

Communications

Synthetic Approach to an Analog of Plakoridine-A using Malate Enolate-Imine Condensation

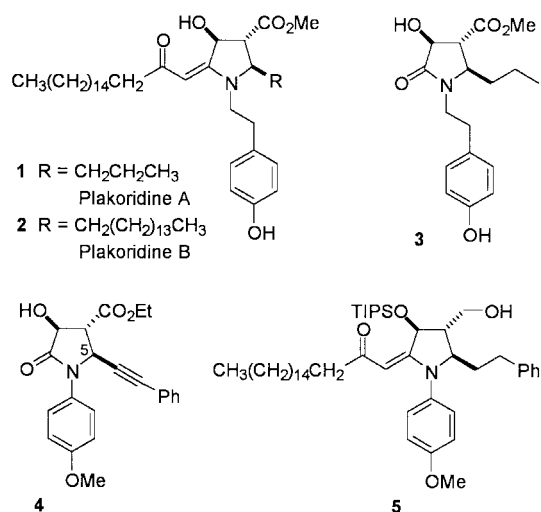
In-Hae Ye, Won-Keun Choung, Kyoung Hoon Kim, and Deok-Chan Ha*

Department of Chemistry, Korea University, 5-1-2 Anam-dong, Seoul 136-701, Korea
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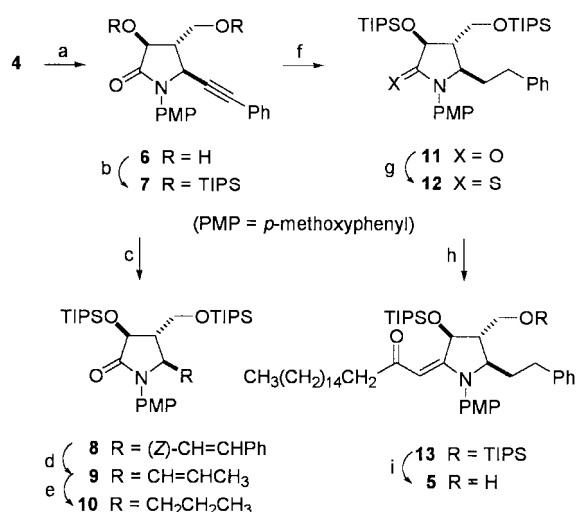
Diverse structurally unique secondary metabolites, including peroxy fatty acids, were isolated from Okinawan marine sponges *Plakortis*.¹ Structural elucidation of the very minor constituents from the metabolites have revealed fully functionalized pyrrolidines, Plakoridine A (**1**) and B (**2**), with unprecedented tyramine-containing nitrogenated carbon framework.² Due to the shortage of the isolated materials, the absolute stereochemistry of the Plakoridines remained undetermined. Plakoridine A (**1**) was found to be cytotoxic against murine lymphoma L1210 cell line. A couple of synthetic approaches has been explored, including 1,3-dipolar cycloaddition of nitron,³ and Michael addition of chiral amine to unsaturated ester followed by aldol condensation,⁴ to construct the key 2-pyrrolidinone intermediate **3**.

We have previously reported that highly functionalized 2-pyrrolidinones can be constructed in a single step by the condensation between the enolate dianion of malate and non-enolizable imine.⁵ Though the yield and diastereoselectivity of the enolate-imine condensation were less than the desired, this approach provides the 2-pyrrolidinone with appropriate substituents and stereochemistry for the synthesis of Plakoridine A and B. In this report, our study on functional modification of 2-pyrrolidinone **4** for the synthesis of **5**, a model compound for Plakoridine A, is described. Selection of model **5** was based on the easy access to 2-phenylethyl group at C(5) from **4** and selective protection of the 1,3-diol for the regeneration of the β -hydroxyester which may not tolerate with the conditions employed at the early stage of our projected synthetic approach.

Enolate dianion generated from diethyl (*S*)-malate by treating with two equivalents of $\text{NaN}(\text{TMS})_2$ was reacted with phenylpropargylidene *p*-anisidine at -78°C in THF to give **4** (47%) and its C(5)-epimer (11%). Selective reduction of the ester moiety of pyrrolidinone **4** with LiBH_4 in diglyme fol-



lowed by the protection of the resulting diol **6** provided **7**. Conversion of the phenylethynyl group of **7** to propyl group was accomplished with a conventional method. Thus, partial hydrogenation of **7** with Lindlar catalyst gave the (*Z*)-olefin **8**, which was converted to **10** through ozonolysis and *in situ* Wittig olefination followed by catalytic hydrogenation. This routine four-step sequence from **7** to **10** was a rather tedious process considering the simplicity of the propyl group, but was inevitable with this approach since the enolate-imine condensation requires non-enolizable imines.⁶ After catalytic hydrogenation of **7**, the resulting amide **11** was converted to thioamide **12** with Lawesson's reagent.⁷ The conversion of **12** to the vinylogous amide of **13** was successfully carried out employing the Eschenmoser coupling and sulfide contraction method.⁸ Thus, reaction of **12** with 1-iodo-2-octadecanone, prepared from oxidation of 1-octadecene with silver chromate-iodine,⁹ followed by sequential treatments



Scheme 1. Reagents: (a) LiBH₄, diglyme, 91% (b) TIPSCl, Et₃N, cat. DMAP, DMF, 98% (c) H₂ (30 psi), Lindlar cat., EtOAc, 96% (d) O₃, CH₂Cl₂; Me₂S; Ph₃P=CHCH₃, THF, 90% (e) H₂ (1 atm), Pd-C, EtOAc, 98% (f) H₂ (1 atm), Pd-C, EtOH, 98% (g) (p-MeOPhPS)₂S₂, PhH, reflux, 97% (h) 1-iodo-2-octadecanone, CH₂Cl₂, rt. DABCO; P(OEt)₃, 50% (i) *n*-Bu₄NF, THF, rt, 74%.

with 1,4-diazabicyclo[2.2.2]octane (DABCO) and triethylphosphite in CH₂Cl₂ at ambient temperature produced the desired **13** in 50% yield. Selective desilylation of **13** to **5** required for the ester of **1** was achieved with slight excess of *n*-Bu₄NF in THF with short reaction time.¹⁰

In summary, we have shown that the condensation between the enolate dianion of diethyl malate and imine, combined with the Eschenmoser coupling, provides an expedient approach to an analog of new class of pyrrolidine alkaloids. Plakoridine A and B, having vinylogous amide structure. Further study to improve the efficiency in introducing the C(5)-propyl group and tyramine unit of **1** is in

progress and will be reported in due course.

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References

- Gerwick, W. H.; Nagle, D. G.; Proteau, P. J. *Topics in Current Chemistry*, Vol. 167, *Marine Natural Products. Diversity and Biosynthesis*; Scheuer, P. J., Ed.; Springer-Verlag: Berlin, 1993; p 167.
- (a) Takeuchi, S.; Kikuchi, T.; Tsukamoto, S.; Ishibashi, M.; Kobayashi, J. *Tetrahedron* **1995**, *51*, 5979. (b) Takeuchi, S.; Ishibashi, M.; Kobayashi, J. *J. Org. Chem.* **1994**, *59*, 3712.
- Stafford, J. A. *Tetrahedron Lett.* **1995**, *36*, 681.
- Ma, D.; Sun, H. *Tetrahedron Lett.* **2000**, *41*, 1947.
- Ha, D.-C.; Yun, K.-S.; Park, H.-S.; Choung, W.-K.; Kwon, Y.-E. *Tetrahedron Lett.* **1995**, *36*, 8445.
- Hart, D. J.; Ha, D.-C. *Chem. Rev.* **1988**, *89*, 1447.
- For review, see: Cava, M. P.; Levinson, M. I. *Tetrahedron* **1985**, *41*, 5061.
- (a) Roth, M.; Dubs, P.; Götsch, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710. (b) Eschenmoser, A. *Quart. Rev.* **1970**, *24*, 366.
- Cardillo, G.; Shimizu, M. *J. Org. Chem.* **1977**, *42*, 4268.
- Selected ¹H NMR (CDCl₃, 300 MHz) data: **4**: δ 7.18 (d, 2H, *J* = 9 Hz), 7.03 (m, 5H), 6.93 (d, 2H, *J* = 9 Hz), 5.87 (s, 1H), 4.94 (s, 1H), 3.84 (s, 3H), 3.62 (m, 2H), 3.50 (m, 1H), 2.70 (m, 1H), 2.50-2.42 (m, 2H), 2.09 (t, 2H, *J* = 6 Hz), 2.05 (m, 2H), 1.25 (m, 28H), 1.14 (m, 42H), 0.88 (t, 3H, *J* = 6.3 Hz). **12**: δ 7.22 (m, 5H), 7.06 (d, 2H, *J* = 9 Hz), 6.94 (d, 2H, *J* = 9 Hz), 4.62 (s, 1H), 4.05 (m, 1H), 3.82 (s, 3H), 3.75 (m, 2H), 2.60 (m, 2H), 2.45 (m, 1H), 2.10-1.90 (m, 2H), 1.13 (m, 42H).