# Total Synthesis of Natural Products of Microbial Origins(Recent Topics of the Agricultunal Biological Science in Tohoku University)

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# Total Synthesis of Natural Products of Microbial Origins

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## Summary

Microorganisms are an important rich source of secondary metabolites, which could be useful leads to valuable agrochemicals and/or medicinal drugs. This mini-review describes our recent achievements on the total synthesis of biologically active natural products of microbial origins: pteridic acids A and B (strong plant growth promoters), epoxyquinols A and B (anti-angiogenic compounds), communiols A-F, G, and H, and macrotetrolide $\alpha$ (antibiotics), pyricuol and tabtoxinine-$\beta$-lactam (phytotoxins).

## 1. Pteridic Acids A and B

Pteridic acids A (**1**) and B (**2**), isolated from the phytoepiphytic actinomycete *Streptomyces hygroscopicus* TP-A0451, show potent plant growth promoting activity comparable to that of indole-3-acetic acid (Igarashi *et al.*, 2002). Our first enantioselective total synthesis of **1** and **2** is shown in Scheme 1 (Nakahata and Kuwahara, 2005; Nakahata *et al.*, 2006). The aldehyde **4** derived from Evans' oxazolidinone **3** and the acetylene **5** prepared via Fráter's alkylation were coupled to give alcohol **6**. Oxidation of the hydroxy group followed by acidic treatment afforded spiroketal **7** as a single diastereomer. Pteridic acid A (**1**) was finally prepared by the side chain elongation using Horner-Emmons olefination. Treatment of the methyl ester of **1** with $MgBr_2$ resulted in epimerization at the 11-position, and the resulting epimer led to pteridic acid B (**2**). The overall yield of **1** is 22% (14 steps from **3**).

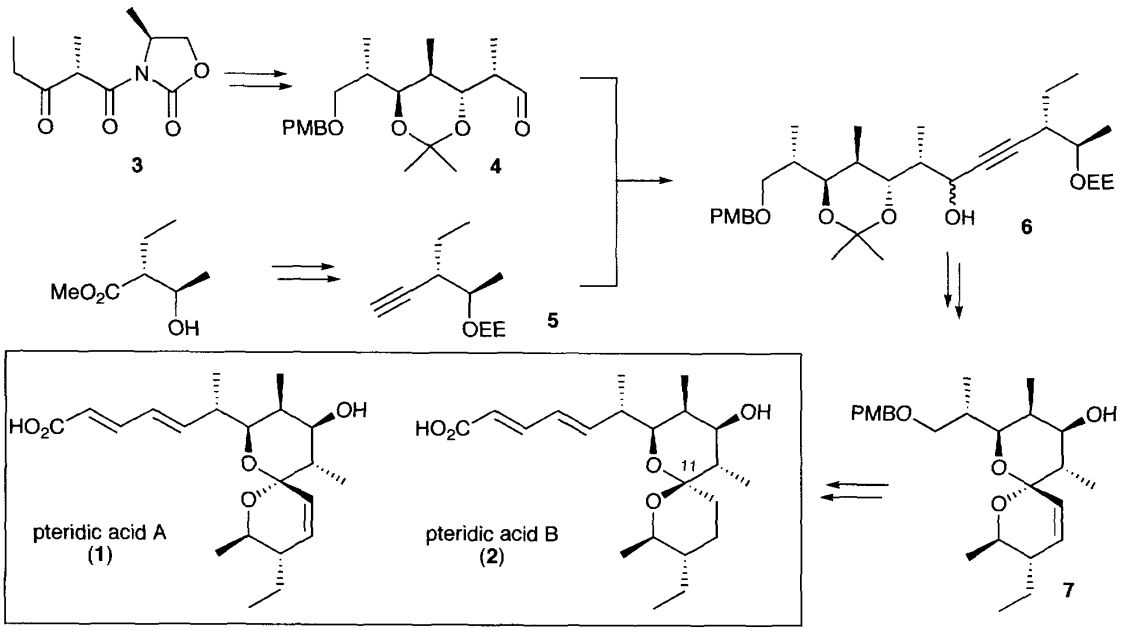


FIG. 1. Total synthesis of pteridic acids A and B.

## 2. Epoxyquinols A and B

Epoxyquinols A (**8**) and B (**9**) were isolated from a fermentation broth of an uncharacterized fungus of soil origin (Kakeya *et al.*, 2002a, 2002b). Several total syntheses have been reported due to their complicated unique structures and strong anti-angiogenic activity (references cited in Kuwahara and Imada, 2005). Synthesis of **8** and **9** were based on Kakeya's proposal that oxidation of the

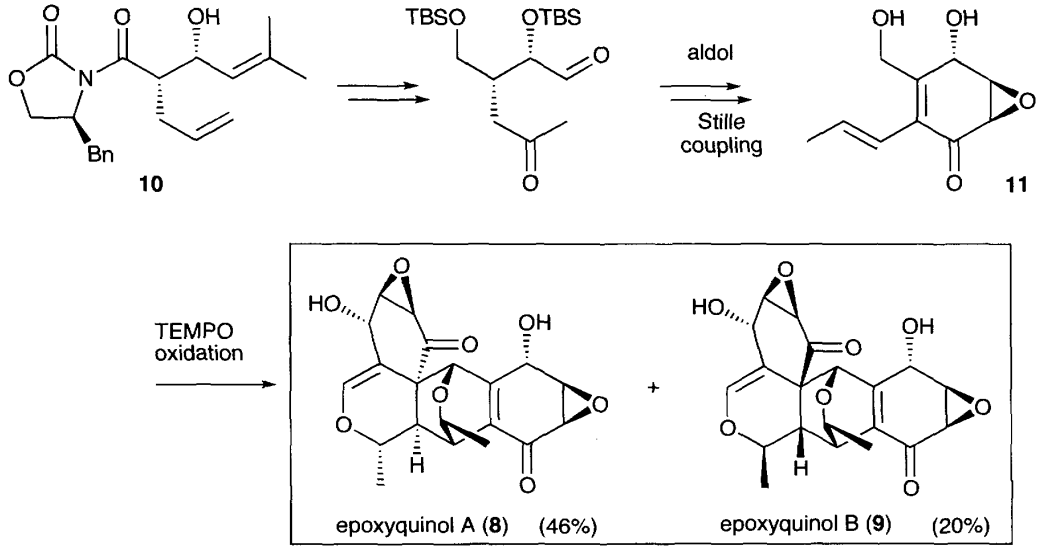


FIG. 2. Total synthesis of epoxyquinols A and B.

primary hydroxy group of **11** would lead to **8** and **9** via dimerization (Kuwahara and Imada, 2005). As shown in scheme 2, Evans' aldol product **10** were converted to **11** via aldol and Stille coupling reactions as the key steps. As expected, TEMPO oxidation of **11** afforded the target compounds. The overall yield of **8** was 22%.

## 3. Communiols A-F, and H

Communiols A-D (**12a-d**) and E-H (**12e-h**) were isolated from the culture broth of the coprophilous fungus, *Podospora communis* (Che *et al.*, 2004, 2005). These metabolites exhibit significant antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. We were interested in their rare 2,4-disubstituted tetrahydrofuran structures and began the synthetic studies. Comprehensive total synthesis of communiols A-F, and H from the common intermediate lactone **13** culminated in the revision of their stereochemistries as shown Scheme 3 (Kuwahara and Enomoto, 2005; Enomoto and Kuwahara., 2006; Enomoto *et al.*, 2006).

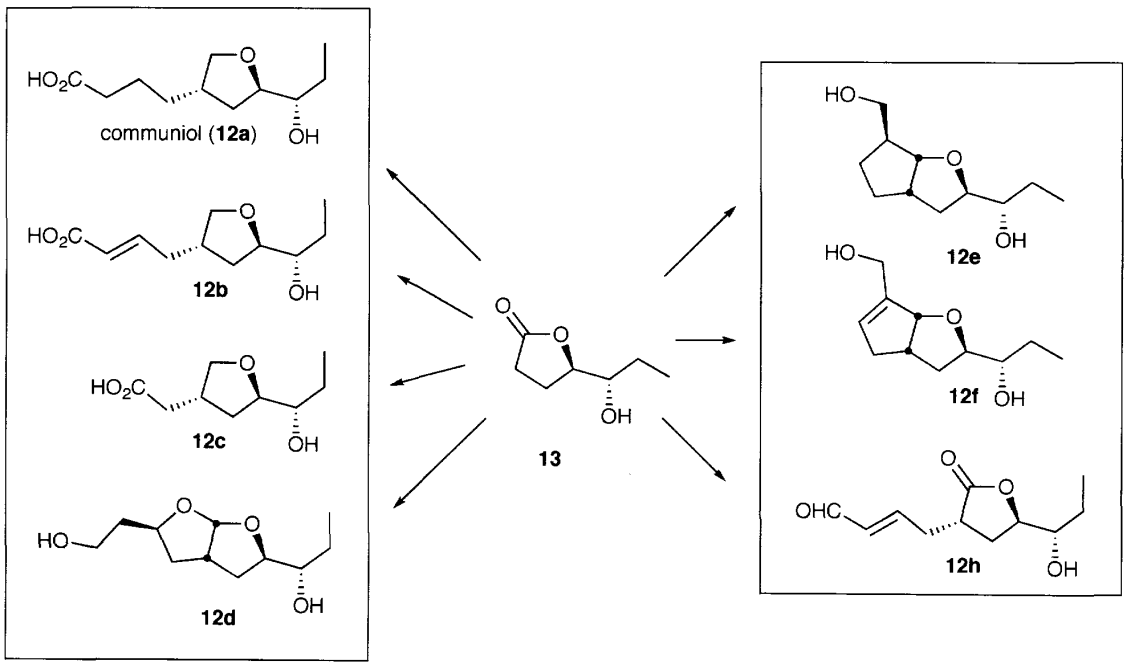


FIG. 3. Comprehensive total synthesis of communiols.

## 4. Polynactins (Actins)

The macrotetrolide ionophore antibiotic "polynactin" family (**14**), which have been isolated from various *Streptomyces* species, are composed of both monomeric enantiomers of nonactic acid (R=Me), homononactic acid (R=Et) or bishomononactic acid (R=*i*-Pr) arranged in an alternating order, namely, a meso-like-form (references cited in Hanadate *et al.*, 2000). Curiosity about these structures has already led many chemists to synthesize these monomers and tetramers (Fleming and Ghosh, 1996). A mixture of the parts (R=Me and/or Et) is used as an acaricide for fermentative production. To study the biological activities of the analog containing bishomononactic acid (R=*i*-Pr), designed bulky analog macrotetrolide $\alpha$ was prepared (Hanadate *et al.*, 2000). Iodoetherification of the $\gamma$, $\delta$-Unsaturated *t*-butyl ether **17** prepared from **16** afforded selectively *cis*-tetrahydrofuran **18**. Each enantiomeric counterparts **19** and **20** resolved from racemic **18** were condensed to give tetraolide **15**. The yield

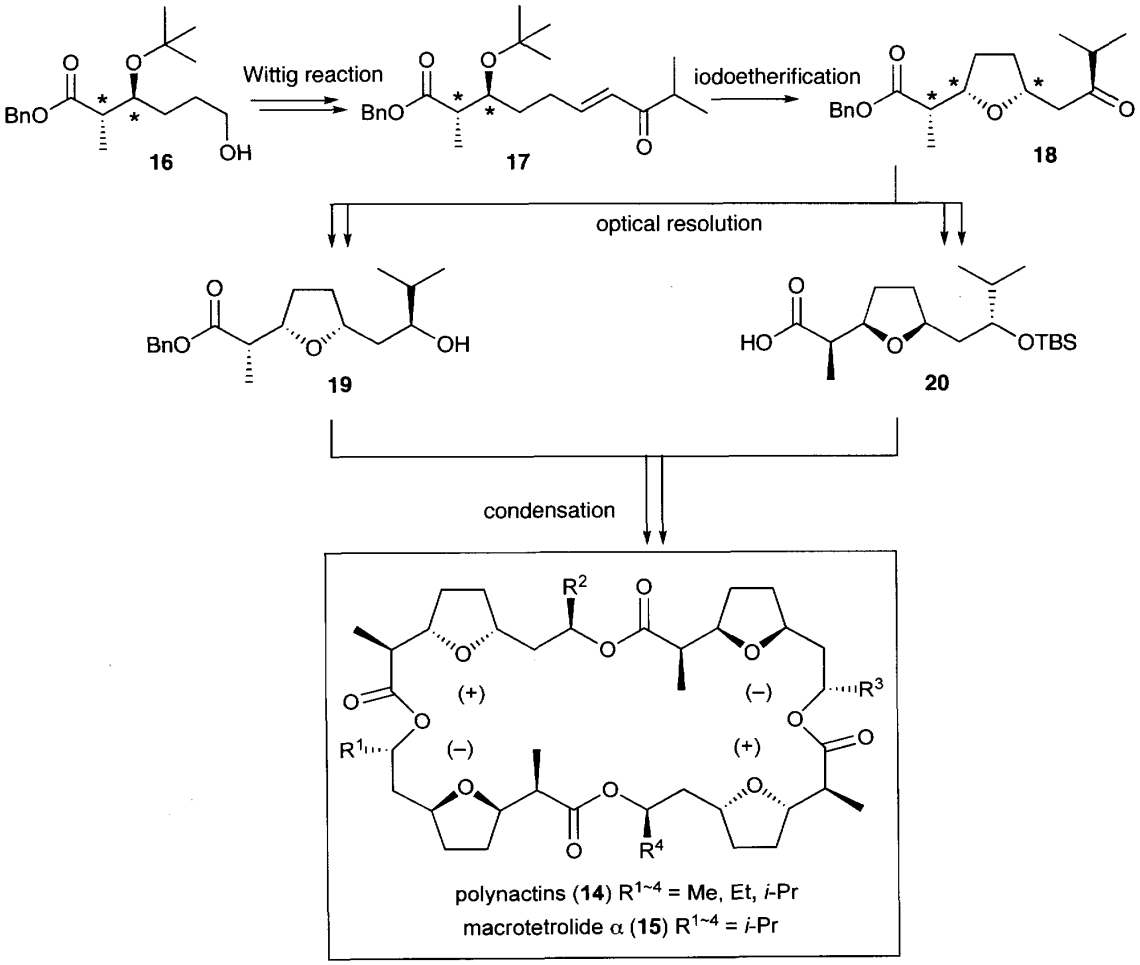


FIG. 4. Total synthesis of macrotetrolide $\alpha$.

of the condensation steps were nearly quantitative based on recovered starting materials.

## 5. Tabtoxinine-$\beta$-lactam (T$\beta$L)

Wildfire disease has been the most serious pest for tobacco since the early-twentieth century (Wolf and Foster, 1917). The causal compound tabtoxin (**21**) is inactive itself, however, when it is hydrolyzed by host plant aminopeptidases, the resulting true phytotoxin tabtoxinine-$\beta$-lactam (**22**) causes chlorosis by irreversible inactivation of the host plant glutamine synthetase (Thomas *et al.*, 1983). Although tabtoxin is available by fermentation, hydrolysis of the amide bond is complicated by isomerization to stable isotabtoxins or tabtoxinine-$\delta$-lactam (T$\delta$L) ($t_{1/2}=24$ h at pH 7.0 and 15 min at pH 4.5) (Stewart, 1971). To date two total syntheses were reported (Baldwin *et al.*, 1985; Doll *et al.*, 1992). Our new synthesis of **22** was achieved from L-serine using a zinc-mediated coupling reaction (**23** to **24**), Sharpless asymmetric dihydroxylation (**24** to **25**) and lactamization of *N*-OBn amide **26** as the key steps. The overall yield was 24% in 15 steps from L-serine (Kiyota *et al.*, 2004, 2007; Kiyota, 2006).

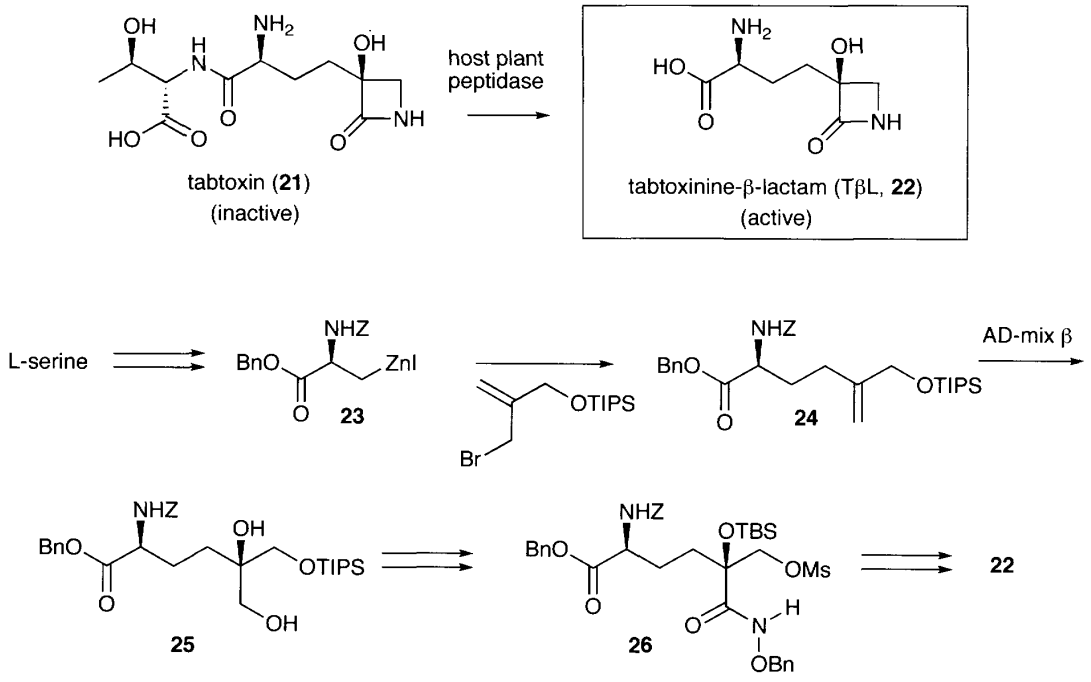


FIG. 5. Total synthesis of tabtoxinine-$\beta$-lactam.

## 6. Pyricuol

Rice blast disease, caused by infection of rice blast fungus *Magnaporthe grisea*, has been the most serious pest for rice. To date several salicylaldehyde type pathogenic compounds have been isolated from the fungus such as pyriculol (**27**) and pyriculariol (**28**) (Iwasaki *et al.*, 1969; Nukina *et al.*, 1981). Recently, an additional compound with a novel carbon framework, pyricuol (**29**), was isolated from the culture filtrate of the fungus, *M. grisea* (Hebert) Barr (imperfect stage of *Pyricularia oryzae* Cavara) (Kim *et al.*, 1998). Racemic and chiral synthesis of **29** was achieved to confirm its absolute configuration (Kiyota *et al.*, 2003, Nakamura *et al.*, 2005). Stille coupling reaction of styryl stannane **31**, derived from vinyl acetylene **30**, with iodide **32** gave **33**. This compound was converted to **34** and the key [2, 3]-Wittig rearrangement reaction afforded a desired primary alcohol **35**, and then pyricuol (**29**). The overall yield was 27% from **30** in six steps.

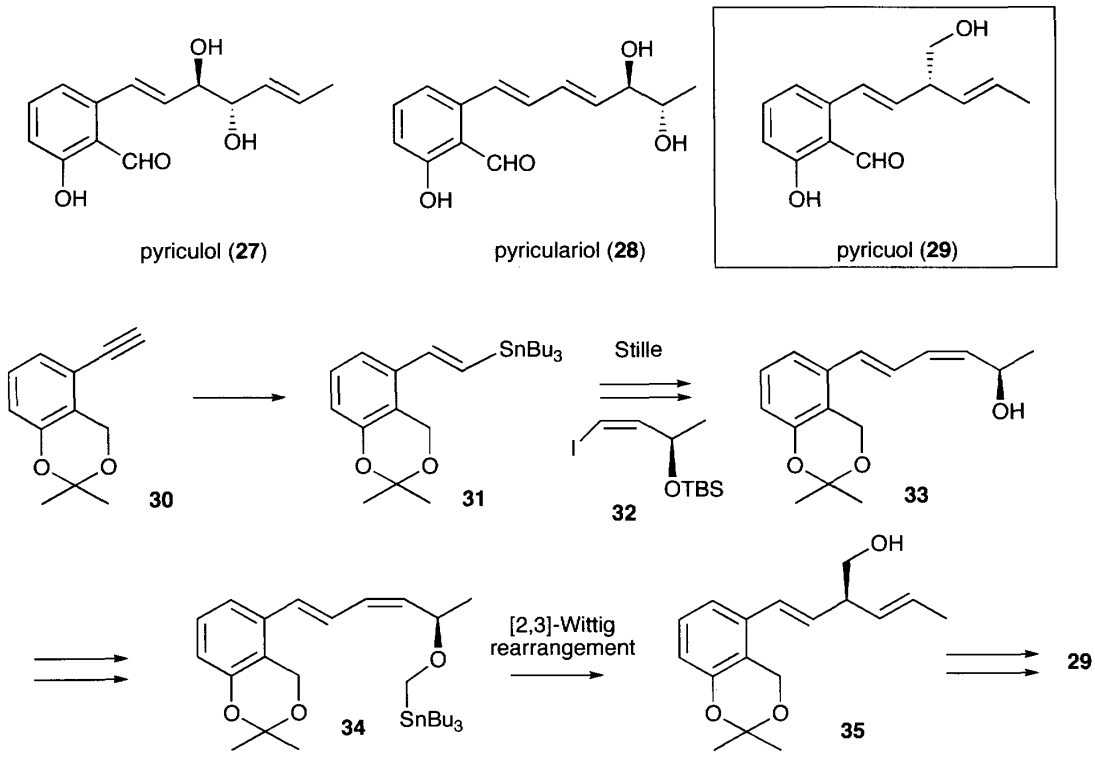


FIG. 6. Total synthesis of pyricuol.

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