# Total Synthesis of (±)-Thielocin A1β: A Novel Inhibitor of Phospholipase $A_2$

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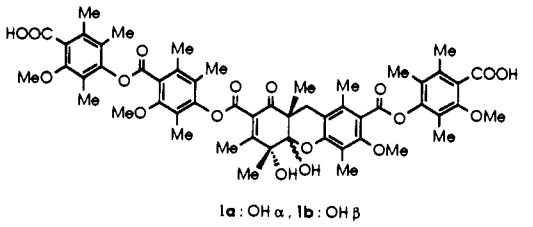
Thielocin A1β (**1b**) (Figure 1) is an unusual pentameric dypside recently isolated together with a minor amount of its α isomer (**1a**) from culture broths of an ascomycetes *Thielavia terricola* RF-143.[2] Thielocin A1β is reported to be a uniquely potent and specific inhibitor of group II phospholipase $A_2$ ($PLA_2$) from rat platelet with an $IC_{50}$ of 3.3 nM relative to an $IC_{50}$ of 21.0 μM for rat pancreatic $PLA_2$ (group I).[3] This compound may provide a lead for further chemical modification and serve as a useful tool for pharmacological evaluation of selective inhibition of type II $PLA_2$ in models of shock and inflammation.

We report the first total synthesis of (±)-thielocin A1β based on the efficient, highly chemo- and stereoselective condensation of a suitably protected hydroxy dienone (**2**), quinone methide (**3**), and benzoic acid (**4**) (Figure 2), all derived from a common phenolic synthon **5** (Scheme 1).

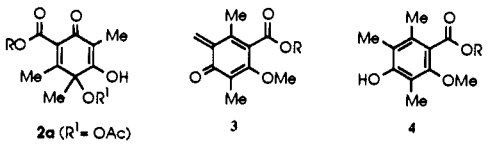
The dienone component **2** was envisaged to derive from oxidation of **6** (Scheme 1). Conversion of the pivotal intermediate **5**[4] to the hydroxy dienone **2b** was effected as follows (Scheme 1). Clemmensen reduction provided **6a** (88%), which on transesterification with sodium (trimethylsilyl)ethoxide (benzene, 110 °C) gave the (trimethylsilyl)ethyl (TMSE) ester **6b** (63%). Attempted oxidation of the diol **6b** did not furnish useful results. However, after selective protection of the more reactive para hydroxy group (TBDPSiCl, $Et_3N$, DMAP) to give **6c** (91%), regioselective oxidation was achieved with phenyliodonium diacetate[5] in acetic acid to provide **7** (57%). Hydrolysis of the acetate and the TBDPS enol ether (LiOH, 12-crown-4, aqueous THF) gave the desired hydroxy dienone **2b** (70%).

We envisioned the quinone methide fragment **3** to arise from decomposition of a derivative **11** (Scheme 2), where R is a leaving group such as a tertiary amine *N*-oxide or quaternary ammonium salt.[6] Model studies indicated that *N*-oxides such as **11a** were not useful for our purpose,[7] and therefore the salt **11b** was prepared. Transesterification of **5** ($HOCH_2CCl_3$, $H_2SO_4$) yielded trichloroethyl (TCE) ester **8** (60%). Methylation ($(MeO)_2SO_2$, $K_2CO_3$) provided monomethyl ether **9** (91%), where reaction occurred exclusively ortho to the ester group. Reductive amination (piperidine, $NaBH_3CN$) afforded benzylic amine **10** (82%), and protection of the hydroxyl group (TBDMSCl, NaH) followed by quaternization of the amino group with methyl trifluoromethanesulfonate gave the salt **11b** (95% combined yield).



**1a** : OH α , **1b** : OH β

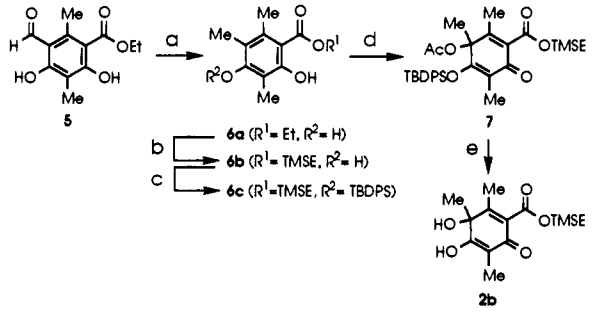
**Figure 1.**



**2a** ($R^1$ = OAc)
**2b** ($R^1$ = OH)

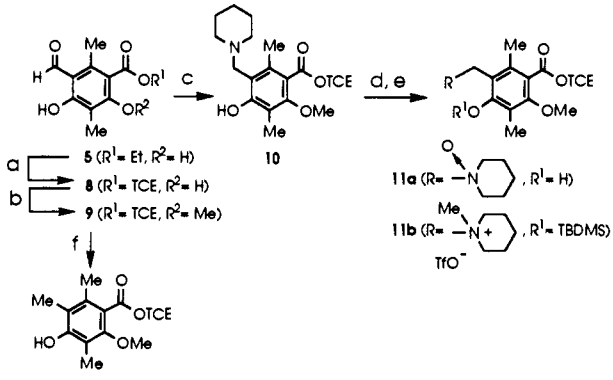
**Figure 2.**

**Scheme 1**[a]



[a] (a) Zn–Hg/HCl, EtOH, reflux, 2 h; (b) 4 equiv of $(Me)_3Si(CH_2)_2ONa$, $(Me)_3Si(CH_2)_2OH$/benzene (2:1), 110 °C, 4 h; (c) 2.5 equiv of TBDPSiCl, 4 equiv of $Et_3N$, 0.2 equiv of DMAP, $CH_2Cl_2$, 25 °C, 48 h; (d) 1.5 equiv of $PhI(OAc)_2$, AcOH, 25 °C, 5 h; (e) 3.5 equiv of LiOH, 0.4 equiv of 12-crown-4, $THF/H_2O$ (9:1), 25 °C, 15 h.

**Scheme 2**[a]



[a] (a) $HOCH_2CCl_3/H_2SO_4$ (3:2), 25 °C, 72 h; (b) 1.05 equiv of $(MeO)_2SO_2$, 1.2 equiv of $K_2CO_3$, acetone, reflux, 2 h; (c) 2.2 equiv of piperidine, 1.5 equiv of $NaBH_3CN$, MeCN, 25 °C, 9 h; (d) 2.2 equiv of TBDMSCl, 1.5 equiv of NaH, THF, 25 °C, 15 h; (e) 1.05 equiv of $MeOSO_2CF_3$, $CH_2Cl_2$, −10 to 25 °C, 0.5 h; (f) 12 equiv of $(Et)_3SiH$, TFA, 25 °C, 15 h.

The fluoride ion catalyzed coupling of **2b** and **11b** (TBAF, −20 °C to room temperature) proceeded *in essentially quantitative yield and with complete stereoselection*, with formation of the carbon–carbon bond *syn* to the tertiary hydroxyl group,[8] to afford the tricyclic compound **12** (95%) (Scheme 3) as a thermodynamic mixture of two hemiketals. Treatment of this mixture with carbonyldiimidazole and triethylamine provided a single carbonate **13** (95%).

The assembly of the pentameric skeleton was achieved as follows. The required phenolic monomer **4** was easily derived

(1) On leave (1991–1992) from Industrial Research Ltd., P.O. Box 31-310, Lower Hutt, Petone, New Zealand.
(2) Inoue, K.; Matsutani, S.; Kawamura, Y. EP-395,418, Oct 31, 1990.
(3) Yoshida, T.; Nakamoto, S.; Sakazaki, R.; Matsumoto, K.; Terui, Y.; Sato, T.; Arita, H.; Matsutani, S.; Inoue, K.; Kudo, I. *J. Antibiot.* **1991**, *44*, 1467. Tanaka, K.; Matsutani, S.; Matsumoto, K.; Yoshida, T. *J. Antibiot.* **1992**, *45*, 1071.
(4) Obtained from ethyl 2,4-dihydroxy-3,6-dimethylbenzoate (Elix, J. A.; Norfolk, S. *Aust. J. Chem.* **1975**, *28*, 1113) by formylation: Pulgarin, C.; Gunzinger, J.; Tabacchi, R. *Helv. Chim. Acta* **1985**, *68*, 1948.
(5) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677. The assigned regiochemistry was based on extensive NMR studies of the oxidation product.
(6) This approach was inspired by unpublished work of Professor D. A. Evans, who has studied reactions of *o*-quinone methides derived from benzylic amine *N*-oxides. We are thankful to him for this suggestion.
(7) Either basic or Lewis acid catalyzed decomposition of the *N*-oxides yielded only elimination–addition product, as a result of the trapping of the quinone methide by the leaving hydroxylamine anion.

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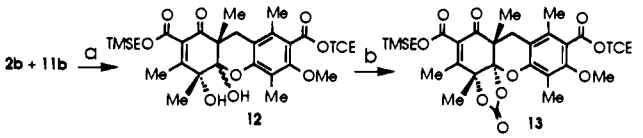
**Scheme 3**[a]

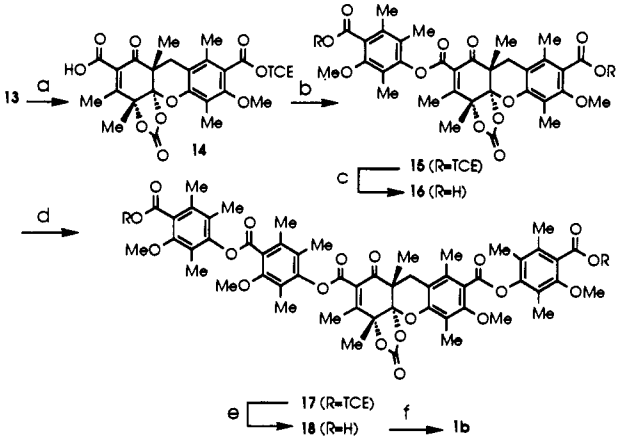


[a] (a) 1.05 equiv of TBAF, $CH_2Cl_2$, −20 to 25 °C, 5 h; (b) 3 equiv of carbonyldiimidazole, 2.2 equiv of $Et_3N$, $CH_2Cl_2$, 25 °C, 1 h.

from **5**. Thus reduction of the aldehyde **9** with triethylsilane in trifluoroacetic acid[9] afforded **4** (96%) (Scheme 2). Selective removal of the TMSE ester from intermediate **13** (TBAF, DMF) gave monoacid **14** (81%) (Scheme 4). After conversion to the corresponding acid chloride ($Cl_2CHOCH_3$, $CH_2Cl_2$, reflux),[10] reaction with phenol **4** ($Et_3N$, $CH_2Cl_2$) yielded the trimeric ester **15** (87% combined yield). Concomitant hydrolysis of the two TCE esters (Cd, DMF/HOAc)[11] gave dicarboxylic acid **16** (82%), and bis-esterification of **16** with **4** (TFAA, benzene)[12] afforded the protected thielocin A1$\alpha$ **17** (84%). Removal of the TCE esters (Cd, DMF/HOAc) provided the penultimate carbonate **18** (82%).

Hydrolysis of **18** proceeded smoothly upon treatment with 0.5 N NaOH/dioxane at −10 °C to afford **1b**[13] (59%), which gave physical and spectral data essentially identical ($^1$H NMR, $^{13}$C NMR, MS, IR) or comparable (mp)[14] to those reported for the natural compound.[2]

**Scheme 4**[a]



[a] (a) 1.1 equiv of TBAF, DMF, 25 °C, 15 h; (b) 8.5 equiv of $Cl_2CHOCH_3$, $CH_2Cl_2$, reflux, 4 h, then 1.6 equiv of **4**, 2.2 equiv of $Et_3N$, $CH_2Cl_2$, 25 °C, 4 h; (c) 50 equiv of Cd, DMF/HOAc (1:1), 25 °C, 15 h; (d) 5 equiv of **4**, 50 equiv of TFAA, benzene, 25 °C, 15 h; (e) 50 equiv of Cd, DMF/HOAc (1:1), 25 °C, 15 h; (f) 0.5 N NaOH/dioxane (1:1), −10 °C, 15 h.

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**Supplementary Material Available:** Characterization data ($^1$H NMR, $^{13}$C NMR, IR, MS, elemental analysis) for **4**, **6b**, **7**, **8**, **10**, **13**, **15**, and **17** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) NMR studies on orthoesters derived from the diethyl ester analog of **12** allowed determination of the relative stereochemistry: Bernstein, M. A.; Trimble, L. A. Unpublished results. This assignment has been confirmed by an X-ray diffraction study of the $\alpha$ isomer of the corresponding free diol: Ball, R. G.; Springer, J. Unpublished results. Full details of these studies will be published in a subsequent full paper. It is noteworthy that a much lower degree of stereoselectivity was observed in this series when the acetoxy dienone **2a** was used as nucleophile. This finding suggests a decisive contribution of the free tertiary alcohol to the stereochemical outcome of this coupling reaction, likely through a stabilizing hydrogen bond in the transition state.

(9) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675.

(10) Rieche, A.; Gross, H. *Chem. Ber.* **1959**, *92*, 83.

(11) Hancock, G.; Galpin, I. J.; Morgan, B. A. *Tetrahedron Lett.* **1982**, *23*, 249. Treatment with Zn in AcOH yielded only decomposition when applied to **15**.

(12) Parish, R. C.; Stock, L. M. *J. Org. Chem.* **1965**, *30*, 927.

(13) The reaction provided the thermodynamically more stable $\beta$ isomer. Thielocins A1$\alpha$ and A1$\beta$ are known to form an equilibrium mixture largely in favor of the $\beta$ isomer.[3]

(14) Melting point 198–201 °C (ether) observed for the synthetic racemate is to be compared with mp 190–194 °C reported for the natural chiral material.