqueous EtOH (2.5, 5, 10, 30% EtOH–$H_2O$, each 4 L) was carried out. The entire process was repeated two more times.

The combined 2.5–5% aqueous EtOH eluate from charcoal chromatography was evaporated to yield 7 g of crude acromelic acid fraction, which was divided into three batches, and each was subjected to chromatography on weakly basic ion-exchange resin (270 g, 4.5 × 22 cm, $HCO_2^-$ form). After the fractions were washed with water, stepwise elution with aqueous $HCO_2H$ (5, 10, 20% $HCO_2H$, each 2 L) was carried out. The combined 10–20% aqueous $HCO_2H$ eluate was evaporated, and the residue (1 g) was subsequently subjected to PEP (46 × 20 cm, 50 sheets). A fluorescent band at +9 cm was cut out, eluted with water, and evaporated. The residue (52 mg) was then placed on cellulose TLC (20 × 20 cm, 10 sheets) and developed with a solvent system of *n*-BuOH–$HCO_2H$–$H_2O$ (6:1:2). Acromelic acid A was obtained from the band at $R_f$ 0.41 (9 mg) and acromelic acid B at $R_f$ 0.28 (6 mg). Acromelic acid A was further purified by cellulose TLC (*n*-BuOH–AcOH–$H_2O$, 4:1:5, 20 × 20 cm, 10 plates, developed three times, $R_f$ 0.35, yield 2 mg) and finally by PEP (20 × 46 cm, three sheets) to afford ca. 110 μg of a pure sample: UV 242, 317 (pH 7) 240, 313 (pH 2) 241, 312 (pH 12) nm; $^1$H NMR (360 MHz, $D_2O$) δ 2.01 (1 H, dd, *J* = 10.8, 16.5), 2.54 (1 H, dd, *J* = 5.4, 16.5), 3.12 (1 H, dddd, *J* = 5.4, 7.1, 8.1, 10.8), 3.73 (1 H, dd, *J* = 7.1, 12.0), 3.76 (1 H, dd, *J* = 7.1, 12.0), 3.82 (1 H,

(16) Ochiai, E. *Aromatic Amine Oxides*; Elsevier: Amsterdam, 1967.
(17) Boekelheide, V.; Lehn, W. L. *J. Org. Chem.* **1961**, *26*, 428–430.
(18) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Heterocycles* **1986**, *24*, 2169–2172.
(19) Shinozaki, H., Ishida, M.; Okamoto, T. *Brain Res.* **1986**, *399*, 395–398.

q, $J$ = 7.1), 4.13 (1 H, d, $J$ = 8.1), 6.98 (1 H, d, $J$ = 7.2), 7.54 (1 H, d, $J$ = 7.2).

Acromelic acid B was finally purified by PEP (46 × 20 cm, six sheets) to afford ca. 40 μg of a purified sample: UV 239, 310 (pH 7) 242, 313 (pH 2), 235, 302 (pH 12) nm; $^1$H NMR (360 MHz, $D_2O$) δ 2.23 (2 H, d, $J$ = 7.7), 3.15 (1 H, ddt, $J$ = 3.6, 7.2, 7.7), 3.67 (1 H, t, $J$ = 11.7), 3.78 (1 H, dd, $J$ = 7.2, 11.7), 4.16 (1 H, d, $J$ = 3.6), 4.47 (1 H, dt, $J$ = 11.7, 7.2), 6.68 (1 H, d, $J$ = 9.3), 7.63 (1 H, d, $J$ = 9.3).

**3-Methyl-6-carboxy-2-pyridone (5).** To a solution of 3-methyl-6-carboxy-2-pyrone[20] (17 mg) in water (1 mL) was added 25% $NH_3$(aq) (0.1 mL), and the mixture was left overnight at room temperature. The solvent was evaporated, and the crystalline residue was recrystallized from MeOH to afford **5** (8 mg) as white crystals: mp 209–210 °C; HR-MS, $m/z$ 153.0399 ($M^+$) calcd for $C_7H_7NO_3$ 153.0424; IR (Nujol) 3400–2400, 1720, 1650, 1593, 1100, 1055 cm$^{-1}$; UV (pH 7) 241, 306 (2.040, 6.720), (pH 2) 242, 310 (1.620, 7.140), (pH 12) 245, 307 (1.020, 5.870) nm; $^1$H NMR 100 MHz, $D_2O$) δ 2.40 (3 H, q, $J$ = 1.0), 6.99 (1 H, d, $J$ = 7.1), 7.62 (1 H, dq, $J$ = 7.1, 1.0).

**β-(6-Carboxy-2-oxopyrid-3-yl)alanine (6).** This compound was prepared according to the procedure reported by Senoh:[21] $^1$H NMR (400 MHz, $D_2O$) δ 3.00 (1 H, dd, $J$ = 8.1, 14.7), 3.22 (1 H, dd, $J$ = 3.9, 4.7), 4.03 (1 H, dd, $J$ = 3.9, 8.1), 7.08 (1 H, d, $J$ = 7.0), 7.66 (1 H, d, $J$ = 7.0).

**5-Methyl-6-carboxy-2-pyridone (7).** To a solution of 5-methyl-6-carboxy-2-pyrone[22] (3.5 mg) was added 25% $NH_3$(aq) (1 drop), and the mixture was left overnight at room temperature. The solvent was evaporated, and the crystalline residue was purified by cellulose TLC ($R_f$ 0.52, $n$-BuOH–water, saturated) to yield ca. 1 mg of **7** as white crystals: mp 295 °C dec; HR-MS, $m/z$ 153.0395 calcd for $C_7H_7NO_3$ 153.0424; UV (pH 7) 231, 308, (pH 2) 227, 300, (pH 12) 241, 311 nm; $^1$H NMR (100 MHz, $D_2O$) δ 2.24 (3 H, br s), 6.68 (1 H, d, $J$ = 9.3), 7.63 (1 H, d, $J$ = 9.3).

**Dimethyl *N*-*t*-Boc-kainate.** To a stirred solution of L-α-kainic acid (5 g, 23.5 mmol) and triethylamine (8 mL, 58.7 mmol, 2.5 equiv) in 1:1 dioxane–water (50 mL–50 mL) was added 2-[[(*tert*-butoxycarbonyl)-oxy]imino]-2-phenylacetonitrile (Boc-ON) (6.5 g, 25.9 mmol, 1.1 equiv), and the mixture was stirred at room temperature for 3 h. The mixture was poured into water and extracted with ethyl acetate (200 mL × 2). The water layer was acidified to pH 3 with 10% citric acid solution and extracted with ethyl acetate (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to give white crystals of *t*-Boc-kainic acid: mp 139–141 °C; $[\alpha]_D$ −51.1° ($c$ 1.08, $CHCl_3$); HR-MS, $m/z$ 313.1574 ($M^+$) calcd for $C_{15}H_{23}NO_6$ 313.1525; IR (Nujol) 3500–2200, 1737, 1713, 1635, 1260, 1220, 1175, 1150, 908 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 1.40 (9 H, s), 1.65 (3 H, s), 4.63 (1 H, s), 4.88 (1 H, s), 8.78 (2 H, br s).

To a solution of the diacid in MeOH was added $CH_2N_2$ in ether solution until the yellow color was developed, and then the solvent was removed to afford dimethyl *N*-*t*-Boc-kainate (8 g, 100%) as an oil: $[\alpha]_D$ −19.8° ($c$ 1.20, $CHCl_3$); HR-MS, $m/z$ 341.1856 ($M^+$) calcd for $C_{17}H_{27}NO_6$ 341.1838; IR (neat) 1748, 1705, 1445, 1405, 1373, 1250, 1205, 1175, 1135, 1008, 897 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 1.41 (9 H, s), 1.70 (3 H, s), 3.70 (3 H, s), 3.76 (3 H, s), 4.70 (1 H, s), 4.92 (1 H, s).

**(3*S*,4*S*,5*S*)-1-(*tert*-Butyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)-oxy]methyl]-3-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-(1-methyl-ethenyl)pyrrolidine (11).** To a suspension of $LiAlH_4$ (2.2 g, 57.9 mmol, 2.5 equiv) in THF (80 mL) was gradually added a solution of dimethyl *N*-*t*-Boc-kainate (8 g, 23.5 mmol) in THF (80 mL) at 0 °C, and the mixture was stirred at 0 °C. After 30 min, the mixture was diluted with ether (160 mL) and then acidified to pH 3 with 1 N HCl at 0 °C. After filtration through a glass filter, the filtrate was poured into water and extracted with ethyl acetate (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to afford white crystals of the diol (6.7 g, 100%): mp 79–80 °C; $[\alpha]_D$ −45.8° ($c$ 0.80, $CHCl_3$); HR-MS, $m/z$ 285.1989 ($M^+$) calcd for $C_{15}H_{27}NO_4$ 285.1940; IR (Nujol) 3500, 3420, 1675, 1410, 1170, 1138, 1110, 1068, 1020 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 1.46 (9 H, s), 1.71 (3 H, s), 4.66 (1 H, s), 4.88 (1 H, s).

To a solution of the diol (6.7 g, 23.5 mmol) and imidazole (7 g, 103 mmol), 2.4 equiv) in dimethylformamide (65 mL) at 0 °C under argon was added a solution of TBDMSCl (7.8 g, 51.7 mmol, 1.2 equiv) in dimethylformamide (65 mL), and the mixture was stirred at 0 °C for 30 min and then at room temperature for 30 min. The reaction was quenched with $NH_4Cl$(aq), and the mixture was poured into water and extracted with ether (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The oily residue was purified by silica gel column chromatography (200 g, 2–5% ether–hexane) to afford silyl ether **11** as an oil (9 g, 70%): $[\alpha]_D$ −27.8° ($c$ 1.0, $CHCl_3$); HR-MS, $m/z$ 513.3678 ($M^+$) calcd for $C_{27}H_{55}NO_4Si_2$ 513.3668; IR (neat) 1703, 1482, 1403, 1374, 1260, 1181, 1097, 840, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.0 (12 H, s), 0.85 (18 H, s), 1.43 (9 H, s), 1.68 (3 H, s), 4.60 (1 H, s), 4.83 (1 H, s).

**(2*S*,3*S*,4*S*)-1-(*tert*-Butyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)-oxy]methyl]-3-[2-[[(*tert*-butyloxy)dimethylsilyl]oxy]ethyl]-4-[1-(hydroxy-methyl)ethenyl]pyrrolidine (12).** To a stirred solution of silyl ether **11** (9 g, 17.5 mmol) in $CH_2Cl_2$ (180 mL) was added mCPBA (7.5 g, 43.4 mmol, 2.4 equiv), and the mixture was stirred at room temperature overnight. The mixture was diluted with ether (180 mL), treated with 10% $Na_2SO_3$(aq), poured into $NaHCO_3$ solution, and extracted with ether (200 mL × 3). The combined extracts were washed with $NaHCO_3$ solution, followed by brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (250 g, 10–20% ether–hexane) to afford epoxide as an oil (9 g, 97%): $[\alpha]_D$ −31.0° ($c$ 0.75, $CHCl_3$); HR-MS, $m/z$ 529.3623 ($M^+$) calcd for $C_{27}H_{55}NO_5Si_2$ 529.3618; IR (neat) 1703, 1482, 1258, 1100, 840, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.00 (12 H, s), 0.85 (18 H, s), 1.30 (3 H, s), 1.40 (9 H, s).

To a stirred solution of 2,2,6,6-tetramethylpiperidine (11.4 mL, 67.9 mmol, 4 equiv) in dry ether (90 mL) at 0 °C under argon was added 1.5 M *n*-BuLi–hexane solution (45 mL, 67.5 mmol, 4 equiv) and stirred at 0 °C for 15 min. To the LiTMP–ether solution was added a solution of the epoxide (9 g, 17 mmol) in dry ether (90 mL) at 0 °C under argon. The mixture was stirred at 0 °C for 1 h and then at room temperature for 1 h. The reaction was quenched with $NH_4Cl$(aq) (90 mL), and the mixture was poured into water and extracted with ether (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The brown residue was purified by silica gel column chromatography (270 g, 10 → 20 → 40% ether–hexane) to afford allylic alcohol **12** as colorless oil (5.4 g, 60%): $[\alpha]_D$ −27.5° ($c$ 1.08, $CHCl_3$); HR-MS, $m/z$ 529.3575 ($M^+$) calcd for $C_{27}H_{55}NO_5Si_2$ 529.3616; IR (neat) 3520, 1703, 1680, 1480, 1400, 1370, 1258, 1180, 1100, 840, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.00 (13 H, s), 0.85 (18 H, s), 1.43 (9 H, s), 4.03 (2 H, s), 4.82 (1 H, s), 5.19 (1 H, s).

**(3*S*,4*S*,5*S*)-2-[1-(*tert*-Butyloxycarbonyl)-4-[2-[(*tert*-butyldimethyl-silyl)oxy]ethyl]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-pyrrolidinyl]-acrylaldehyde (14).** To a stirred solution of allylic alcohol **12** (5.4 g) in hexane (275 mL) was added activated $MnO_2$ (27.5 g), and the mixture was stirred at room temperature. After 1 h, the mixture was filtered through Celite, and the filtrate was evaporated to yield aldehyde **14** (4.63 g, 86%) as pale yellow oil: $[\alpha]_D$ −27.0° ($c$ 1.15, $CHCl_3$); HR-MS, $m/z$ 527.3501 ($M^+$) calcd for $C_{27}H_{53}NO_5Si_2$ 527.3461; IR (neat) 1698, 1484, 1410, 1375, 1181, 1100, 840, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.00 (6 H, s), 0.05 (6 H, s), 0.86 (9 H, s), 0.88 (9 H, s), 1.46 (9 H, s), 6.13 (1 H, s), 6.16 (1 H, s), 9.52 (1 H, s).

**Adduct 20.** To a stirred solution of thiophenol (1.08 mL, 10.5 mmol, 1.2 equiv) and triethylamine (1.47 mL, 10.6 mmol, 1.2 equiv) in THF (70 mL) under argon at 0 °C was added a solution of aldehyde **14** (4.63 g, 8.8 mmol) in THF (30 mL), and the mixture was stirred at 0 °C. After 1 h, the mixture was poured into water and extracted with ether (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (130 g, 20% ether–hexane) to afford adduct **20** (5.19 g, 93%) as a mixture of 1:1 diastereoisomers. Although the isomers were readily separable, the mixture was used directly for the next step.

**Less polar isomer** ($R_f$ 0.52, 25% ether–hexane): $[\alpha]_D$ −3.6° ($c$ 0.90, $CHCl_3$); HR-MS, $m/z$ 637.3608 ($M^+$) calcd for $C_{33}H_{59}NO_5SSi_2$ 637.3650; IR (neat) 1732, 1695, 1590, 1478, 1398, 1255, 1178, 1100, 837, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.00 (6 H, s), 0.01 (6 H, s), 0.85 (9 H, s), 0.86 (9 H, s), 1.43 (9 H, s), 7.1–7.4 (5 H, br s), 9.67 (1 H, d, $J$ = 1.3).

**More polar isomer** ($R_f$ 0.41, 25% ether–hexane): $[\alpha]_D$ −33.6° ($c$ 0.70, $CHCl_3$); HR-MS, $m/z$ 637.3690 ($M^+$) calcd for $C_{33}H_{59}NO_5SSi_2$ 637.3650; IR (neat) 1732, 1695, 1590, 1478, 1398, 1255, 1178, 1100, 837, 780 cm$^{-1}$; $^1$H NMR (90 MHz, $CDCl_3$) δ 0.00 (12 H, s), 0.85 (18 H, s), 1.38 (9 H, s), 7.1–7.4 (5 H, br s), 9.55 (1 H, d, $J$ = 2.6).

**Keto Sulfide 21.** To a suspension of NaH (230 mg, 9.6 mmol, 1.2 equiv) in THF (50 mL) at 0 °C under argon was added a solution of diethyl acetonyl phosphate (1.8 g, 9.3 mmol, 1.2 equiv) in THF (15 mL), and the mixture was stirred at room temperature for 15 min. To this solution was added a solution of aldehyde **20** (5.9 g, 7.8 mmol) in THF (15 mL) at 0 °C, and the mixture was stirred at 0 °C overnight. The reaction was quenched with $NH_4Cl$(aq), and then the mixture was poured into water and extracted with ether (200 mL × 3). The combined

(20) Higginbotham, L.; Lapworth, A. *J. Chem. Soc.* **1923**, *123*, 1325–1332.
(21) Senoh, S. *Nippon Kagaku Zassi* **1965**, *86*, 1087–1104.
(22) Fried, J.; Elderfield, R. C. *J. Org. Chem.* **1941**, *6*, 566–576.

extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residual oil was purified by silica gel column chromatography (150 g, 10 → 20% ether–hexane) to afford ketone **21** (4.2 g, 79%) as a mixture of diastereoisomers. Although the isomers were readily separable, the mixture was used directly for the next step.

**Less polar isomer** ($R_f$ 0.38, 25% ether–hexane): $[\alpha]_D$ +2.2° (*c* 0.65, $CHCl_3$); HR-MS, *m/z* 677.4003 ($M^+$) calcd for $C_{36}H_{63}NO_5SSi_2$ 677.3960; IR (neat) 1700, 1635, 1590, 1480, 1372, 1259, 1180, 1100, 830, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 0.00 (6 H, s), 0.08 (9 H, s), 0.88 (9 H, s), 0.93 (9 H, s), 1.48 (9 H, s), 2.17 (3 H, s), 6.09 (1 H, d, *J* = 15.8), 6.54 (1 H, dd, *J* = 8.1, 15.8), 7.1–7.4 (5 H, br s).

**More polar isomer** ($R_f$ 0.22, 25% ether–hexane): $[\alpha]_D$ −45.2° (*c* 1.00, $CHCl_3$); HR-MS, *m/z* 678.4066 [$(M + H)^+$] calcd for $C_{36}H_{64}NO_5SSi_2$ 678.4043; IR (neat) 1700, 1635, 1590, 1480, 1402, 1372, 1256, 1180, 1100, 830, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 0.00 (12 H, s), 0.84 (9 H, s), 0.86 (9 H, s), 1.38 (9 H, s), 2.10 (3 H, s), 5.96 (1 H, d, *J* = 15.8), 6.42 (1 H, dd, *J* = 8.1, 15.8), 7.1–7.4 (5 H, br s).

**(3*S*,4*S*,5*S*)-5-[1-(*tert*-Butyloxycarbonyl)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-pyrrolidinyl]-2-methylpyridine (24).** To a stirred solution of ketone **21** (3.70 g, 5.5 mmol) in 4:1 MeOH–$H_2O$ (296 mL–74 mL) was added successively $Na_2HPO_4$ (3.96 g, 27.9 mmol, 4.8 equiv) and $NaIO_4$ (6 g, 28.0 mmol, 4.8 equiv), and the solution stirred at room temperature overnight. The mixture was filtered, and the filtrate was poured into water and extracted with ethyl acetate (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to afford crude sulfoxide **22** (3.82 g) as syrup.

To a stirred solution of the sulfoxide **22** in $CH_2Cl_2$ (88 mL) was added pyridine (22 mL, 272 mmol, 50 equiv) and then trifluoroacetic anhydride (15.5 mL, 110 mmol, 20 equiv) at 0 °C under argon, and the mixture was stirred at 0 °C. After 1 h, the mixture was diluted with MeOH (44 mL), bubbled with $NH_3$ gas at 0 °C for 30 min and stirred at room temperature overnight. The mixture was poured into water, and the extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The brown residue was passed through a silica gel column (150 g, 20% AcOEt–PhH) to yield crude methylpyridine (2.5 g), which was rechromatographed with silica gel (75 g, 5 → 10 → 20% AcOEt–PhH) to afford pure methylpyridine **24** (1.97 g, 64%) as pale brown oil: $[\alpha]_D$ −31.5° (*c* 0.80, $CHCl_3$): HR-MS, *m/z* 564.3730 ($M^+$) calcd for $C_{30}H_{56}N_2O_4Si_2$ 564.3776; UV (EtOH), 268 (4.570) nm; IR (neat) 1696, 1605, 1480, 1370, 1255, 1170, 1100, 838, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ −0.10 (6 H, s), 0.00 (6 H, s), 0.77 (9 H, s), 0.83 (9 H, s), 1.41 (9 H, s), 2.46 (3 H, s), 7.01 (1 H, d, *J* = 8.1), 7.27 (1 H, dd, *J* = 1.8, 8.1), 8.21 (1 H, d, *J* = 1.8).

**Methyl (3*S*,4*S*,5*S*)-5-[1-(*tert*-Butyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-5-(methoxycarbonyl)-3-pyrrolidinyl]-2-pyridinecarboxylate (25).** A suspension of methylpyridine **24** (2.28 g, 4 mmol) and selenium dioxide (1.35 g, 12 mmol, 3 equiv) in dry pyridine (11.5 mL) was heated at 120 °C overnight. The cooled, brown mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated, and the residue was dissolved in small amount of MeOH. To this solution was added $CH_2N_2$ in ether (completion of the reaction was checked by TLC), and the solvent was evaporated. The dark brown residue was dissolved in THF (60 mL). To this solution was added 1 M *n*-$Bu_4NF$/THF (16 mL, 16 mmol, 4 equiv), and the mixture was stirred at room temperature for 30 min under argon. The mixture was poured into water and extracted with ethyl acetate (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was passed through a silica gel column (60 g, 2% MeOH–$CHCl_3$) to yield a brownish oil of diol–ester (665 mg, 43%): $[\alpha]_D$ −43.0° (*c* 1.00, $CHCl_3$); HR-MS, *m/z* 381.1938 [$(M + H)^+$] calcd for $C_{19}H_{29}N_2O_6$ 381.1978; UV (EtOH) 269 (4.900) nm; IR (neat) 3400, 1734, 1685, 1600, 1580, 1415, 1380, 1324, 1260, 1174, 1140, 1055, 1030, 763 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.49 (9 H, s), 4.00 (3 H, s), 7.56 (1 H, dd, *J* = 2.0, 8.1), 8.09 (1 H, d, *J* = 8.1), 8.54 (1 H, d, *J* = 2.0).

A solution of the diol–ester (665 mg, 1.8 mmol) and PDC (3.9 g, 10.4 mmol, 6 equiv) in dimethylformamide (13 mL) was stirred at room temperature overnight under argon. The mixture was diluted with water, acidified to pH 3 with 1 N HCl, and extracted with ethyl acetate (50 mL × 3). The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was dissolved in a small amount of MeOH, and $CH_2N_2$ in ether was added to this solution until the yellow color was developed. The solvent was removed, and the residue was purified by silica gel column chromatography (20 g, 1% acetone–$CHCl_3$) to furnish triester **25** (366 mg, 48%) as a thick oil: $[\alpha]_D$ +6.5° (*c* 0.73, $CHCl_3$); HR-MS, *m/z* 437.1905 [$(M + H)^+$] calcd for $C_{21}H_{29}N_2O_8$ 437.1921; UV (EtOH) 269 (5.130) nm; IR (neat) 1747, 1708, 1590, 1570, 1410, 1210, 1030, 763 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.38 (9 H, s), 3.55 (3 H, s), 3.72 (3 H, s), 3.94 (3 H, s), 7.47 (1 H, dd, *J* = 2.0, 8.1), 8.03 (1 H, d, *J* = 8.1), 8.42 (1 H, d, *J* = 2.0).

**Methyl (3*S*,4*S*,5*S*)-5-[1-(*tert*-Butyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-5-(methoxycarbonyl)-3-pyrrolidinyl]-2-pyridinecarboxylate 1-Oxide (26).** To a solution of triester **25** (330 mg, 0.76 mmol) in $CH_2Cl_2$ (5 mL) was added mCPBA (315 mg, 1.79 mmol, 2.4 equiv), and the mixture was stirred at room temperature overnight. A solution of $CH_2N_2$ in ether was added until the yellow color was developed, and the mixture was evaporated. The residue was purified by silica gel column chromatography (10 g, 1% MeOH–$CHCl_3$) to afford *N*-oxide **26** (264 mg, 77%) as a thick oil: $[\alpha]_D$ +16.0° (*c* 0.90, $CHCl_3$); HR-MS, *m/z* 452.1798 ($M^+$) calcd for $C_{21}H_{28}N_2O_9$ 452.1795; UV (EtOH) 274 (7.400) nm; IR (neat) 1745, 1696, 1610, 1408, 1260, 1210, 1175, 1100, 1000 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.44 (9 H, s), 3.66 (3 H, s), 3.78 (3 H, s), 3.99 (3 H, s), 6.98 (1 H, dd, *J* = 1.5, 8.1), 7.60 (1 H, d, *J* = 8.1), 8.05 (1 H, d, *J* = 1.5).

**Methyl (3*S*,4*S*,5*S*)-5-[1-(*tert*-Butyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-5-(methoxycarbonyl)-3-pyrrolidinyl]-1,6-dihydro-6-oxo-2-pyridinecarboxylate (27).** To a solution of *N*-oxide **26** (150 mg, 0.33 mmol) in dimethylformamide (1.5 mL) was added trifluoroacetic anhydride (0.47 mL, 3.3 mmol, 10 equiv) under argon, and the mixture was stirred at room temperature overnight. The excess TFAA was removed under reduced pressure, and the mixture was poured into water and extracted with benzene (20 mL × 3). The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (4.5 g, 1% MeOH–$CHCl_3$) to afford pyridone **27** (102 mg, 68%) as a thick oil: $[\alpha]_D$ −114.3° (*c* 0.74, $CHCl_3$); HR-MS, *m/z* 452.1792 ($M^+$) calcd for $C_{21}H_{28}N_2O_9$ 452.1792; UV (EtOH) 241, 321 (7.940, 16.600) nm; IR (neat) 1745, 1700, 1650, 1621, 1570, 1400, 1298, 1170, 1005, 760 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.44 (9 H, s), 3.77 (3 H, s), 3.83 (3 H, s), 3.97 (3 H, s), 6.96 (1 H, d, *J* = 7.0), 7.24 (1 H, d, *J* = 7.0).

**(3*S*,4*S*,5*S*)-5-[5-Carboxy-4-(carboxymethyl)-3-pyrrolidinyl]-1,6-dihydro-6-oxo-2-pyridinecarboxylic Acid (Acromelic Acid A, 1).** To a solution of pyridone **27** (102 mg, 0.23 mmol) in MeOH (4.2 mL) was added 1 N KOH (2.1 mL, 2.1 mmol, 9 equiv), and the mixture was left at room temperature overnight. The solvent was removed, and the residue was passed through a column of Amberlite IRC-50 ($H^+$ form, 2 × 9 cm) to yield *N*-*t*-Boc-acromelic acid A (74 mg, 80%).

The acid (74 mg) was dissolved in trifluoroacetic acid (1.5 mL), and the solution was stirred at room temperature for 30 min and then diluted with water and evaporated. The residue was subjected to a column of Amberlite IR-120B ($H^+$ form, 2 × 9 cm). The water eluate gave acromelic acid A, and the 2.5% $NH_3$(aq) eluate gave its ammonium salt. The ammonium salt was passed through a column of IRC-50 ($H^+$ form, 2 × 9 cm) to furnish the free acid. The purified acid was collected as white crystals (47 mg overall, 84%): mp >310 °C; $[\alpha]_D$ +27.8° (*c* 0.35, $H_2O$); SIMS, *m/z* 311 [$(M + H)^+$]; IR (Nujol) 3600–2400, 1725, 1705, 1650, 1620 $cm^{-1}$; UV (pH 7) 240, 313 (5.130, 9.550), (pH 2) 242, 317 (4.370, 8.910), (pH 12) 242, 313 (5.130, 9.910); CD ($H_2O$) 205 (−14.600), 245 (+4.600), 313 (+5.800) nm; $^1H$ NMR (500 MHz, $D_2O$) δ 2.23 (1 H, dd, *J* = 9.8, 17.1), 2.65 (1 H, dd, *J* = 4.9, 17.1), 3.16 (1 H, dddd, *J* = 4.9, 7.3, 7.8, 9.8), 3.67 (1 H, dd, *J* = 7.1, 12.2), 3.70 (1 H, dd, *J* = 7.3, 12.2), 3.80 (1 H, q, *J* = 7.8), 4.10 (1 H, d, *J* = 7.3), 6.92 (1 H, d, *J* = 7.3), 7.50 (1 H, d, *J* = 7.3); cellulose TLC, $R_f$ 0.21 (*n*-BuOH–AcOH–$H_2O$, 4:1:5), 0.46 (*n*-BuOH–$HCO_2H$–$H_2O$, 6:1:2), 0.19 (*i*-PrOH–$H_2O$, 3:1), 0.18 (*n*-BuOH–py–AcOH–$H_2O$, 15:10:3:12); PEP, +7.8 cm (pH 3.5, py–AcOH–$H_2O$, 1:10:190, 600 V, 1.5 h), +9.5 (pH 4.6, py–AcOH–$H_2O$, 3:3:994, 600 V, 1.5 h), 10.2 (pH 7.5, 0.05 M $(Et_3N$–$H_2CO_3$, 600 V, 1.5 h), +12.1 (pH 9.2, 0.05 M Borax, 600 V, 1.5 h).

**Allylic Alcohol 33.** To a stirred suspension of NaH (158 mg, 6.6 mmol), 1.2 equiv) in THF (35 mL) was added diethyl (carboethoxymethyl)phosphonate (1.5 g, 6.7 mmol, 1.2 equiv) in THF (15 mL) at 0 °C, and the mixture was stirred at room temperature for 15 min under argon. To the resulting clear solution was added the aldehyde **20** (3.5 g, 5.5 mmol) in THF (15 mL), and the solution was stirred at 0 °C for 30 min. The reaction was quenched with water, and then the mixture was poured into water and extracted with ether (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (100 g, 5 → 20% ether–hexane) to afford the ester (3.8 g, 98%) as inseparable mixture of diastereoisomers. The mixture was used directly for the next step.

To a solution of the ester (3.8 g, 5.4 mmol) in toluene (76 mL) was added 1.76 M DIBAH–hexane (6.8 mL, 12 mmol, 2.2 equiv) at 0 °C under argon, and the mixture was stirred at 0 °C. After 20 min, the mixture was acidified to pH 3 with 0.5 N HCl and filtered through a glass filter. The filtrate was evaporated, and the residue was subjected to silica gel column chromatography (110 g, 20 → 40% AcOEt–hexane) to afford allylic alcohol **33** (3.5 g, 99%) as a mixture of diastereoisomers.

Although the isomers were readily separable, the mixture was used directly for the next step.

**Less polar isomer** ($R_f$ 0.52, 50% ether–hexane): $[\alpha]_D$ −5.3° (*c* 0.75, $CHCl_3$); HR-MS, *m/z* 665.3894 calcd for $C_{35}H_{63}NO_5SSi_2$ 665.3962; IR (neat) 3600, 1700, 1410, 1380, 1260, 1105, 840, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 0.00 (6 H, s), 0.05 (6 H, s), 0.87 (9 H, s), 0.90 (9 H, s), 1.45 (9 H, s), 4.03 (2 H, d, *J* = 5), 5.3–5.7 (2 H, m), 7.25 (5 H, br s).

**More polar isomer** ($R_f$ 0.19, 50% ether–hexane): $[\alpha]_D$ −32.5° (*c* 0.80, $CHCl_3$); HR-MS, *m/z* 665.3985 calcd for $C_{35}H_{63}NO_5SSi$ 665.3962; IR (neat) 3560, 1705, 1410, 1380, 1160, 1100, 840, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 0.03 (12 H, s), 0.86 (18 H, s), 1.43 (9 H, s), 3.95 (2 H, d, *J* = 5), 5.3–5.7 (2 H, m), 7.2 (5 H, br s).

**Unsaturated Aldehyde 34.** To a solution of the allylic alcohol **33** (3.5 g, 5.3 mmol) in 1:4 $H_2O$–MeOH (35 mL–140 mL) was added $Na_2HPO_4$ (3.6 g, 25.3 mmol, 4.8 equiv) and $NaIO_4$ (5.4 g, 25.3 mmol, 4.8 equiv). The mixture was stirred at 40 °C for 1 h, diluted with water, and filtered. The filtrate was extracted with ethyl acetate (200 mL × 3), and the combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to afford the sulfoxide (3.5 g, 98%).

To a solution of the sulfoxide (3.5 g, 5.16 mmol) in $CH_2Cl_2$ (84 mL) was added successively pyridine (21 mL, 258 mmol, 50 equiv) and trifluoroacetic anhydride (14.5 mL, 103 mmol, 20 equiv) at 0 °C under argon, and the mixture was stirred at 0 °C for 10 min and then at room temperature for 20 min. To the solution was added 1.5 M $Na_2CO_3$ (69 mL, 103 mmol, 20 equiv) at 0 °C, and the mixture was stirred at 0 °C for 10 min and then at room temperature for 1 h. The mixture was poured into water and extracted with ethyl acetate (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was passed through a silica gel column (100 g, hexane–AcOEt) to eliminate thiophenol (or diphenyl disulfide).

The resulting colorless oil was dissolved in acetonitrile (110 mL), and to the solution was added successively triethylamine (10.8 mL, 77.4 mmol, 15 equiv to **33**) and methanesulfonyl chloride (2 mL, 25.8 mmol, 5 equiv to **33**) at 0 °C under argon. The mixture was stirred at 0 °C for 20 min and then poured into water and extracted with ether (200 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (100 g, 10 → 20% ether–hexane) to afford a colorless oil containing unsaturated aldehyde **34** and its 1,6-adduct of thiophenol (5:1). The mixture was used directly for the next step: $^1H$ NMR (90 MHz, $CDCl_3$, as a mixture of geometrical isomers) δ 0.00 (6 H, s), 0.07 (6 H, s), 0.86 (9 H, s), 0.90 (9 H, s), 1.47 (9 H, s), 5.4–5.9 (2 H, m), 6.5–7.0 (2 H, m), 9.43 (1 H, s).

**Keto Sulfide 35.** To the solution of the above mixture in dimethylformamide (86 mL) was added triethylamine (0.86 mL, 6.2 mmol, 1.2 equiv to **33**) and thiophenol (0.27 mL, 2.6 mmol, 0.5 equiv to **33**) at 0 °C under argon. To the stirred mixture was added dropwise a 0.1 M PhSH–DMF solution at 0 °C, and the reaction was monitored by TLC at each drop. After the completion of the reaction, the mixture was poured into water and extracted with ether (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (100 g, 20% ether–hexane) to afford the 1,6-adduct (1.67 g, 48% overall yield from **33**) as inseparable mixture of geometrical isomers: $[\alpha]_D$ −24.0° (*c* 0.95, $CHCl_3$); EI-MS, *m/z* 663 ($M^+$); IR (neat) 1710, 1600, 1400, 1260, 835, 775, 740 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 0.01 (6 H, s), 0.04 (6 H, s), 0.86 (9 H, s), 0.89 (9 H, s), 1.47 (9 H, s), 6.20 and 6.50 (1 H, t, *J* = 7), 7.30 (5 H, br s), 9.39 and 9.96 (1 H, each s).

To a solution of the 1,6-adduct (1.67 g, 2.5 mmol) in dry THF (17 mL) at −15 °C under argon was added 1.4 M MeLi–ether (3.6 mL, 5 mmol, 2 equiv), and the mixture was stirred at −15 °C for 30 min. The reaction was quenched with $NH_4Cl$(aq), and then the mixture was poured into water and extracted with ether (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to yield allylic alcohol (1.47 g, 87%) as a mixture of diastereomeric and geometrical isomers.

To a solution of the allylic alcohol (1.47 g, 2.2 mmol) in dimethylformamide (15 mL) was added PDC (1.65 g, 4.4 mmol, 2 equiv), and the mixture was stirred at room temperature overnight under argon. The mixture was poured into water and extracted with ether (100 mL × 3). The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated to give keto sulfide **35** (1.23 g, 83%) as a mixture of geometrical isomers. Although the isomers were readily separable, the mixture was used directly for the next step.

**(3*S*,4*S*,5*S*)-3-[1-(*tert*-Butyloxycarbonyl)-4-[2-[(*tert*-butyldimethylsilyl)oxy]ethyl]-5-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-pyrrolidinyl]-2-methylpyridine (36).** To a solution of keto sulfide **35** (1.23 g, 1.8 mmol) in 1:4 $H_2O$–MeOH (12 mL–48 mL) was added $Na_2HPO_4$ (1.22 g, 8.6 mmol, 4.8 equiv) and $NaIO_4$ (1.84 g, 8.6 mmol, 4.8 equiv), and the mixture was stirred at 40 °C for 1 h. The mixture was filtered, and then the filtrate was poured into water and extracted with ethyl acetate (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated to afford the sulfoxide as syrup.

To a solution of the sulfoxide in $CH_2Cl_2$ (30 mL) was added dry pyridine (7.3 mL, 90 mmol, 50 equiv) and trifluoroacetic anhydride (5.1 mL, 36 mmol, 20 equiv) at 0 °C under argon, and the mixture was stirred at 0 °C. After 20 min, 25% $NH_3$(aq) (30 mL) was added, and the mixture was stirred at room temperature overnight. The mixture was poured into water and extracted with ethyl acetate (100 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (40 g, 10% AcOEt–hexane) to afford methylpyridine **36** (470 mg, 46%) as a thick oil: $[\alpha]_D$ −53.5° (*c* 0.65, $CHCl_3$); HR-MS, *m/z* 565.3842 [(M + H)$^+$] calcd for $C_{30}H_{57}N_2O_4Si_2$ 565.3854; UV (EtOH) 264 (3.910) nm; IR (neat) 1704, 1580, 1405, 1260, 1100, 840, 780 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ −0.06 (6 H, s), 0.08 (6 H, s), 0.83 (9 H, s), 0.92 (9 H, s), 1.48 (9 H, s), 2.56 (3 H, s), 7.02 (1 H, dd, *J* = 5, 8), 7.36 (1 H, dd, *J* = 1, 8), 8.33 (1 H, d, *J* = 1, 5).

**Methyl (3*S*,4*S*,5*S*)-3-[1-(*tert*-Butyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-5-(methoxycarbonyl)-3-pyrrolidinyl]-2-pyridinecarboxylate (37).** A suspension of methylpyridine **36** (282 mg, 0.5 mmol) and selenium dioxide (333 mg, 3 mmol, 6 equiv) in dry pyridine (2.8 mL) was heated at 100 °C overnight. The cooled, brown mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated, and the residue was dissolved in small amount of MeOH. To this solution was added a solution of $CH_2N_2$ in ether (completion of the reaction was checked by TLC). The mixture was evaporated, and the dark brown residue was dissolved in MeOH (5.6 mL). To the solution was added *p*-toluenesulfonic acid (190 mg, 1 mmol, 2 equiv), and the mixture was left at room temperature for 30 min. The reaction was quenched with $Na_2CO_3$ solution, and then the mixture was poured into water and extracted with ethyl acetate (25 mL × 3). The combined extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was passed through a silica gel column (9 g, 2% MeOH–$CHCl_3$) to yield a brownish oil of diol–ester (99 mg, 52%).

A solution of the diol–ester (99 mg, 0.26 mmol) and PDC (980 mg, 2.6 mmol, 10 equiv) in dimethylformamide (10 mL) was stirred at 40 °C overnight under argon. A solution of $CH_2N_2$ in ether was added (completion of the reaction was checked by TLC), and then the mixture was poured into $Na_2CO_3$ solution and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified with silica gel column chromatography (83 g, 1% acetone–$CHCl_3$) to furnish triester **37** (55 mg, 48%) as a thick oil: $[\alpha]_D$ −35.5° (*c* 0.85, $CHCl_3$); HR-MS, *m/z* 436.1845 ($M^+$) calcd for $C_{21}H_{28}N_2O_8$ 436.1845; UV (EtOH) 268 (2.400) nm; IR (neat) 1760, 1715, 1408, 1375, 1305, 1205, 1175, 1135 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.46 (9 H, s), 3.56 (3 H, s), 3.80 (3 H, s), 3.97 (3 H, s), 7.40 (1 H, dd, *J* = 5, 8), 7.61 (1 H, dd, *J* = 1.5, 8), 8.61 (1 H, dd, *J* = 1.5, 5).

**Methyl (3*S*,4*S*,5*S*)-3-[1-(*tert*-Butyloxycarbonyl)-4-[(methoxycarbonyl)methyl]-5-(methoxycarbonyl)-3-pyrrolidinyl]-1,6-dihydro-6-oxo-2-pyridinecarboxylate (38).** To a solution of triester **37** (55 mg, 0.15 mmol) in $CH_2Cl_2$ (1 mL) was added mCPBA (60 mg, 0.35 mmol, 2.4 equiv), and the mixture was stirred at room temperature overnight. A solution of $CH_2N_2$ in ether was added until the yellow color was developed, and the mixture was evaporated. The residue was purified with silica gel column chromatography (150 g, 1% MeOH–$CHCl_3$) to afford the *N*-oxide (43 mg, 75%) as a thick oil: $[\alpha]_D$ −32.8° (*c* 0.50, $CHCl_3$); HR-MS, *m/z* 452.1771 ($M^+$) calcd for $C_{21}H_{28}N_2O_9$ 452.1794; UV (EtOH) 272 (9.010) nm; IR (neat) 1760, 1715, 1443, 1410, 1295, 1130 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.45 (9 H, s), 3.64 (3 H, s), 3.77 (3 H, s), 4.00 (3 H, s), 7.00 (1 H, dd, *J* = 0.4, 8), 7.27 (1 H, dd, *J* = 6, 8), 8.16 (1 H, dd, *J* = 0.4, 6).

To a solution of the *N*-oxide (43 mg, 0.1 mmol) in dimethylformamide (0.45 mL) was added trifluoroacetic anhydride (0.15 mL, 1 mmol, 10 equiv) under argon, and the mixture was stirred at room temperature overnight. The excess TFAA was removed under reduced pressure, and the mixture was poured into water and extracted with benzene (10 mL × 3). The combined extracts were washed twice with brine, dried over anhydrous sodium sulfate, and evaporated. The residue was purified with silica gel column chromatography (150 mg, 1% MeOH–$CHCl_3$) to afford pyridone **38** (26 mg, 62%) as a thick oil: $[\alpha]_D$ −28.0° (*c* 0.15, $CHCl_3$); HR-MS, *m/z* 452.1788 ($M^+$) calcd for $C_{21}H_{28}N_2O_9$ 452.1794; UV (EtOH) 317 (2.600) nm; $^1H$ NMR (90 MHz, $CDCl_3$) δ 1.47 (9 H, s), 3.58 (3 H, s), 3.78 (3 H, s), 3.94 (3 H, s), 6.75 (1 H, d, *J* = 10), 7.28 (1 H, d, *J* = 10).

**(3S,4S,5S)-3-[5-Carboxy-4-(carboxymethyl)-3-pyrrolidinyl]-1,6-dihydro-6-oxo-2-pyridinecarboxylic Acid (Acromelic Acid B, 2).** To a solution of pyridone **38** (26 mg, 0.06 mmol) in MeOH (1.1 mL) was added 1 N KOH (0.54 mg, 0.54 mmol, 9 equiv), and the mixture was left at room temperature overnight. The solvent was removed, the residue was dissolved in trifluoroacetic acid (0.5 mL), and the mixture was stirred at room temperature. After 30 min, the mixture was diluted with water and evaporated. The residue was purified with PEP (20 × 46 cm, 10 sheets, +9 cm at pH 4.6, py-AcOH-$H_2O$, 3:3:996, 600 V, 2 h) to afford acromelic acid B (13 mg, 73%) as amorphous powder: $[\alpha]_D$ 50.1° (*c* 0.45, $H_2O$); SIMS, *m/z* 311 $(M + H)^+$; UV (pH 7) 239 (5.150) and 311 (3.250), (pH 2) 241 (4.650) and 312 (2.960), (pH 12) 236 (6.320), and 302 (2.920) nm; FT-IR 3165-3045, 1715, 1695, 1620 $cm^{-1}$; CD ($H_2O$) 225 (+3.500) nm; $^1H$ NMR (500 MHz, $D_2O$) δ 2.22 (2 H, d, *J* = 7.3), 3.15 (1 H, ddt, *J* = 3.4 8.3, 7.3), 3.66 (1 H, t, *J* = 11.7), 3.76 (1 H, dd, *J* = 8.3, 11.7), 4.14 (1 H, d, *J* = 3.4), 4.47 (1 H, dt, *J* = 11.7, 8.3), 6.67 (1 H, d, *J* = 9.3), 7.67 (1 H, d, *J* = 9.3); cellulose TLC $R_f$ 0.16 (*n*-BuOH-AcOH-$H_2O$, 4:1:5), 0.25 (*n*-BuOH-$HCO_2H$-$H_2O$, 6:1:2), 0.07 (*i*-PrOH-$H_2O$, 3:1), 0.21 (*n*-BuOH-py-AcOH-$H_2O$, 15:10:3:12); PEP, +7.7 cm (pH 3.5, py-AcOH-$H_2O$, 1:10:190, 600 V, 2 h), +8.2 (pH 4.6, py-AcOH-$H_2O$, 3:3:994, 600 V, 2 h), +8.8 (pH 6.5, py-AcOH-$H_2O$, 100:4:900, 600 V, 2 h), +11.3 (pH 9.2, 0.05 M Borax, 600 V, 2 h).

# A New Route to the Prostaglandin Skeleton via Radical Alkylation. Synthesis of 6-Oxoprostaglandin $E_1$†

**Takeshi Toru,* Yoshio Yamada, Toshio Ueno, Eturô Maekawa, and Yoshio Ueno**

*Contribution from the Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466, Japan.* *Received February 8, 1988. Revised Manuscript Received May 4, 1988*

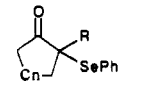
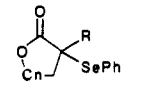
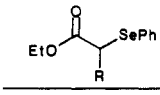
**Abstract:** A new, mild, and efficient method for the construction of the prostanoid skeleton involving cuprate addition to α-(phenylseleno)cyclopentenones followed by radical-based coupling to the resulting products with allylstannane derivatives is described. The method is applied to the synthesis of 6-oxoprostaglandin $E_1$, a biologically active and naturally occurring compound.

A large number of strategies toward prostaglandins (PGs) have been reported[1] since the first pioneering syntheses of these molecules were developed by the Corey[2a] and Upjohn groups.[2b] Among these methods, that starting with a protected 4-hydroxy-2-cyclopenten-1-one should be noted as one of the most efficient approaches to the PG skeleton.[3] We have been interested in finding an effective way to PGs via a free-radical chain process, which is attractive due to its characteristic mode of reaction.[4] Heretofore, a few methods involving a radical process have appeared; Stork[5a] and Keck[5b] with their collaborators have reported intramolecular radical cyclization reactions to give PG intermediates. We now report (1) a radical-based allylation of several α-phenylseleno carbonyl compounds, (2) a new synthesis of 6-methyleneprostaglandin $E_1$ (6-methylene-$PGE_1$) via a free-radical alkylation of a β-substituted α-(phenylseleno)cyclopentanone, readily obtainable from the cyclopentenone, and (3) the transformation of 6-methylene-$PGE_1$ methyl ester to 6-oxoprostaglandin $E_1$ (6-oxo-$PGE_1$), a biologically and pharmacologically important prostanoid.[6]

The electrophilic alkylation of α-carbanions of α-phenylseleno carbonyl compounds followed by deselenenylation is a widely used method for the synthesis of naturally occurring compounds.[7] Construction of the PG skeleton along these lines appears unattractive due to the base-labile nature[8] of the β-alkoxycarbonyl moiety of the cyclopentanone framework. A free-radical pathway, however, which can be carried out under neutral conditions may be the method of choice for the direct alkylation to a carbonyl group.

We first studied the photolytic allylation of α-phenylseleno carbonyl compounds with allyltributylstannane.[9] Several representative results are summarized in Table I. Allylated products were obtained in high yields from primary, secondary, or tertiary selenides. On the basis of these results we next applied this radical-based allylation to base-labile and sterically hindered, seleno-substituted β-(silyloxy)cyclopentanones, aiming at a new synthesis of the PG skeleton.

**Table I.** Photoinitiated Allylation of α-Phenylseleno Carbonyl Compounds with Allyltributylstannane[a]

| selenide | R | *n* | reaction time, h | allylated product,[b] % |
|---|---|---|---|---|
|  | H | 1 | 1 | 80 |
| | H | 2 | 1.5 | 81 |
| | H | 3 | 1.5 | 79 |
| | Me | 1 | 4.5 | 63 |
|  | H | 1 | 1 | 90[c] |
| | H | 2 | 1 | 81 |
| | H | 3 | 3 | 76 |
| | Me | 1 | 2.5 | 64 |
|  | H | | 1 | 74 |
| | Me | | 1 | 79 |

[a] Two equivalents of allyltributylstannane/1 equiv of substrate/degassed benzene solution (1 mL/mmol of substrate). [b] Isolated yields. [c] Irradiation (1 h) with 1.3 equiv of allyltributylstannane also afforded the allylated product in high yield (90%).

† This paper is dedicated to Professor E. J. Corey on the occasion of his 60th birthday.

(1) For recent review of PG syntheses, see: (a) Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*; Academic: New York, 1982. (b) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847. (c) Taylor, R. J. K. *Synthesis* **1985**, 364. (d) Pike, J. E.; Morton, D. R. *Chemistry of Prostaglandins and Leukotrienes*; Raven: New York, 1985.

(2) (a) Corey, E. J.; Andersen, N. H.; Carlson, R. M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R. E. K. *J. Am. Chem. Soc.* **1968**, *90*, 3245. (b) Corey, E. J.; Vlattas, I.; Andersen, N. H.; Harding, K. *Ibid.* **1968**, *90*, 3247. (c) Schneider, W. P.; Axen, U.; Lincoln, F. H.; Pike, J. E.; Thompson, J. L. *Ibid.* **1968**, *90*, 5895.

(3) For the synthesis of prostaglandins via the three-component coupling process, see: (a) Suzuki, M.; Yanagisawa, A.; Noyori, R. *J. Am. Chem. Soc.* **1985**, *107*, 3348. (b) Johnson, C. R.; Penning, T. D. *Ibid.* **1986**, *108*, 5655. (c) Corey, E. J.; Niimura, K.; Konishi, Y.; Hashimoto, S.; Hamada, Y. *Tetrahedron Lett.* **1986**, *27*, 2199. See also ref 1 for trapping enolates by acid chlorides, aldehydes, a ketone dithioacetal, or an α-nitro olefin.

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