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The first stereoselective total synthesis of antiviral antibiotic, xanthocillin X dimethylether and its stereoisomer

Kuniaki Tatsuta* and Takahiro Yamaguchi

Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

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Abstract—Xanthocillin X dimethylether (**1**) has been stereoselectively synthesized from the propiolic acid **6** through an oxidative rearrangement of the stannyl vinyl amide **27** to give the vinyl isocyanate **30** and a homocoupling of the stannyl *N*-formylenamine **31**.

Xanthocillin X dimethylether (**1**) and mono-methylether, which showed antiviral activity against Newcastle disease virus, vaccinia and herpes simplex viruses, were produced by *Aspergillus* sp. and determined spectrometrically to be the derivatives of 1,4-bis-(4-hydroxyphenyl)-2,3-diisonitrilo-1,3-butadiene.[1,2] The configuration of **1** was deduced from the structure of xanthocillin X (**2**), which was confirmed by X-ray crystallographic analysis.[3] Further investigation has been hampered by the scarcity and instability of such natural products, although the synthesis of **1** was reported in 1962 before isolation of the natural product without any detailed experimental data and references to the stereochemistry.[4]

Needless to say, the challenge of creating the vinyl isonitrile structure in the laboratory added to the attractiveness of the project.[5–7]

Herein, we describe the first stereoselective total synthesis of xanthocillin X dimethylether (**1**) to demonstrate the utility and the versatility of our method.

Figure 1 illustrates two possible routes to **1** by our retrosynthetic analysis.

Route 1 is based on a cross-coupling reaction of the vinyl bromide **4** and the vinylstannane **5** followed by

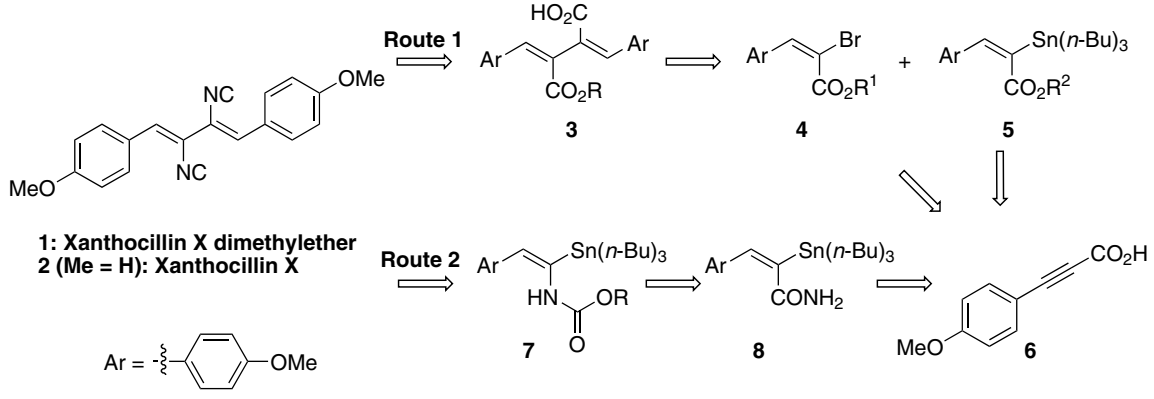

Figure 1.

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* Corresponding author. Tel./fax: +81 3 3200 3203; e-mail: tatsuta@waseda.jp

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step-wise Curtius rearrangements of the mono-carboxylic acid **3**. On the other hand, Route 2 is based on a homo-coupling of the stannyl enamine derivative **7**, which is prepared from the stannyl vinyl amide **8** by oxidative rearrangement. Namely, the key point of the routes depends on the rearrangements before or after coupling of the properly constructed vinyl derivatives, which could be derived from the common propiolic acid **6**.

First of all, the synthesis was carried out according to Route 1 (Scheme 1).

The (*E*)-vinyl bromide **12** and (*E*)-vinylstannane **13** were prepared from anisaldehyde according to the modified procedures of the Tanabe Seiyaku group[8] as follows. The propiolic acid **6**[9] was obtained from anisaldehyde by treatment with PPh_3 and CBr_4 to give the dibromo-olefin followed by carboxylation of the lithiated compound.[8] The carboxylic acid **6** was converted into two esters **9** and **10** by treatment with MOM-Cl and trimethylsilylethanol, respectively. Hydrostannation of **9** and **10** gave the (*E*)-vinylstannanes **11** and **13**, respectively, the former of which was brominated to the (*E*)-vinyl bromide **12**. The configurations of **11** and **13** were confirmed by the NMR studies, especially their coupling constants between the vinyl proton and the Sn atom ($J_{H,Sn}$ = 29.6 and 30.4 Hz) in comparison with those of the (*Z*)-isomers **21** and **23** ($J_{H,Sn}$ = 51.2 and 52.8 Hz) according to the experimental rule.[11]

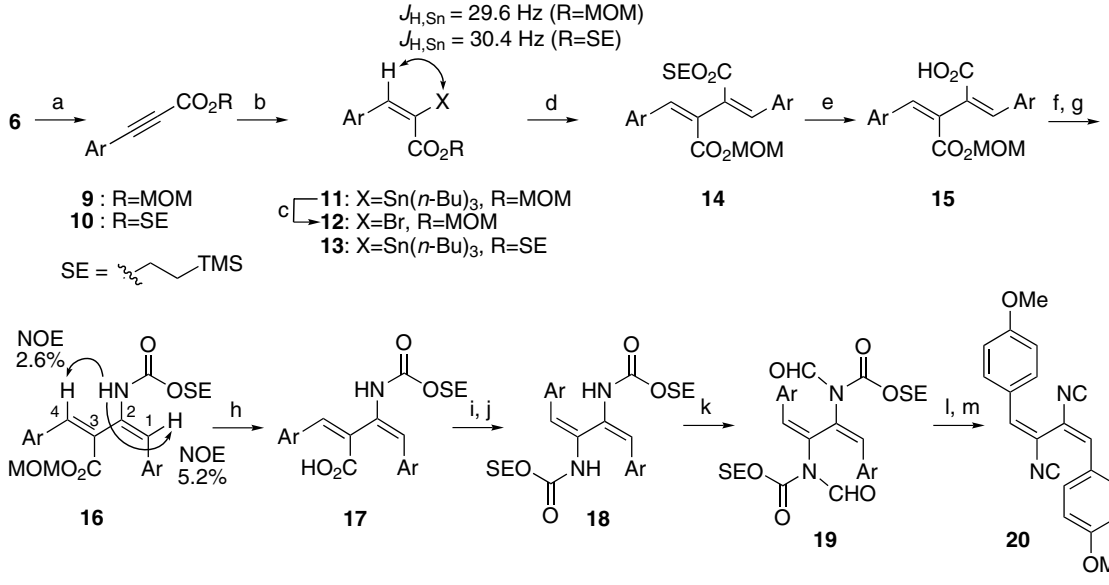
Coupling of both segments **12** and **13** with $Pd(PPh_3)_2Cl_2$ and CuI gave the (*Z*,*Z*)-diene **14**, which was selectively and quantitatively deprotected to the mono-carboxylic acid **15**. This was submitted to Curtius rearrangement[12,13] by reaction with diphenylphosphoryl azide (DPPA) and NaH to give the isocyanate followed by trapping with TMS ethanol to yield the *N*-Teoc-enamine **16**. However, the NOE studies between NH and H-1 revealed **16** to be the (*E*,*Z*)-isomer, showing that unexpected isomerization occurred during the rearrangement.

The carbamate **16** was further converted to the other mono-carboxylic acid **17**. The Curtius rearrangement was conducted under the aforesaid conditions to give the (*E*,*E*)-diene **18**, the NMR spectrum of which showed the simple signal pattern due to the symmetrical structure. *N*-Formylation of **18** with acetic formic anhydride to give **19** was successively followed by deprotection and dehydration to give the very labile diisonitrile **20**. This corresponded to the (*E*,*E*)-isomer of the natural product **1**.

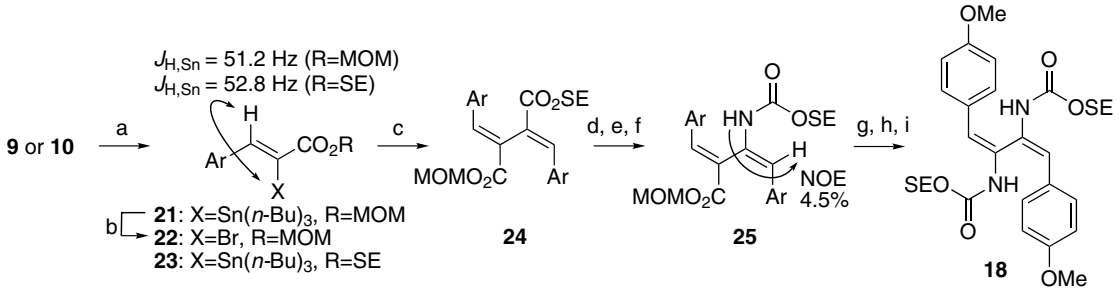
Also, the (*E*,*E*)-isomer **20** was synthesized from the (*Z*)-isomers **22** and **23** (Scheme 2).

Radical hydrostannation of **9** and **10** gave the (*Z*)-vinylstannanes **21** and **23**, the former of which was converted to the (*Z*)-vinyl bromide **22**. Coupling of **22** and **23** under the aforementioned Pd-catalyzed conditions provided the (*E*,*E*)-diene **24**, which was transformed to **18** in six steps through **25** without isomerization under similar conditions as shown in the synthesis of **18** from **14**.

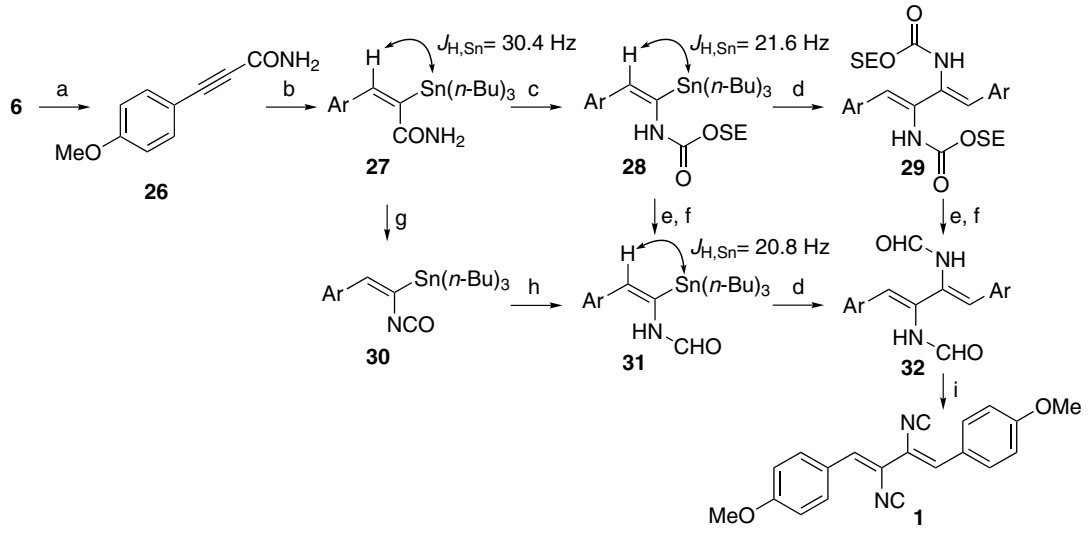
These findings showed that the Curtius rearrangements using DPPA gave stereochemically more stable (*E*)-carbamates **16** and **25** than the corresponding (*Z*)-isomers. Thereby, before coupling of two segments, a proper rearrangement was reasonably required for the construction of the (*Z*)-enamine structures.



Scheme 1. Reagents and conditions: (a) MOM-Cl, *i*-Pr_2NEt, CH_2Cl_2, 0 °C to rt, 4 h, 98% or $TMS(CH_2)_2OH$, DCC, DMAP, CH_2Cl_2, −20 °C to rt, 12 h, 96%; (b) *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, 0 °C, 0.5 h, **11**: 82%, **13**: 85%; (c) Br_2, CH_2Cl_2, 0 °C, 0.5 h, 97%; (d) $Pd(PPh_3)_2Cl_2$, CuI, DMF, 60 °C, 6 h, 54%; (e) TBAF, THF, rt, 7 h, quant.; (f) DPPA, NaH, DMF, 0 °C to rt, 3 h, 63%; (g) $TMS(CH_2)_2OH$, Py., THF, 60 °C, 12 h, 62%; (h) $MgBr_2{\cdot}OEt_2$, Et_2O, rt, 5 h, 70%; (i) DPPA, NaH, DMF, 0 °C to rt, 2 h, 50%; (j) $TMS(CH_2)_2OH$, Py., THF, 60 °C, 12 h, 50%; (k) LHMDS, HMPA, acetic formic anhydride, THF, −78 °C, 2 h, 32%; (l) TBAF, THF, 0 to rt, 6 h, 29%; (m) $POCl_3$, Py., 0 °C, 0.5 h, 72%.



Scheme 2. Reagents and conditions: (a) *n*-Bu_3SnH, AIBN, PhH, rt, 5 h, **21**: 75%, **23**: 67%; (b) Br_2, CH_2Cl_2, 0 °C, 2 h, 91%; (c) $Pd(PPh_3)_2Cl_2$, CuI, DMF, 70 °C, 4 h, 69%; (d) TBAF, THF, rt, 18 h, quant.; (e) DPPA, NaH, DMF, 0 °C to rt, 2 h, 89%; (f) $TMS(CH_2)_2OH$, Py., THF, 60 °C, 12 h, 78%; (g) $MgBr_2{\cdot}OEt_2$, Et_2O, rt, 5 h, quant.; (h) DPPA, NaH, DMF, 0 °C to rt, 2 h, 32%; (i) $TMS(CH_2)_2OH$, Py., THF, 60 °C, 12 h, 42%.



Scheme 3. Reagents and conditions: (a) $ClCO_2Et$, Et_3N, THF; aq NH_3, 0 °C, 1 h, 95%; (b) *n*-Bu_3SnH, $Pd(PPh_3)_4$, THF, 0 °C, 0.5 h, 68%; (c) $Pb(OAc)_4$, $TMS(CH_2)_2OH$, DMF, 0 °C to 50 °C, 8 h, 67%; (d) $Pd(OAc)_2$, $CuCl_2$, THF, 0 °C, 0.5 h, **29**: 41%, **32**: 62%; (e) LHMDS, HMPA, acetic formic anhydride, THF, −78 °C, 2 h; (f) TBAF, THF, 0 °C to rt, 2 h, **31**: 66% (in two steps), **32**: 33% (in two steps); (g) $Pb(OAc)_4$, THF, rt, 0.5 h, 88%; (h) $LiEt_3BH$, THF, −78 to −30 °C, 2 h, 70%; (i) $POCl_3$, Py., 0 °C, 1 h, 59%.

The Route 2 was examined in practice as follows (Scheme 3).

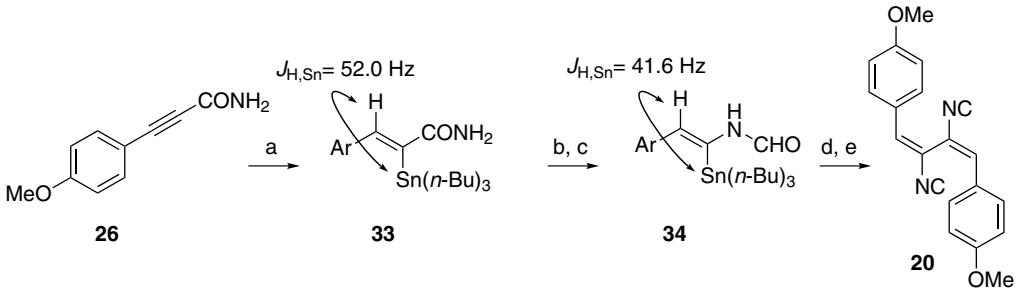
The mixed anhydride of **6** was treated with ammonia to give the amide **26**, which was converted to the (*E*)-vinylstannane **27**. The configurations of **27** and **31** were also supported by their coupling constants[11] ($J_{H,Sn}$ = 30.4 and 20.8 Hz) in comparison with those of (*Z*)-isomers **33** and **34** ($J_{H,Sn}$ = 52.0 and 41.6 Hz). After some experimentation, a remarkable procedure for converting **27** into **28** was discovered. The Baumgarten oxidative rearrangement[14] of **27** with $Pb(OAc)_4$ and TMS ethanol stereoselectively gave the carbamoyl (*E*)-vinylstannane **28**, the configuration of which was also determined by the magnitude of the coupling constant $J_{H,Sn}$. Compound **28** was submitted to Pd-catalyzed homocoupling[15] to give the symmetrical (*Z*,*Z*)-diene **29** (mp 140 °C). Finally, the (*Z*,*Z*)-configuration was verified by X-ray crystallographic analysis to show the reactions to proceed from **27** to **29** with retention of the configurations.[16] Compound **29** was formylated to the diformimide, followed by deprotection to **32**. This showed a complex NMR signal pattern due to the rotational hindrance of its *N*-formyl groups, while **29** showed a simple pattern as expected from the symmetrical structure.

Alternatively, the intermediate **28** was first formylated and deprotected to the stannyl *N*-formylenamine **31**. This was converted to the (*Z*,*Z*)-diene **32** by homocoupling with $Pd(OAc)_2$ and $CuCl_2$.

The shorter processes from **27** to **31** were tested under various conditions, and the best result was realized by oxidative rearrangement of **27** to give the isocyanate **30**. This was isolated to be reduced by $LiEt_3BH$ to the *N*-formamide **31**.[12]

In the final stage, dehydration of **32** with $POCl_3$ in pyridine smoothly proceeded to afford the (*Z*,*Z*)-diisonitrile **1**, which was fairly stable even in the solid states.

The IR and ^1H NMR spectra of the synthetic isonitrile **1** were identical with the reported data[17] of the natural



Scheme 4. Reagents and conditions: (a) n-Bu_3SnH, AIBN, THF, 0 °C, 3.5 h, 63%; (b) $Pb(OAc)_4$, THF, rt, 0.5 h, 90%; (c) $LiEt_3BH$, THF, −78 °C, 2 h, 79%; (d) $Pd(OAc)_2$, $CuCl_2$, THF, 0 °C, 0.5 h, 66%; (e) $POCl_3$, Py., 0 °C, 0.5 h, 72%.

xanthocillin X dimethylether, completing the stereoselective total synthesis of the natural product **1** to confirm its absolute structure.

As the present synthesis through **30** and **31** proved to be quite effective, a similar process was applied to the synthesis of the unnatural product **20** (Scheme 4).

Radical hydrostannation of the amide **26** gave the (*Z*)-isomer **33**, which was led to the *N*-formamide **34** with retention of the configuration. Homocoupling of **34** followed by dehydration afforded the unnatural **20**[18] as expected.

Now that the utility of this unique methodology for synthesis of the vinyl isonitrile derivatives has been illustrated, its application for the construction of other related substances is an exciting prospect.

Acknowledgements

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References and notes

1. Takatsuki, A.; Suzuki, S.; Ando, K.; Tamura, G.; Arima, K. *J. Antibiot.* **1968**, *56*, 671.
2. Takatsuki, A.; Tamura, G.; Arima, K. *J. Antibiot.* **1968**, *56*, 676.
3. Gleason, W. B.; Glick, M. *Cryst. Struct. Commun.* **1981**, *10*, 1497.
4. Hagedorn, I.; Eholzer, U. *Angew. Chem.* **1962**, *74*, 215.
5. Isshiki, K.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Tatsuta, K. *J. Antibiot.* **1987**, *40*, 1199.
6. Isshiki, K.; Takahashi, Y.; Sawa, T.; Naganawa, H.; Takeuchi, T.; Umezawa, H.; Tatsuta, K. *J. Antibiot.* **1987**, *40*, 1202.
7. Isshiki, K.; Imoto, M.; Sawa, T.; Umezawa, K.; Takeuchi, T.; Umezawa, H.; Tsuchida, T.; Yoshioka, T.; Tatsuta, K. *J. Antibiot.* **1987**, *40*, 1209.
8. Sai, H.; Ogiku, T.; Nishitani, T.; Hiramatsu, H.; Horikawa, H.; Iwasaki, T. *Synthesis* **1995**, 582.
9. All compounds were purified by silica-gel column chromatography and/or recrystallization, and were fully characterized by spectroscopic means. ^{1}H NMR spectra (300, 400 MHz, δ; TMS = 0) were in $CDCl_3$ solution, unless otherwise stated. Significant ^{1}H NMR spectral data of **1**, **20** and other compounds (only vinyl protons) are the following. Compound **1**: 7.79 (4H, d, J = 8.8 Hz), 7.02 (2H, s), 6.99 (4H, d, J = 8.8 Hz), 3.88 (6H, s). Compound **11**: 6.66 (1H, s). Compound **12**: 7.34 (1H, s). Compound **13**: 6.61 (1H, s). Compound **14**: 6.82 (1H, s), 6.79 (1H, s). Compound **16**: 6.92 (2H, br s). Compound **16** (in C_6D_6): 7.37 (1H, br s), 6.89 (1H, s). **18**: 7.00 (2H, br s). Compound **19**: 6.46 (2H, s). Compound **20**: 7.34 (4H, d, J = 8.8 Hz), 6.99 (2H, s), 6.85 (4H, d, J = 8.8 Hz), 3.81 (6H, s). Compound **21**: 8.38 (1H, s). Compound **22**: 8.23 (1H, s). Compound **23**: 8.30 (1H, s). Compound **24**: 7.92 (1H, s), 7.88 (1H, s). Compound **25**: 7.79 (1H, s), 7.12 (1H, br s). Compound **27**: 6.58 (1H, s). Compound **28**: 5.69 (1H, s). Compound **29**: 6.43 (2H, s). Compound **30**: 5.89 (1H, s). Compound **31**: 5.92 (1H, s, major),[10] 5.75 (1H, s, minor). Compound **33**: 7.33 (1H, s). Compound **34**: 7.04 (1H, s, major),[10] 6.99 (1H, s, minor).
10. Compounds **31** and **34** are mixture due to the rotational hindrance of their *N*-formyl groups.
11. Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285.
12. Kuramochi, K.; Osada, Y.; Kitahara, T. *Chem. Lett.* **2002**, 128.
13. Chenera, B.; Chuang, C. P.; Hart, D. J.; Lai, C. S. *J. Org. Chem.* **1992**, *57*, 2018.
14. Baumgarten, H. E.; Smith, H. L.; Staklis, A. *J. Org. Chem.* **1975**, *40*, 3554.
15. Parrish, J. P.; Flanders, V. L.; Floyd, R. J.; Jung, K. W. *Tetrahedron Lett.* **2001**, *42*, 7729.
16. The X-ray data of **29** has been deposited with CCDC (CCDC 267408).
17. Morino, T.; Nishimoto, M.; Itou, N.; Nishikiori, T. *J. Antibiot.* **1994**, *47*, 1546.
18. Biological activities of **1** and **20** including SAR studies will be published elsewhere.