Pergamon

Tetrahedron Letters 42 (2001) 7469–7471

TETRAHEDRON LETTERS

Stereoselective synthesis of pinnamine, an alkaloidal marine toxin from *Pinna muricata*

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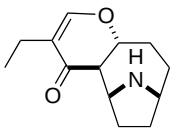
Received 25 July 2001; accepted 24 August 2001

Abstract—Pinnamine, an alkaloidal marine toxin isolated from the bivalve *Pinna muricata*, was synthesized from *N*-Z-pyroglutamic acid in 16 steps.

Pinnamine (**1**), an alkaloidal marine toxin, was isolated from the Okinawan bivalve *Pinna muricata*.[1] The absolute stereostructure of **1** was determined by spectral analysis including CD measurement. The structural features of **1** are a 9-azabicyclo[4.2.1]nonane moiety and a dihydro-γ-pyrone structure. Although pinnamine (**1**) exhibits characteristic toxic symptoms such as scurry, the scarcity of its natural supply has prevented further biological studies of it. We describe herein the enantioselective synthesis of pinnamine (**1**).



pinnamine (**1**)

Synthesis of **1** was started from *N*-Z-pyroglutamic acid (**2**) (Scheme 1). Reduction of the carboxyl group gave alcohol **3** in 61% yield.[2,3] Alcohol **3** was further reduced with DIBAL-H to afford hemiaminal **4**[4] (92% yield), the acid treatment of which in methanol provided diastereomeric hemiaminal methyl ether **5** in 93% yield. No pyranoside derivatives were isolated. Compound **5** was transformed into iodide **7** in two steps. Four-carbon homologation of **7** with the dianion of ethyl acetoacetate afforded the desired β-ketoester **12b** in poor yield because of the instability of the Z protecting group during the coupling reaction.

To avoid strongly basic conditions during homologation, the Wittig reaction and the Claisen condensation were employed. Alcohol **5** was oxidized with SO_3–pyridine to give aldehyde **8**, the Wittig reaction of which afforded the conjugated ester **9** (87% yield in two steps). Conjugated reduction of the α,β-unsaturated ester group in **9** with $NaBH_4$–CuCl[5] quantitatively provided saturated ester **10**, which was hydrolyzed to carboxylic acid **11** in 84% yield. Carboxylic acid **11** was converted into the corresponding imidazolide, which was condensed with *tert*-butyl acetate to give β-ketoester **12a** in 62% yield.

Lewis acid treatment[6] of the silyl enol ether of **12a** provided the bicyclo compound **13** in 78% yield, which was stereoselectively reduced with $NaBH_4$ to give alcohol **14** (90% yield). Compounds **13** and **14** were obtained as single products, and their stereochemistry was deduced by comparison of the coupling constants of α hydrogen to the carbo-*t*-butoxy group in **14** with those simulated using computer-calculated models with four possible types of stereochemistry, **14A**–**14D** (Fig. 1).[7] The stereochemistry of **13** could be explained by the formation of a chelated tin enolate intermediate and the cyclization via a product-like transition state (Fig. 2). The stereoselectivity of this reduction could be predicted by considering the conformation of **13** to be attacked from the less hindered *exo* orientation (Fig. 2).[7]

Keywords: pinnamine; marine metabolite; acute toxicity; homotropane alkaloid; synthesis.
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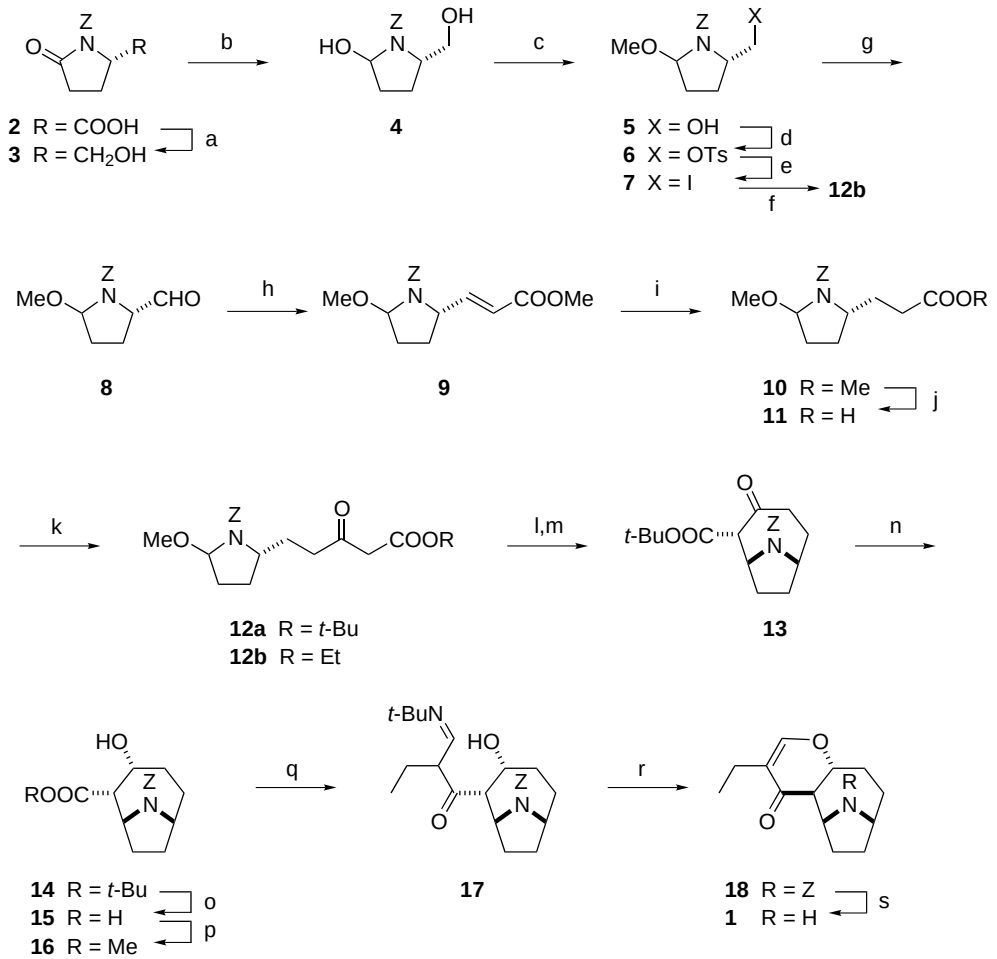
0040-4039/01/$ - see front matter
PII: S0040-4039(01)01583-0



Scheme 1. (a) 1. $ClCO_2Et$, *N*-methylmolphorine, THF, −10°C; 2. $NaBH_4$, MeOH, 0°C (61%); (b) DIBAL-H, CH_2Cl_2, −78°C (92%); (c) *p*-TsOH, MeOH, rt (93%); (d) TsCl, pyridine, 0°C (90%); (e) NaI, $CaCO_3$, DMF, 80°C (60%); (f) ethyl acetoacetate, NaH, *n*-BuLi, rt (5%); (g) SO_3–pyridine, Et_3N, DMSO, rt; (h) $Ph_3P{=}CHCO_2Me$, THF, rt (87% in two steps); (i) $NaBH_4$, CuCl, MeOH, THF, 0°C (100%); (j) 1 M NaOH aq., MeOH, rt (84%); (k) 1. 1,1′-carbonyldiimidazole, THF, rt; 2. LDA, *t*-BuOAc, 0°C (62%); (l) TBSCl, Et_3N, THF, 40°C; (m) $Sn(OTf)_2$, CH_2Cl_2, 0°C (78% in two steps); (n) $NaBH_4$, MeOH, 0°C (90%); (o) TFA, CH_2Cl_2, rt; (p) $TMSCHN_2$, MeOH, rt (74% in two steps); (q) *t*-BuN=$CHCH_2CH_2CH_3$, LDA, THF, 0°C (73%); (r) TFA, THF, H_2O, rt (91%); (s) TMSI, MeCN, 0°C (77%).

Removal of the *tert*-butyl group in **14** and subsequent methylation afforded methyl ester **16** (74% yield from **14**). Condensation of **16** with the lithium anion[8] of *N*-*tert*-butylbutyraldimine gave a complex mixture of the isomeric keto imine **17**[9] (73%). Acid treatment of **17** resulted in cyclization and concomitant epimerization to provide Z-pinnamine (**18**) in 91% yield. Finally, removal of the Z protecting group with TMSI afforded pinnamine[10] (**1**) in 77% yield. Synthetic **1** was found to correspond uniquely to natural **1** by comparison of their spectral data including their CD spectra and acute toxicity data.[11]

In conclusion, pinnamine (**1**), a marine alkaloid isolated from the bivalve *Pinna muricata*, was synthesized from *N*-Z-pyroglutamic acid (**2**) in 16 steps in 7% overall yield, which confirmed the absolute stereostructure and bioactivity of natural pinnamine (**1**). Further biological studies using synthetic **1** are in progress.

Acknowledgements

This work was supported in part by Grants-in-Aid for Scientific Research on Priority Areas ‘Targeted Pursuit of Challenging Bioactive Molecules’ (Nos. 11175101 and 13024215) from the Ministry of Education, Science, Sports, and Culture, Japan. We are indebted to Wako Pure Chemical Industries, Ltd., Banyu Pharmaceutical

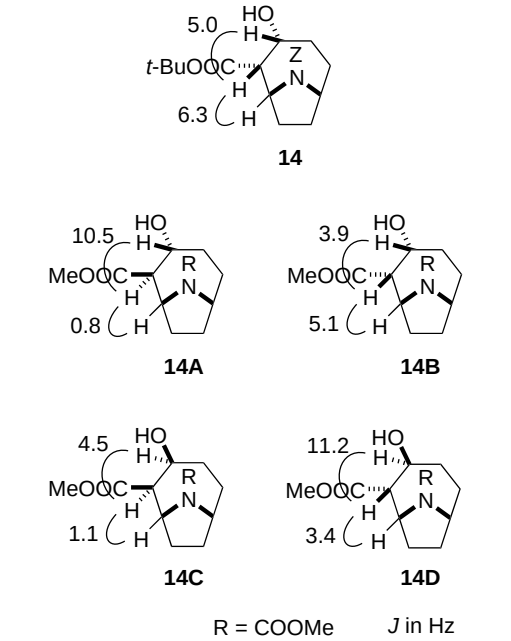


Figure 1. Coupling constants observed for **14** in $CDCl_3$ and calculated for models with four possible types of stereochemistry, **14A**–**14D**, in Hz.

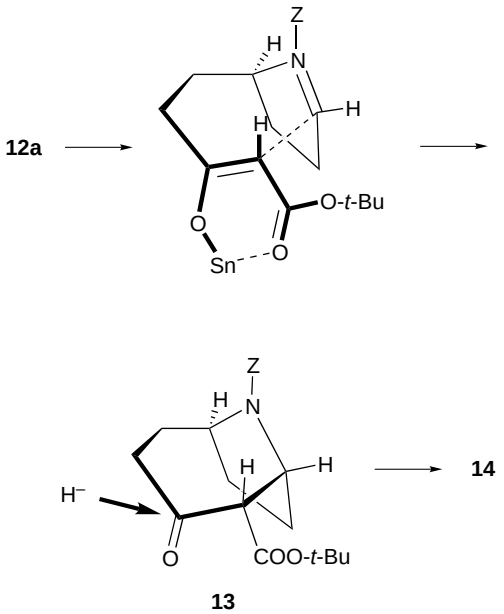


Figure 2. Plausible reaction pathway from **12a** to **14**.

Co., Ltd., and Suntory Institute for Bioorganic Research, for their financial support.

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2. Altmann, K.-H. *Tetrahedron Lett*. **1993**, *34*, 7721–7724.
3. Because of the resisted rotation of the urethane bond, some NMR signals were observed as a pair with a ratio of 1:1 for most compounds possessing the Z protecting group.
4. Satisfactory spectral (IR, ^1H and ^{13}C NMR, and mass) and analytical (high-resolution mass analyses) data were obtained for all new compounds.
5. Narisada, M.; Horibe, I.; Watanabe, F.; Takeda, K. *J. Org. Chem*. **1989**, *54*, 5308–5313.
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7. Molecular mechanics calculations were performed using the MacroModel package (ver. 6.0, MM2* force field).
8. For lithiation of *N-tert*-butylaldimines with LDA, see: Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett*. **1976**, 7–10.
9. Compound **17** might be in the imine and/or enamine form.
10. Colorless oil; $[\alpha]_D^{27}$ +71.2 ($c=0.0399$, MeOH); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR (800 MHz, CD_3OD, −15°C) δ 7.47 (s, 1H), 4.89 (dd, $J=10.2$, 2.2 Hz, 1H), 4.26 (dd, $J=13.6$, 11.4 Hz, 1H), 4.15 (m, 1H), 2.89 (d, $J=13.6$ Hz, 1H), 2.50 (m, 1H), 2.26 (m, 1H), 2.18 (m, 4H), 2.11 (m, 1H), 2.02 (ddd, $J=13.9$, 9.8, 4.4 Hz, 1H), 1.96 (br d, $J=15.4$ Hz, 1H), 1.85 (dd, $J=15.4$, 13.2 Hz, 1H), 1.05 (t, $J=7.5$ Hz, 3H); CD (MeOH) λ_{ext} 306 nm ($\Delta\varepsilon$ −0.067), 273 (+0.219), 263 (+0.232), 255 (+0.197); FABMS (*m*-nitrobenzyl alcohol) *m*/*z* 222 $[M+H]^+$; HRFABMS (*m*-nitrobenzyl alcohol) *m*/*z* calcd for $C_{13}H_{20}NO_2$ $[M+H]^+$ 222.1494, found 222.1515 (Δ 2.1 mmu).
11. Acute toxicity of synthetic **1** was examined by i.p. injection into a ddY male mouse with a dose of 0.8 mg/kg (LD_{99} for natural **1**: 0.5 mg/kg).[1] Within 5 min after injection, the mouse was dead with the same toxic symptoms as those of the natural sample.