水溶液中での異常な脱硫—水和反応
（強力かつ新規な抗ガン物質の不斉合成に向けて）

（課題番号　15550031）

平成15年度～平成16年度科学研究費補助金
（基盤研究(C)(2)）研究成果報告書

平成17年3月

研究代表者　依田秀実
（静岡大学工学部助教授）

水溶液中での異常な脱硫一水和反応
(強力かつ新規な抗ガン物質の不斉合成に向けて)

(課題番号　15550031)

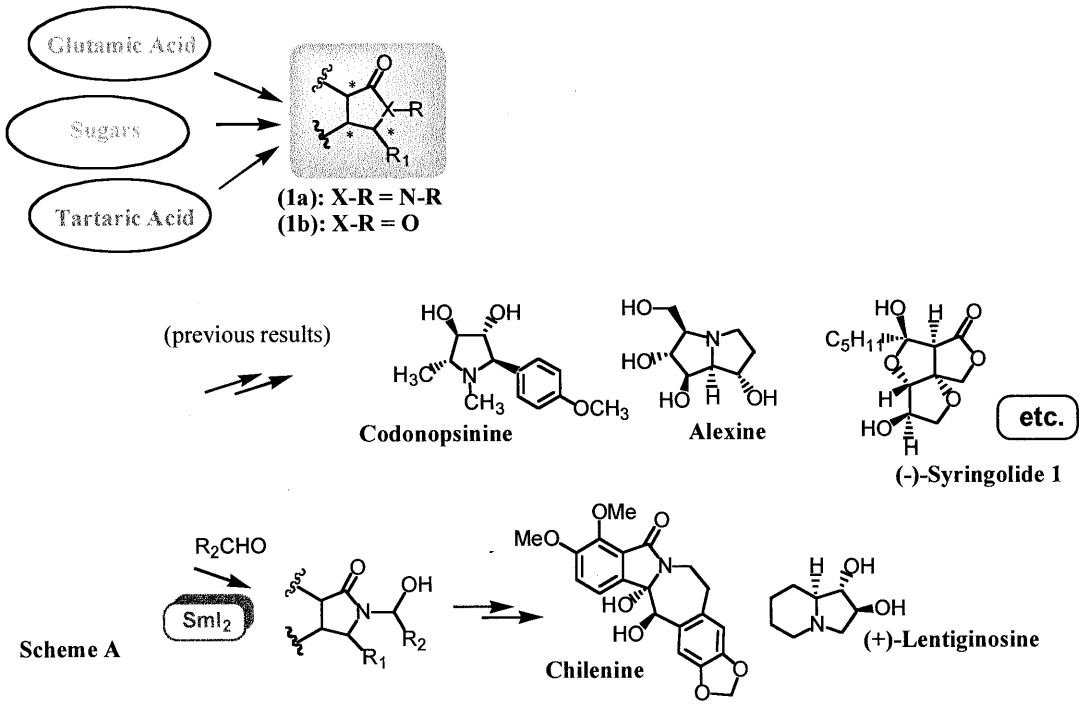
平成15年度～平成16年度科学研究費補助金
(基盤研究(C)(2))研究成果報告書

平成17年3月

研究代表者　　依 田 秀 実
(静岡大学工学部助教授)

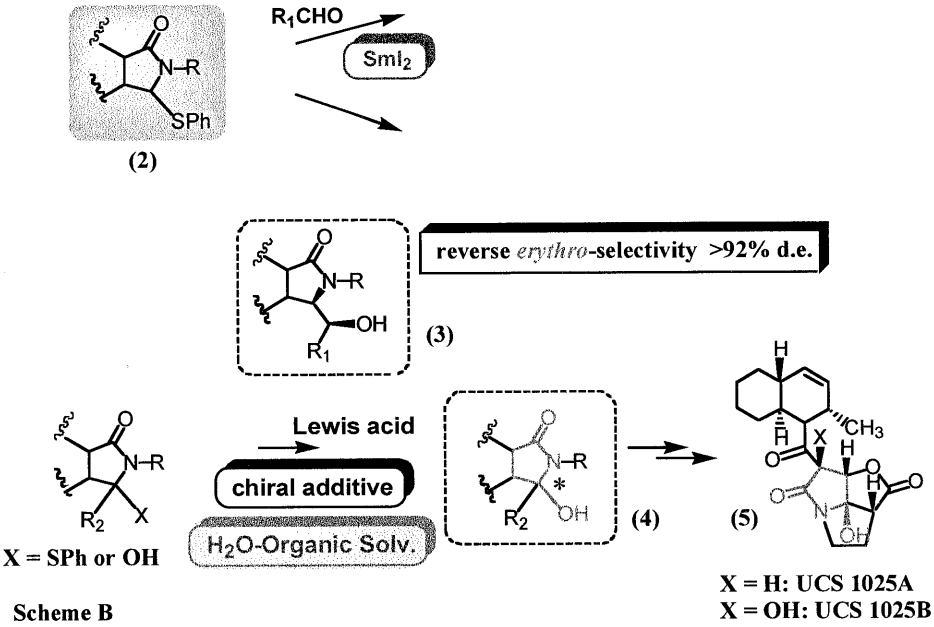
はしがき

生体内では酵素が極めて高い不斉識別を行っており、その詳細が近年具体的に解明されつつある。一方、有機化学的手法による立体区別反応は、生体内反応では得ることが困難な鏡像体を自由に構築することが可能となるために、新しい試薬、反応や触媒の開発、応用に関して高い関心が寄せられている。申請者はすでに様々な天然資源を利用することによって、光学活性なラクタム類及びラクトン類などの重要なカイロン中間体(**1**)を得る新手法の開発を行い、これを用いて数多くの生理活性天然物の全合成に成功している(Scheme A)。一方前回の本申請においては、これらから誘導される *N*-H ラクタムに対し、SmI_2 による１電子移動反応をカルボニル化合物の存在下で実施したところ、これまでに報告例のないＮ－Ｃヘテロカップリング反応が進行することを発見し、インドリジジンあるいはベンズアゼピン系生理活性物質の全合成に成功したことを報告した。



今回申請者は、これらの研究を遂行する際に得られたイオウ置換ラクタム(**2**)が SmI_2 存在下での１電子移動反応に対しても、あるいは Lewis 酸のみが存在する

水溶液中においても、*脱硫*-カップリング反応や、これまでにまったく知られていない*脱硫*-*ヒドロキシル化*反応を極めて位置および立体選択的に起こし、開環反応を伴わずに付加生成物(**3**)あるいは(**4**)を与えることを見い出した(Scheme B)。そこでこれらの極めて未知で興味深い現象を解明するとともに、後者の新反応の新たな展開として、酵素を超えた緩やかな水溶液中での弱い配位環境に基づく、chemzymatic な不斉*脱硫*—*ヒドロキシル化*反応の開発を行い、新規で強力な生理活性物質(UCS 1025)(**5**)合成への利用についても詳細に検討することを目的とした。



Scheme B

まとめると、本報告書は次の六つの章より成り立っている。

第一章　A New Entry for the Preparation of Substituted Aromatic Carbonyl Compounds Mediated by SmI_2

第二章　Novel and Practical Asymmetric Synthesis of an Azetidine Alkaloid, Penaresidin B

第三章　First Total Synthesis of a New Pyrrolizidine Alkaloid, Amphorogynine A

第四章　First Total Synthesis of a New Sesquiterpenoid Natural Product, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone

第五章　Lewis Acid-promoted Tandem Desulfurization and Hydroxylation of _-Phenylthio-substituted lactams: Novel Synthetic Strategy of Isoindolobenzazepine Alkaloid, Chilenine

第六章　Novel and Stereoselective Asymmetric Synthesis of an Amino Sugar Analogue, Furanodictine A

第七章　Studies Toward a Synthesis of Trilobatin B, a Lignan from the Liverwort *Bazzania Trilobata*: Asymmetric Construction of the Tetrahydrofuran Segment

SmI_2 存在下での１電子移動反応による*脱硫-カップリング*反応は、これまでに Skrydstrup ら(*J. Am. Chem. Soc.* **2000**)によるペプチド鎖上での反応のみが知られている。また水溶液中での異常な*脱硫-ヒドロキシル化*反応に関しては全く報告されていない。今回の申請ではこの異常な反応性を詳細（Lewis 酸の種類、温度、水相との混合溶媒の種類等）に検討するとともに、Lewis 酸に容易に配位可能な chiral additive(アミノ酸や光学活性アミン等)を添加することにより、弱い配位環境に基づく chemzymatic な不斉*脱硫-ヒドロキシル化*反応の可能性を詳細に調査する。ついでこの不斉*脱硫-ヒドロキシル化*反応を利用し、糸状菌より単離構造決定され、杆状菌やブドウ状球菌などの細菌類に対して極めて強い殺菌作用があるだけでなく、腸ガンや腎臓ガンの細胞分裂を強く抑制することが昨年明らにされた新しい化合物、UCS 1025 類(**5**)(Scheme B)の不斉全合成を目的としている。この化合物は直接的な骨格構築が難しく、申請者が検討しているヒドロキシル化法以外に開環反応を伴わずに立体選択的に水酸基を導入する

術はないと考えられる。

水酸基を含む複素環系生理活性天然物の多くは、われわれ生体系を維持コントロールする重要な物質であるが、極めて不安定であり取り扱う研究室も少なく、独自の操作方法に関する know-how を有している。本申請でもこれまでに蓄えたこれら不安定化合物に関する知識を最大限利用し、加えて今回発見した新知見を開拓、応用することにより、新しくかつ切れ味の鋭い生理活性物質の新構築法の確立を実施するものである。

文部省科学研究費補助金（基盤研究（C）（2））
研究成果報告書

研究課題　　水溶液中での異常な脱硫—水和反応
（強力かつ新規な抗ガン物質の不斉合成に向けて）

課題番号　　１５５５００３１

研究組織　　研究代表者　　依　田　秀　実

研究経費（単位千円）

	直接経費
平成１５年度	２，５００
平成１６年度	１，３００
合計	３，８００

研究発表

1．学会誌等

(1) Studies Toward a Synthesis of Trilobatin B, a Lignan from the Liverwort *Bazzania Trilobata*: Asymmetric Construction of the Tetrahydrofuran Segment
H. Yoda,* Y. Nakaseko and K. Takabe, *Tetrahedron Letters*, *45*, pp. 4217-4220 (2004). (Journal Ranking: 0.73, Impact Factor: 2.19)

(2) Novel and Stereoselective Asymmetric Synthesis of an Amino Sugar Analogue, Furanodictine A
H. Yoda,* Y. Suzuki and K. Takabe, *Tetrahedron Letters*, *45*, pp. 1599-1601 (2004). (Journal Ranking: 0.73, Impact Factor: 2.19)

(3) First Asymmetric Synthesis of a Marine Furanosester-terpene Natural Product, (18*S*)-Variabilin, Employing Enzymatic Desymmetrization of Propanediol Derivatives
K. Takabe,* H. Hashimoto, H. Sugimoto, M. Nomoto and H. Yoda, *Tetrahedron Asymmetry*, *15*, pp. 909-912 (2004). (Journal Ranking: 0.78, Impact Factor: 2.52)

(4) Convenient Synthesis of Pulchellalactam, a CD45 Protein Tyrosine Phosphatase Inhibitor from the Marine Fungus *Corollospora Pulchella*, and its Related Compounds
J. Bessho, Y. Shimotsu, S. Mizumoto, N. Mase, H. Yoda, and K. Takabe,* *Heterocycles*, *63*, pp. 1013-1016 (2004). (Journal Ranking: 0.49, Impact Factor: 1.01)

(5) Lewis Acid-promoted Tandem Desulfurization and Hydroxylation of γ-Phenylthio-substituted lactams: Novel Synthetic Strategy of Isoindolobenzazepine Alkaloid, Chilenine
H. Yoda,* K. Inoue, Y. Ujihara, N. Mase and K. Takabe, *Tetrahedron Letters*, *44*, pp. 9057-9060 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

(6) First Total Synthesis of a New Sesquiterpenoid Natural Product, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone
H. Yoda,* K. Maruyama and K. Takabe, *Tetrahedron Letters*, *44*, pp. 1775-1777 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

(7) First Total Synthesis of a New Pyrrolizidine Alkaloid, Amphorogynine A
H. Yoda,* T. Egawa and K. Takabe, *Tetrahedron Letters*, *44*, pp. 1643-1646 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

(8) Novel and Practical Asymmetric Synthesis of an Azetidine Alkaloid, Penaresidin B
H. Yoda,* T. Uemura and K. Takabe, *Tetrahedron Letters*, *44*, pp. 977-979 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

(9) A New Entry for the Preparation of Substituted Aromatic Carbonyl Compounds Mediated by SmI_2
H. Yoda,* N. Kohata and K. Takabe, *Synthetic Communications*, *33*, pp. 1087-1094 (2003). (Journal Ranking: 0.4, Impact Factor: 0.83)

(10) Chemoenzymatic Synthesis of (*E*)-3,7-Dimethyl-2-octene-1,8-diol Isolated from the Hairpencils of Male *Danaus chrysippus* (African Monarch)
K. Takabe,* N. Mase, H. Hashimoto, A. Tsuchiya, T. Ohbayashi and H. Yoda, *Bioorg. Med. Chem. Lett.*, *13*, pp. 1967-1969 (2003). (Journal Ranking: 0.7, Impact Factor: 1.56)

(11) Enantioselective Alkylation Using a New C_3 symmetric Amine-based Chiral Phase-transfer Catalyst
N. Mase, T. Ohno, N. Hoshikawa, K. Ohishi, H. Morimoto, H. Yoda and K. Takabe,* *Tetrahedron Letters,44*, pp. 4073-4075 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

(12) Highly regioselective lipase-catalyzed acetylation and hydrolysis of acyclic α,ω-terpenediols and their diacetates
K. Takabe,* N. Mase, T. Hisano and H. Yoda, *Tetrahedron Letters, 44*, pp. 3267-3269 (2003). (Journal Ranking: 0.73, Impact Factor: 2.19)

2．口頭発表

(1) フロフラン型リグナン系生理活性天然物の合成研究
依田秀実，鈴木祐二，高部圀彦，第３５回中部化学関係学協会支部連合秋季大会，2004, 9, 17. 名古屋.

(2) SmI_2によるイオウ置換環状イミド類の新規脱硫—カップリング反応
依田秀実，加畑雅之，高部圀彦，第３５回中部化学関係学協会支部連合秋季大会，2004, 9, 17. 名古屋.

(3) ムチゴケ科新規リグナン類の置換テトラヒドロフラン骨格の不斉合成
依田秀実，中世古祐果，遠藤隼人，高部圀彦，日本化学会第８４春季年会，2004, 3. 神戸.

(4) アラビノース誘導体を用いた神経細胞の分化活性物質 furanodictine A の不斉合成
依田秀実，鈴木祐二，高部圀彦，日本化学会第８４春季年会，2004, 3, 28. 神戸.

(5) SmI_2によるイオウ置換環状イミド類の新規脱硫—カップリング反応
依田秀実，加畑雅之，高部圀彦，日本化学会第８４春季年会，2004, 3, 29. 神戸.

(6) イオウ置換カルボニル化合物の脱硫－ヒドロキシル化反応を利用した生理活性天然物 chilenine の全合成
依田秀実，井上圭一，高部圀彦，日本化学会第８４春季年会，2004, 3, 29. 神戸.

(7) イオウ置換カルボニル化合物の脱硫—ヒドロキシル化反応の開発

依田秀実，氏原保明，井上圭一，高部圀彦，日本化学会第８３春季年会，2003, 3, 29. 東京.

(8) *N*-アシル置換ラクタム類の官能基選択的反応の開発
依田秀実，遠藤隼人，高部圀彦，日本化学会第８３春季年会，2003, 3, 29. 東京.

(9) *cis*-アリル化反応を利用する新規ピロリジジン系アルカロイド amphorogynine 類の不斉合成
依田秀実，江川貴久，高部圀彦，日本化学会第８３春季年会，2003, 3, 29. 東京.

(10) SmI_2 によるイオウ置換ラクタム類の立体選択的脱硫反応の開発
依田秀実，小畑直紀，高部圀彦，日本化学会第８３春季年会，2003, 3, 29. 東京.

目　次

Chapter 1

A NEW ENTRY FOR THE PREPARATION OF SUBSTITUTED AROMATIC CARBONYL COMPOUNDS MEDIATED BY SAMARIUM(II) IODIDE

Hidemi Yoda,* Naoki Kohata, and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

ABSTRACT

A new route to substituted aromatic lactones and lactams via SmI_2-promoted desulfurization is described. Direct replacement of the phenylthio substituent by hydroxyalkylated groups featuring the novel accessible process for the construction of continuous quaternary carbon centers could be accomplished when the same type of reactions was undertaken with carbonyl compounds in the presence of SmI_2.

INTRODUCTION

During the past 10 years, many studies have been devoted to reactivity of samarium(II) species[1] with a variety of carbonyl compounds (aldehydes, ketones, esters,[2] acid chlorides,[3] and acid anhydrides[4]) for ring closure and/or C-C bond formation reactions. In addition, intramolecular and intermolecular Barbier-type reactions with haloalkanes toward the carbonyl group of ketones[5] and imides[6] have been reported. In this connection recent disclosures from this laboratory have demonstrated the first pinacolic cross-coupling reaction between phthalimides and carbonyl compounds and its application to two types of complete *threo*-selective reactions.[7] Although significant progress, thus, has been made in advancing the versatility of samarium(II) compounds, the lack of studies concerning the reactivity toward simple amides is surprising except in some special cases.[8] This low reactivity sometimes permits some selective transformations, for example Barbier-type reaction with amide ketones[9] or selective side chain introduction onto small peptides mediated by SmI_2.[10] Herein we wish to report our new successful entry for the preparation of substituted aromatic lactones and lactams via desulfurization mediated by SmI_2, and the coupling reactions with carbonyl compounds[11] under mild conditions, leading to the continuous quaternary α-hydroxyalkylated lactams (Scheme 1), since little effort with SmI_2 has been made for the utilization to desulfurization reactions.

Scheme 1

RESULTS AND DISCUSSION

Experiments have been initially performed on SmI_2-promoted desulfurization reaction employing γ-alkyl substituted derivatives **3** obtained from alkylation of sulfur-containing phthalides **2**.[12] The results from our survey are summarized in Table 1. To begin with, treatment of allylated phenylsulfonyl- or phenylthio phthalide **3** with 2.0 equiv. of SmI_2 at ambient temperature provided the desired desulfurized product **4** but in low yield, respectively (entries 1,6) together with the recovered starting material. The use of 3 equiv. of this reagent (entries 2,7) or the presence of an additive such as HMPA (entries 3,8) or *t*-BuOH (entries 4,9) had an effect on the rate to some extent, giving **4** in moderate yield (up to 42%) within 5 min. Finally, we found that the use of excess SmI_2 (entries 10,11) could effect these reactions in reasonable yield (up to 68%) without by products.

Table 1

Next, we examined the same type of reactions by the use of sulfur-substituted lactams **7** prepared from **5** in a similar manner as described above. As shown in Table 2, the reactions with allylated *N*-benzyl phenylsulfonyl lactam did not proceed in satisfactory yield when a small excess of SmI_2 were again used (entries 1,2), whereas the desulfurization reactions of phenylthio derivative changed the results and rapidly brought about the desired product **8** in 52% yield under the same reaction conditions along with the starting lactam (entry 4). The further beneficial result was obtained in reaction employing HMPA as an additive (entry 5) to afford **8** in 73% isolated yield. Furthermore, it became apparent that this procedure was applicable for the production of a wide range of lactams through replacement of the γ-substituents together with a

change of the *N*-functional groups. Especially, we were delighted to find that 5 equiv. of this reagent in the presence of HMPA (3.0 equiv.) effect these reactions in excellent yield (up to 93%) to provide various types of γ- and *N*-substituted lactams **8** (entries 9, 11-14).

Table 2

Although an in-depth mechanistic investigation of the above experiments was not pursued, a tentative explanation of these results could be possible. Thus, the presence of the nitrogen atom in the substrate would stabilize the Sm(III) species obtained from subsequent reduction of the desulfurization-derived benzyl radical with the excess equiv. of SmI_2.

As a further illustration of the scope of the above outcome, we turned our attention to the construction of the quaternary carbon center via direct replacement of the sulfur substrate to alkyl groups. The reactions of lactam **7** with haloalkane did not proceed under any conditions even in the use of excess SmI_2. When **7** was, however, in turn treated with butanal (3.0 equiv.) in the presence of SmI_2 as shown in Table 3 (entry 1), it afforded the desired coupling product **9** with the crucial hydroxyalkylated quaternary carbon center (41%) accompanying the formation of the normal desulfurized compound **8** (51%). It will be of interest to note that enhancement of the yield was observed upon employing the sterically more hindered ketones (up to 71%), leading to the various types of coupling products containing the continuous quaternary carbon centers (entries 2,3,5,6).

Table 3

In summary, we have achieved a short and easily accessible entry not only for the preparation of a variety of substituted aromatic carbonyl compouds but also for the development of the coupling reaction with several carbonyl compounds via

desulfurization mediated by SmI_2, leading to the continuous quaternary α-hydroxyalkylated lactams. This procedure will find more convenient alternative to existing desulfurization reactions and proved to be a superior quaternary C-C bond formation method.

EXPERIMENTAL

Typical experimental conditions (entry 5 in Table 3): To a deep-blue THF (5 mL) solution prepared from samarium metal powder (0.228 g, 1.53 mmol) and diiodomethane (0.393 g, 1.474 mmol) under Ar was added a solution of *N*-methyl-3-methyl-3-phenylthiophthalimidine (0.079 g, 0.295 mmol) and acetone (0.051 g, 0.885 mmol) in THF (1 mL) at 0 °C. After the mixture was stirred for 1 h at room temperature, it was poured into a dilute HCl (4 mL) and extracted with ethyl acetate. The product was chromatographed after evaporation (eluted with hexane-ethyl acetate (1:1)) to give *N*-methyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (0.046 g, 0.21 mmol) in 71% and *N*-methyl-3-methylphthalimidine (0.012 g, 0.074 mmol) in 25% yields, respectively.

N-benzyl-3-methyl-3-(1-hydroxybutyl)phthalimidine (entry 1 in Table 3); IR (thin film) 3255, 1661, 766, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.62-0.96 (t, J = 6.6 Hz, 3H), 0.96-1.62 (m, 4H), 1.42 (s, 3H), 3.71 (br, 1H), 4.01 (t, J = 6.6 Hz, 1H), 4.83 (s, 2H), 7.05-7.62 (m, 8H), 7.71-8.13 (m, 1H). *Anal.* Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.75; H, 7.42; N, 4.39.

N-benzyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (entry 2 in Table 3); IR (thin film) 3266, 1656, 760, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (s, 3H), 1.35 (s, 3H), 1.51 (s, 3H), 2.12 (br, 1H), 4.98 (s, 2H), 7.11-7.68 (m, 8H), 7.75-7.82 (m, 1H). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.29; H, 7.11; N, 4.71.

N-methyl-3-benzyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (entry 3 in Table 3); IR (thin film) 3286, 1672, 756, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.01 (s, 3H), 1.33 (s, 3H), 2.38 (br, 1H), 3.20 (s, 3H), 3.48, 3.53 (2s, 2H), 7.48-7.05 (m, 5H), 7.15-7.81 (m, 4H). *Anal.* Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.38; H, 7.09; N, 4.66.

N-methyl-3-methyl-3-(1-hydroxybutyl)phthalimidine (entry 4 in Table 3); IR (thin film) 3266, 1655, 746, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.59-0.93 (t, J = 6.6 Hz, 3H), 0.96-1.75 (m, 4H), 1.36, 1.45 (2s, 3H), 2.49 (br, 1H), 2.88, 3.01 (2s, 3H), 3.71 (br, 1H), 4.05 (t, J = 5.6 Hz, 1H), 7.15-7.56 (m, 3H), 7.61-7.94 (m, 1H). *Anal.* Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.94; H, 8.19; N, 6.13.

N-methyl-3-methyl-3-(1-methyl-1-hydroxyethyl)phthalimidine (entry 5 in Table 3); IR (thin film) 3250, 1668, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (s, 3H), 1.18 (s, 3H), 1.50 (s, 3H), 2.62 (br, 1H), 3.07 (s, 3H), 7.03-7.50 (m, 3H), 7.60-7.92 (m, 1H). *Anal.* Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.40; H, 7.79; N, 6.31.

N-methyl-3-methyl-3-(1-methyl-1-hydroxybutyl)phthalimidine (entry 6 in Table 3); IR (thin film) 3286, 1659, 766, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55-0.85 (t, J = 6.6 Hz, 3H), 0.96-1.45 (m, 4H), 0.85, 1.18 (2s, 3H), 1.50 (s, 3H), 2.45 (br, 1H), 3.03 (s, 3H), 7.15-7.61 (m, 3H), 7.61-7.91 (m, 1H). *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.96; H, 8.47; N, 5.71.

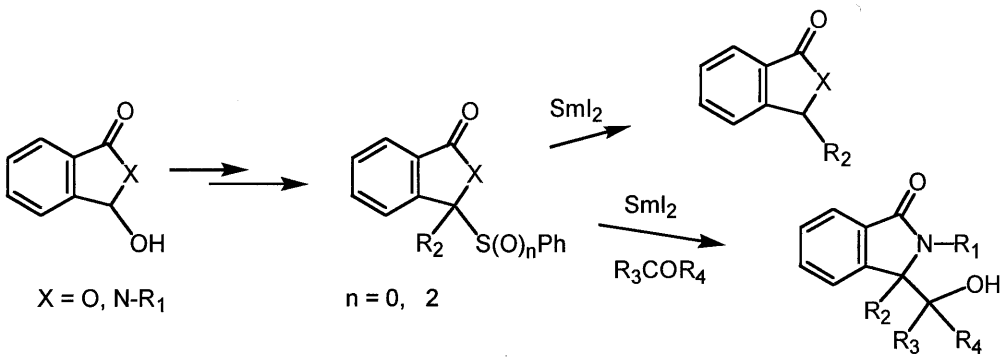
ACKNOWLEDGMENTS

This work was partially supported by a Grant-in Aid (No. 13640530) from the Ministry of Education, Science, Sports and Culture of Japan.

REFERENCES

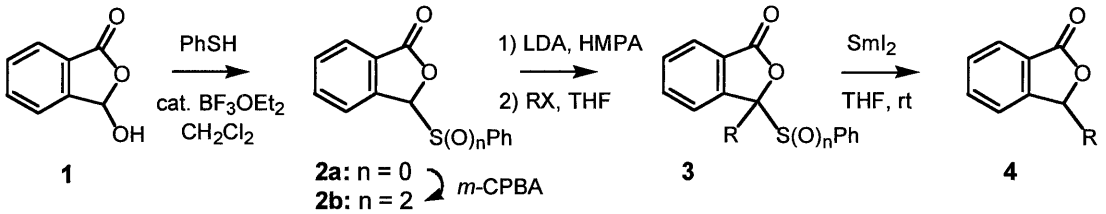
1. (a) Girard, P.; Namy, J.-L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693. (b) Namy, J.-L.; Girard, P.; Kagan, H. B. *Nouv. J. Chim.* **1977**, *1*, 5. (c) Kagan, H. B. *New. J. Chem.* **1990**, *14*, 453.
2. For recent reviews, see: (a) Kagan, H. B.; Namy, J.-L.; Girard, P. *Tetrahedron* **1981**, *37*(Supplement No. 1), 175. (b) Kagan, H. B.; Namy, J.-L. *Tetrahedron* **1986**, *42*, 6573. (c) Kagan, H. B.; Sasaki, M.; Collin, J. *Pure Appl. Chem.* **1988**, *60*, 1725. (d) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (e) Molander, G. A. *Org. React.* **1994**, *46*, 211. (f) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307. (g) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321. (h) Molander, G. A.; Sono, M. *Tetrahedron* **1998**, *54*, 9289. (i) Mochrouhi, F.; Namy, J.-L. *Tetrahedron* **1998**, *54*, 11111. (j) Krief, A.; Laval, A. M. *Chem. Rev.* **1999**, *99*, 745. (k) Matsuda, F. *J. Synth. Org. Chem. Japan* **2001**, *59*, 92. For recent examples, see: (l) Swindell, C. S.; Fan, W. *Tetrahedron Lett.* **1996**, *37*, 2321. (m) Inoue, M.; Sasaki, M.; Tachibana, K. *Tetrahedron* **1999**, *55*, 10949. (n) Dinesh, C. U.; Reissig, H. U. *Angew.Chem. Int. Ed.* **1999**, *38*, 789. (o) Riber, D.; Hazell, R.; Skrydstrup, T. *J. Org. Chem.* **2001**, *65*, 5382. (p) Farcas, S.; Namy, J.-L. *Tetrahedron* **2001**, *57*, 4881.
3. (a) Souppe, J.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1984**, *25*, 2869. (b) Mochrouhi, F.; Namy, J.-L.; Kagan, H. B. *Tetrahedron Lett.* **1997**, *38*, 7183.
4. Mochrouhi, F.; P_lea, E.; Namy, J.-L. *Eur. J. Org. Chem.* **1998**, 2431.
5. (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216. (b) Mochrouhi, F.; Namy, J.-L.; Kagan, H. B. *Synlett* **1996**, 633.
6. (a) Ha, D.-C.; Yun, C.-S.; Yu, E. *Tetrahedron Lett.* **1996**, *37*, 2577. (b) Ha, D.-C.; Yun, C.-S.; Lee, Y. *J. Org. Chem.* **2000**, *65*, 621. (c) Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2000**, *41*, 7299. (d) Farcas, S.; Namy, J.-L. *Tetrahedron Lett.* **2001**, *42*, 879.
7. Yoda, H.; Matsuda, K.; Nomura, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 1775.

8. (a) Ogawa, A.; Takami, N.; Nanke, T.; Ohya, S.; Hirao, T. *Tetrahedron* **1997**, *53*, 12895. (b) Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* **1999**, *40*, 7497. (c) Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem. Soc.* **1987**, *109*, 453. (d) McDonald, C. E.; Galka, A. M.; Green, A. I.; Keane, J. M.; Kowalchick, J. E.; Micklitsch, C. M.; Wisnoski, D. D. *Tetrahedron Lett.* **2001**, *42*, 163. (e) Yoda, H.; Katoh, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 2509.
9. Molander, G. A.; Etter, J. B.; Zinke, P. W. *J. Am. Chem Soc.* **1987**, *109*, 453.
10. Ricci, M.; Blakskjaer, P.; Skrydstrup, T. *J. Am. Chem Soc.* **2000**, *122*, 12413, and references cited therein.
11. Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 9225.
12. Yoda, H.; Shirakawa, K.; Takabe, K. *Chem. Lett.* **1989**, 1391.



Scheme 1

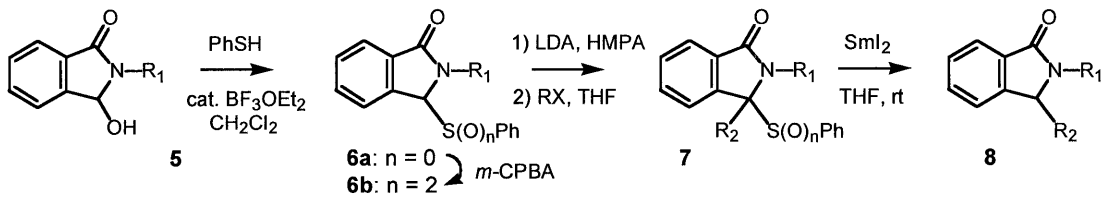
Table 1. SmI_2-promoted desulfurization reaction of lactones (**3**) after alkylation of (**2**).



Entry	n	R	Yield of **3** (%)[a]	SmI_2 (equiv.)	Additives (equiv.)	Yield of **4** (%)[a]
1	2	CH_2=$CHCH_2$	85	2.0	–	6
2	2	CH_2=$CHCH_2$	–	3.0	–	20
3	2	CH_2=$CHCH_2$	–	3.0	HMPA (3.0)	24
4	2	CH_2=$CHCH_2$	–	3.0	*t*-BuOH (1.0)	42
5	2	CH_2=$CHCH_2$	–	5.0	–	42
6	0	CH_2=$CHCH_2$	64	2.0	–	11
7	0	CH_2=$CHCH_2$	–	3.0	–	38
8	0	CH_2=$CHCH_2$	–	3.0	HMPA (3.0)	38
9	0	CH_2=$CHCH_2$	–	3.0	*t*-BuOH (1.0)	42
10	0	CH_2=$CHCH_2$	–	5.0	–	61
11	0	CH_2=$CHCH_2$	–	10.0	–	68
12	0	CH_3	92	5.0	–	32
13	0	CH_2Ph	90	5.0	–	37

a) Isolated yield.

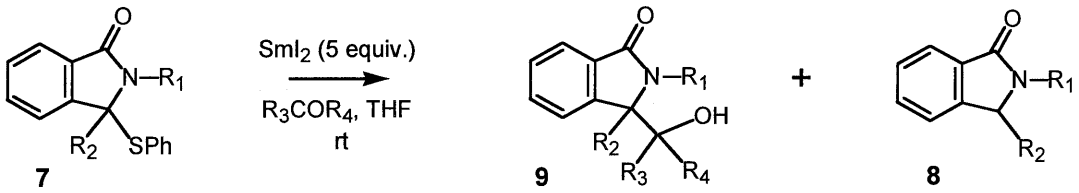
Table 2. SmI_2-promoted desulfurization reaction of lactams (**7**) after alkylation of (**6**).



Entry	n	R_1	R_2	Yield of **7** (%)[a]	SmI_2 (equiv.)	Additives (equiv.)	Yield of **8** (%)[a]
1	2	CH_2Ph	CH_2=$CHCH_2$	78	2.0	–	19
2	2	CH_2Ph	CH_2=$CHCH_2$	–	3.0	–	17
3	0	CH_2Ph	CH_2=$CHCH_2$	96	2.0	–	12
4	0	CH_2Ph	CH_2=$CHCH_2$	–	3.0	–	52
5	0	CH_2Ph	CH_2=$CHCH_2$	–	3.0	HMPA (3.0)	73
6	0	CH_2Ph	CH_3	96	3.0	HMPA (3.0)	53
7	0	CH_2Ph	CH_3	–	3.0	*t*-BuOH (1.0)	43
8	0	CH_2Ph	CH_3	–	3.0	HMPA (3.0)	72
9	0	CH_2Ph	CH_3	–	5.0	HMPA (3.0)	88
10	0	CH_2Ph	CH_2Ph	92	3.0	HMPA (3.0)	73
11	0	CH_2Ph	CH_2Ph	–	5.0	HMPA (3.0)	90
12	0	CH_3	CH_2=$CHCH_2$	96	5.0	HMPA (3.0)	93
13	0	CH_3	CH_3	92	5.0	HMPA (3.0)	84
14	0	CH_3	CH_2Ph	95	5.0	HMPA (3.0)	89

a) Isolated yield.

Table 3. SmI_2-promoted coupling reactions of substituted lactams (**7**) with carbonyl compounds.[a]



7 **9** **8**

Entry	R_1	R_2	R_3	R_4	Yield of **9** (%)[b]	Yield of **8** (%)[b]
1	CH_2Ph	CH_3	*n*-C_3H_7	H	41	51
2	CH_2Ph	CH_3	CH_3	CH_3	62	33
3	CH_3	CH_2Ph	CH_3	CH_3	47	51
4	CH_3	CH_3	*n*-C_3H_7	H	33	66
5	CH_3	CH_3	CH_3	CH_3	71	25
6	CH_3	CH_3	CH_3	*n*-C_3H_7	61	34

a) All reactions employed 3.0 equiv. of carbonyl compouds.

b) Isolated yield.

Chapter 2

Novel and practical asymmetric synthesis of an azetidine alkaloid, penaresidin B

Hidemi Yoda,* Takuya Uemura and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Abstract

A novel and efficient asymmetric synthesis of the potent actomyosin ATPase activator, penaresidin B, is described in a short and complete stereoselective manner by featuring the elaboration of the fully functionalized homochiral lactam, which can also be regarded as an advanced intermediate for the synthesis of other azetidine alkaloids.

Marine sponges have frequently afforded a wide variety of sphingosine-related compounds,[1] in which penaresidins A (**1**) and B (**2**) isolated in 1991 from an Okinawan marine sponge *Penares* sp. by Kobayashi et al. are the first sphingosine-derived alkaloids possessing an interesting azetidine ring structure.[2] Tested as an inseparable mixture, these two compounds exhibit potent actomyosin ATPase-activating activity. As shown in Figure 1, the exact absolute configurations of five stereogenic centers in **1** were established to be 2*S*,3*R*,4*S*,15*S* and 16*S*, and the initially proposed structure of penaresidin B was revised to be **2**3 after structural characterization based on spectroscopic methods[2,4] supplemented by synthetic studies.[3,5,6] On the other hand a new azetidine alkaloid, penazetidine A (**3**), possessing potent protein kinase C inhibitory activity was isolated in 1994 from the Indo-Pacific marine sponge *Penares* sollasi by Crews and his coworkers.[7] The structure of the substituted azetidine closely related to penaresidins was confirmed to be **3** by the synthesis of Mori et al.[8] except for the side-chain stereochemistry.

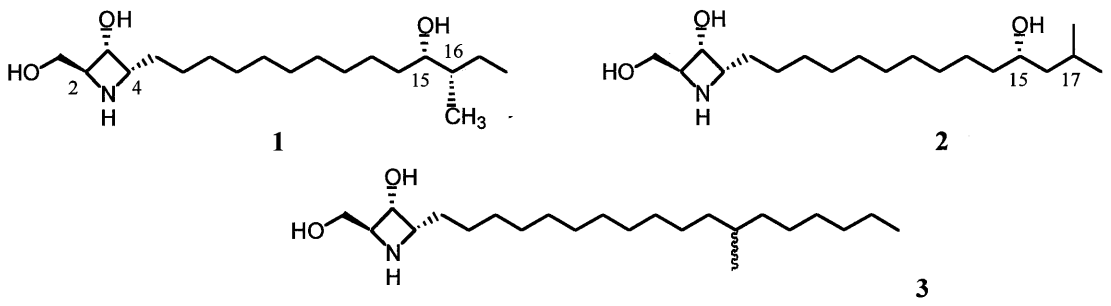


Figure 1. Penaresidin A (**1**), penaresidin B (**2**) and penazetidine A (**3**).

Keywords: penaresidin; azetidine alkaloid; lactam; nucleophilic addition; arabinofuranose.

Due to their significant activities and unique structural characteristics, they have been the subject of extensive synthetic efforts which have culminated in several syntheses.[8,9] Synthetic strategies described to date including our recent method,12b however, in general require multistep reactions or crucial techniques and were not necessarily satisfactory. The purpose of the present communication is to report a novel and convenient process for the asymmetric synthesis of **2**, which in turn would make it possible to provide a new opportunity for the synthesis of other azetidine alkaloids.

As shown in Scheme 1, we investigated the utilization of amino sugar for the synthesis of the functionalized homochiral lactam intermediate with desired stereogenic centers. When the acetylide elaborated from D-leucine[10] via the acetylene zipper reaction[11] was treated with the furanosylamine **5** prepared from D-arabinose derivative **4** at low temperature followed by oxidative degradation with PCC,[12] it afforded the non-terminal alkyne-lactam **6** with three substituents exclusively (>99% d.e., determined by 13C NMR and HPLC) in good yield. After exchange of the MPM(*p*-methoxybenzyl)-protecting group to the *N*-Boc function in **6** to enhance the nucleophilicity, deprotection of the benzyl groups accompanying simultaneous hydrogenation of the triple bond was effected by using Pd (black) in 4.4% HCOOH-MeOH to furnish the dihydroxylactam **7**. Then, **7** was regioselectively transformed through successive Bn- and MOM-protections into the synthetically useful homochiral lactam **8** in 74% and quantitative yields, respectively. No base-induced racemization of the g-position in **8** was observed in these reactions (determined by ^{13}C NMR). Reduction of **8** with $NaBH_4$ cleanly opened the lactam ring and afforded the corresponding acyclic alcohol quantitatively again, which was in turn submitted to MOM-protection followed by debenzylation with Pd (black) to afford the desired *N*-Boc alcohol **9** in extremely high yield. In contrast to Lin's results9d construction of the azetidine ring was accomplished under mild basic conditions after introduction of the methanesulfonyl group to provide the *N*-Boc and tri-*O*-methoxymethylated penaresidin B **10** in 50% yield (two steps).[13] Finally, removal of the protecting groups in **10** was conducted under acidic conditions to complete the total

synthesis of **1** in 12% overall yield from the commercially available D-arabinose derivative **4**, whose structure was characterized after derivatization to the known tetraacetate **11**, $[\alpha]_D^{25}$+47.3° (c 0.75, CHCl3) {lit. $[\alpha]_D^{25}$+47° (c 0.42, $CHCl_3$)$_3$}. The spectral data of synthetic **11** were completely identical to those of the reported values in all respects.[3]

Scheme 1

This process involves no separation of stereoisomers through the entire sequence until penaresidin B was synthesized from the starting D-arabinose derivative **4**, which constitutes a new synthetic strategy and represents a short and easily accessible pathway to penaresidins. We anticipate that the non-terminal alkyne lactam such as **6** will serve as an advanced template for the synthesis of other nitrogen-containing natural alkaloids.

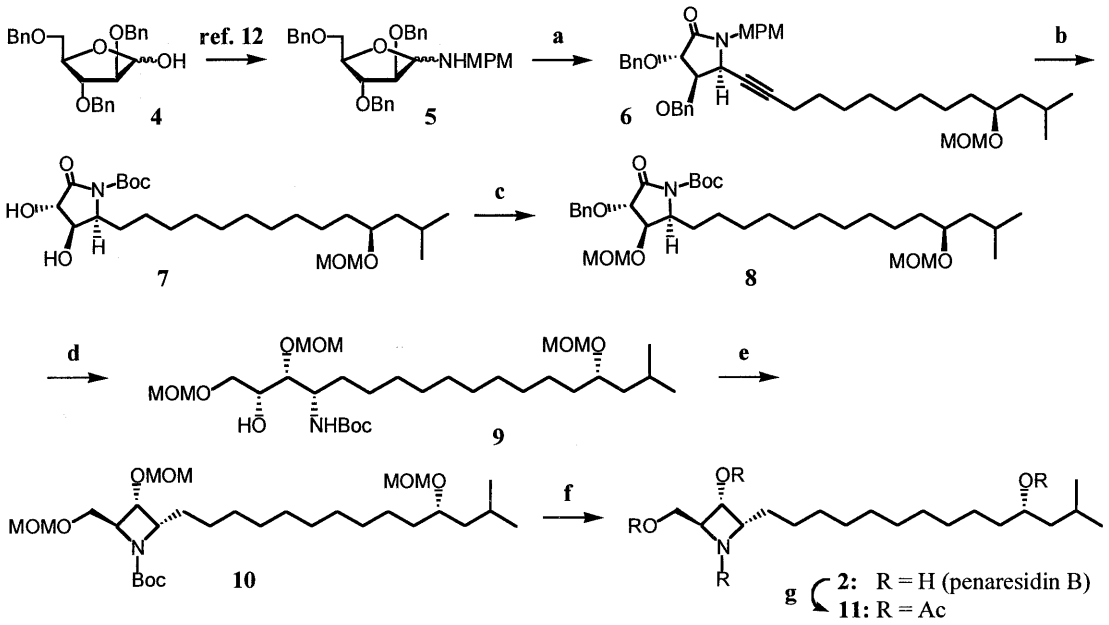
Acknowledgments

We thank Emeritus Professor Kenji Mori (The University of Tokyo) for valuable suggetions and discussions in addition to his kind supply of the copies of the 1H and 13C NMR spectra of penaresidin B tetraacetate. This work was supported in part by a Grant-in-Aid (No. 13640530) for Scientific Research from Japan Society for the Promotion of Science.

References

1. (a) Kaufer, J. M.; Hakomori, S. In *Handbook of Lipids Research Vol. 3, Sphingolipid Biochemistry*, Plenum Press, New York, **1983**; (b) Sweeley, C. C. In *Biochemistry of Lipids and Membranes*; Vance, D. E.; Vance, J. E. Eds.; Benjamin/Commings: Menlo Park, CA, **1985**; (c) Kobayashi, J.; Ishibashi, M. *Heterocycles*, **1996**, *42*, 943-970.
2. Kobayashi, J.; Cheng, J.-f.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135-1137.

3. Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97-111.
4. Kobayashi, J.; Tsuda, M.; Cheng, J.-f.; Ishibashi, M.; Takikawa, H.; Mori, K. *Tetrahedron Lett.* **1996**, *37*, 6775-6776.
5. Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841-4844.
6. Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689-7692.
7. Alvi, K. A.; Jaspars, M.; Crews, P. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2447-2450.
8. Yajima, A.; Takikawa, H.; Mori, K. *Liebigs Ann.* **1996**, 1083-1089.
9. Penaresidin A: (a) ref. 6; (b) ref. 3; (c) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813-3816; (d) Liu, D.-G.; Lin, G.-Q. *Tetrahedron Lett.* **1999**, *40*, 337-340. Penaresidin B: (a) ref. 3; (b) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283-3284.
10. Mori, K. *Tetrahedron* **1976**, *32*, 1101-1106.
11. (a) Brown, C. A.; Yamashita, A. *J. Am. Chem. Soc.* **1975**, *97*, 891-892; (b) Abrams, S. R. *Can. J. Chem.* **1984**, *62*, 1333-1334.
12. (a) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555-4558; (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669-2672.
13 Recently Lin et al. reported that the same type of nitrogen-directed cyclization to azetidine ring did not proceed under any conditions,9d however, in our case the desired cyclized product **10** was obtained in good yield (50%, two steps) with no difficulty. These different results would be ascribed to the steric bulkiness of both hydroxyl- and amino-protecting groups.



Scheme 1. *Reagents and conditions:* (**a**) **1**, (*S*)-HC≡C$(CH_2)_7$CH(OMOM)CH_2CH$(CH_3)_2$, BuLi, THF, -78 - 0 °C; 82%; **2**, PCC, MS 4A, CH_2Cl_2; 62%; (**b**) **1**, CAN, CH_3CN-H_2O (9:1); 66%; **2**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2; quant.; **3**, Pd (black), 4.4% HCOOH-MeOH; 95%; (**c**) **1**, BnBr, Ag_2O, CH_3COOEt; 74%; **2**, MOMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2; quant.; (**d**) **1**, $NaBH_4$, MeOH; quant.; **2**, MOMCl, $(i\text{-Pr})_2NEt$, CH_2Cl_2; quant.; **3**, Pd (black), 4.4% HCOOH-MeOH; quant.; (**e**) **1**, MsCl, Et_3N, CH_2Cl_2; **2**, NaH, THF; 50% (two steps); (f) conc. HCl, MeOH; (g) Ac_2O, pyridine, DMAP; quant..

Chapter 3

First Total Synthesis of a New Pyrrolizidine Alkaloid, Amphrogynine A

Hidemi Yoda,* Takahisa Egawa, and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Abstract

An efficient and stereodefined strategy is described for the first asymmetric synthesis of a new type of pyrrolizidine alkaloids, amphorogynine A and its 1-epi-isomer. The key 2,4-disubstituted pyrrolidine ring was constructed by elaboration of the chiral lactam derivative incorporating the D-malic acid-derived skeleton through asymmetric *cis*-allylation of the functionalized allysilane

Amphorogynine A together with structurally related compounds, amphorogynines B, C, and D, was first isolated in 1998 by Païs and coworkers from the leaves of *Amphorogyne spicata* Stauffer & Hürlimann (Santalaceae) in a research for alkaloids in New Caledonian plants.[1] After structural characterization by the same group based on spectroscopic methods using chemical correlations, these were revealed to be a new class of pyrrolizidine alkaloids possessing a 1,6-disubstituted structure (Figure 1).[1] These alkaloids differ from the position of the substituents on the pyrrolizidine ring. Whereas amphorogynines possess a hydroxyl group at the C(6) position, the well known necines generally bear this substituent at the C(7) position of the pyrrolizidine.[2] Since such alkaloids showing substituted functions at both C(1) and C(6) only have not been reported previously,[3] their structural and stereochemical complexity coupled with their diverse and potentially useful characteristics would make them hereafter inviting targets for synthesis. The synthesis of this type of compounds poses interesting and often unsolved problems of sterecontrol. Consequently, no report concerning the total synthesis of **1** along with related natural products has been appeared to date

Figure 1

Keywords: amphorogynine; pyrrolizidine alkaloid; allylation; lactam; malic acid

With these considerations in mind, we wish to communicate the details of the first asymmetric synthesis of **1** and its 1-epimer (6-epi-amphorogynine B) by means of requisite stereoselective allylation of the a-hydroxypyrrolidine intermediate elaborated from D-malic acid.

As shown in Scheme 1, *N*-MPM(*p*-methoxybenzyl)-imide **6** obtained from D-malic acid (**5**) was reduced regioselectively with $NaBH_4$[4] and readily effected by BF3•OEt2-induced reductive deoxygenation with $Et3SiH_5$ to afford the acetoxylactam intermediate. After exchange of the acetyl group to the benzyl moiety, the lactam **7** thus obtained was transformed into the expected *N*-Boc derivative **8**, $[\alpha]_D^{26}$+16.5° (c 1.03, $CHCl_3$), by four steps through both subsequent *N*- and *O*-deprotection and reprotection sequence (54% overall yield from D-malic acid) for further convenient transformation of the functional groups. Initial experiments have been performed on a coupling reaction via *N*-acyliminium ion promoted by BF_3•OEt_2 at -78 °C between allyltrimethylsilane and a-hydroxypyrrolidine derivative derived from the partial reduction of **8**.[6] These conditions brought about the desired allylated pyrrolidine **9a** as a sole product with complete *cis*-stereoselectivity.[7] These results are in accord with expectations based on the preceding reports.[6a,9] We were delighted to find that the use of the functionalized allyltrimethylsilane reagent (*E*/*Z* = 3.1/1.0) prepared from 3-buten-1-ol according to the Seyferth's procedure[10] also underwent fast reaction to afford the corresponding coupling product **9b** with complete *cis*-relationship again[11] in the pyrrolidine ring, but with about 55% d.e. at the allylic position (determined by 1H NMR), which would be ascribed to the ratio of the starting geometrical isomers.

For the purpose of the construction of a pyrrolizidine ring system, **9b** was in turn submitted to deprotection of the MPM moiety followed by introduction of the bromo function as the leaving group.[12] The olefinic part in the pyrrolidine derivative **10** thus obtained was then cleaved via dihydroxylation to give the aldehyde intermediate, which was successively subjected to bromine-induced oxidation,[13] leading to the corresponding methyl ester **11** in 89% yield. The remaining side unit in

amphorogynines prepared from vanillin was then introduced in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride and DMAP[14] after desilylation. Finally, the coupling product **12** was effected by deprotection with BF3•OEt215 together with concomitant cyclization, followed by debenzylation of the resulting pyrrolizidine **13** with 5% Pd on carbon to produce the desired compound, amphorogynine A (**1**), accompanying with its 1-epimer (6-epi-amphorogynine B) **14**. These were readily separated by column chromatography on silica gel and demonstrated that the less mobile compound (CHCl3/MeOH=3:1; TLC Rf 0.55) corresponded to the natural product **1** (58%), $[\alpha]_D^{26}$+52.1° (c 0.57, CHCl3) {lit. $[\alpha]_D$+53° (c 1, CHCl3)1}, and the more mobile substance ($CHCl_3$/MeOH=3:1; TLC Rf 0.60) was the 1-epi-isomer **1416** of amphorogynine A (6-epi-amphorogynine B) (26%), $[\alpha]_D^{27}$-15.7° (c 0.38, $CHCl_3$), based on their spectral data,1 respectively. The spectral data of synthetic (+)-**1** were completely identical to those of the reported natural product.[1]

Scheme 1

In summary this work constitutes the first synthesis of the natural pyrrolizidine alkaloid, amphorogynine A, and verifies the structure proposed in the literature for this natural product, since no report concerning the total synthesis of amphorogynines has been appeared to date.

Acknowledgments

This work was supported in part by a Grant-in-Aid (No. 13640530) for Scientific Research from Japan Society for the Promotion of Science.

References

1. Huong, D. T. T.; Martin, M.-T.; Litaudon, M.; Sévenet, T.; Païs, M. *J. Nat. Prod.* **1998**, *61*, 1444.

2. (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129 and references cited therein; (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785; (c) Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **2000**, *65*, 2875; (d) Denmark, S., E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046; (e) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672; (f) Wróbel, J. T. In *Alkaloids*; Brossi, A., Ed.; Academic Press: New York, **1985**; *Vol. 26*, Chapt. 7.

3. Hartmann, T.; Witte, L. In *Alkaloids, Chemical and Biological Perspectives*; Pelletier, W. S., Ed.; Elsevier: Amsterdam, **1995**; *Vol. 9*, pp 155.

4. (a) Klaver, W. J.; Hiemstra, H.; Speckamp, W. N. *J. Am. Chem. Soc.* **1989**, *111*, 2588; (b) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 253; (c) Chamberlin, A. R.; Chung, Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653; (d) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313.

5. (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976; (b) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273; (c) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137; (d) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531; (e) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669 and references cited therein.

6. (a) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1992**, *46*, 194; (b) Thaning, M.; Wistrand, L.-G. *Acta Chem. Scand.* **1989**, *43*, 290; (c) Shono, T.; Matsumura, Y.; Tsubata, K.; Uchida, K. *J. Org. Chem.* **1986**, *51*, 2590.

7. The absolute stereochemistry of the newly created carbon center in **9a** was unambiguously proved to be *S* after derivatisation of **9a** to the benzyl ether by comparing its spectral data with those of the *trans*-*N*-Boc-pyrrolidine **19**, which was in turn elaborated from D-tartaric acid-derived C2-imide **15** employing *cis*-selective allylation reaction[8] as shown below.

Scheme 2

8. Ryu, Y.; Kim, G. *J. Org. Chem.* **1995**, *60*, 103.

9. Seebach and Renaud[9a] have also observed a similar stereochemical behavior in the synthesis of 2,4-*cis*-substituted pyrrolidines;[9b] (a) Renaud, P.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1704; (b) Boto, A.; Hernández, R.; Suárez, E. *J. Org. Chem.* **2000**, *65*, 4930; (c) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973 and references cited therein. These results indicate that allylic A1,3-interactions involving the substitutent a to the nitrogen atom and the *N*-Boc group may determine the preferential conformation of the *t*-butoxycarbonyl function in the *N*-acyliminium ion intermediate. On the other hand, Ogasawara and his coworkers recently reported that upon reaction with allyltrimethylsilane in the presence of zinc(II) chloride, *N*-Boc-5-acetoxy-2-methoxypiperidine afforded the unexpected *trans*-selective allylation product predominantly (11:1) based on the anchimeric assistance of the acetate group; Tanaka, H.; Sakagami, H.; Ogasawara, K. *Tetrahedron Lett.* **2002**, *43*, 93.; Sakagami, H.; Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1996**, 1433.

10. (a) Seyferth, D.; Wursthorn, K. R.; Mammarella,R. E. *J. Org. Chem.* **1977**, *42*, 3104; (b) Seyferth, D.; Wursthorn, K. R.; Lim, T. F. O.; Sepelak, D. J. *J. Organometal. Chem.* **1979**, *181*, 293.

11. *Cis*-stereochemistry in the pyrrolidine ring of **9b** was determined based on its spectral data of synthetic (+)-**1**.

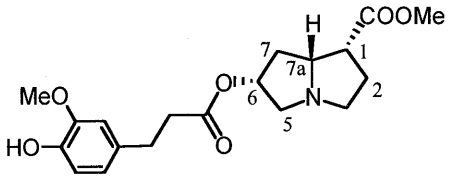
12. To begin with, experiments have been performed on a dihydroxylation reaction mediated by OsO_4 employing the tosylated compound **20** as shown below. The reaction, however, resulted in the preparation of the corresponding simultaneously cyclized products of **21** and **22** as an inseparable mixture.

Scheme 3

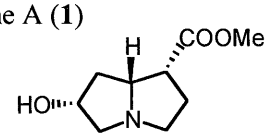
13. (a) Williams, D. R.; Klingler, F. D.; Allen, E. E.; Lichtenthaler, F. W. *Tetrahedron Lett.* **1988**, *29*, 5087; (b) Lichtenthaler, F. W.; Jarglis, P.; Lorenz, K. Synthesis

1988, 790.

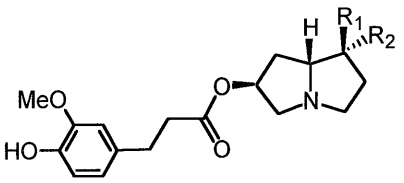
14. Kikuchi, H.; Saito, Y.; Komiya, J.; Takaya, Y.; Honma, S.; Nakahata, N.; Ito, A.; Oshima,Y. *J. Org. Chem.* **2001**, *66*, 6982.



Amphorogynine A (**1**)

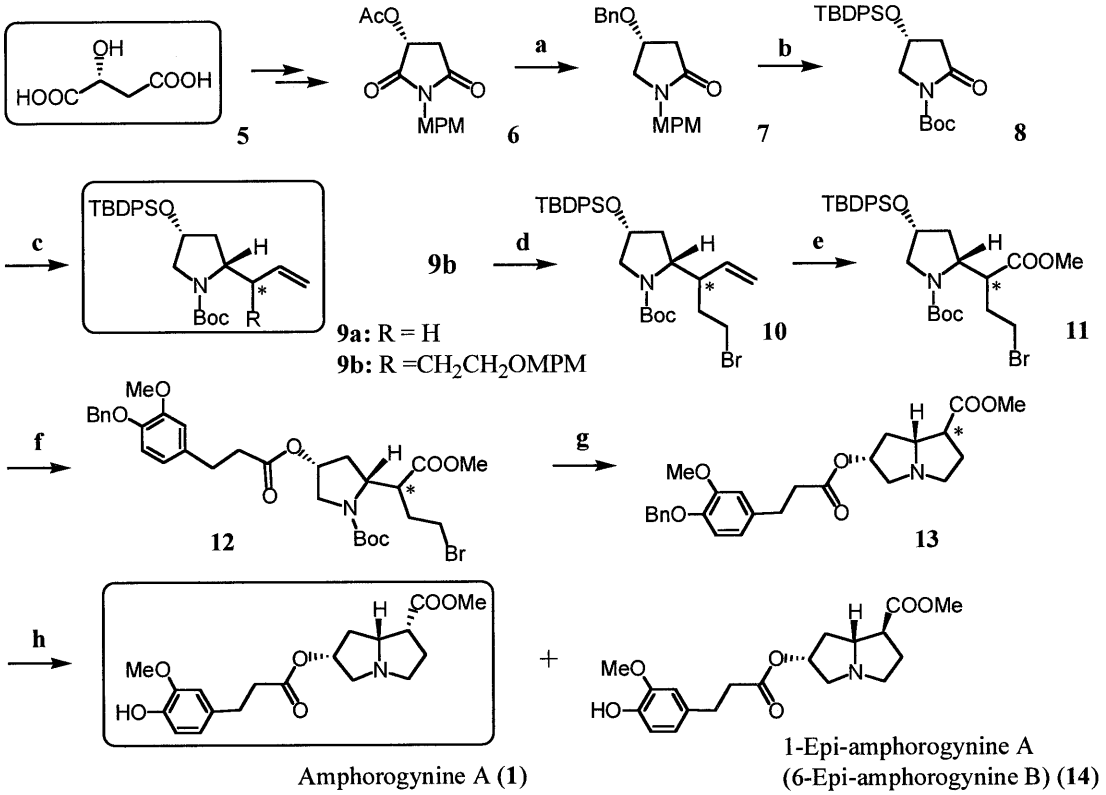


Amphorogynine D (**4**)

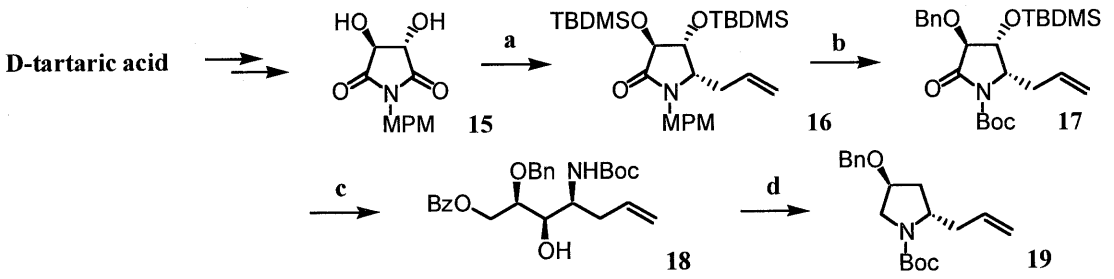


Amphorogynine B (**2**): R_1 = COOMe, R_2 = H
Amphorogynine C (**3**): R_1 = H, R_2 = COOMe

Figure 1

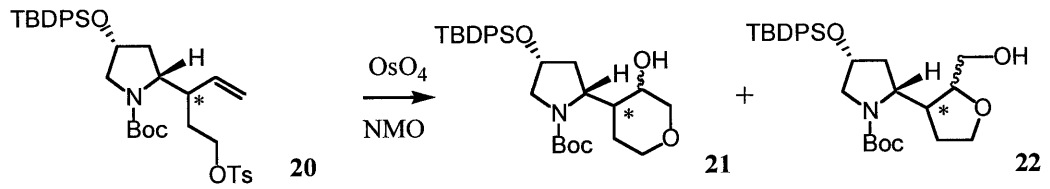


Scheme 1. *Reagents and conditions:* (**a**) **1**, $NaBH_4$, MeOH, 0 °C; **2**, BF_3•OEt_2, Et_3SiH, CH_2Cl_2, 0 °C; 69% (two steps); **3**, K_2CO_3, MeOH; 97%; **4**, BnBr, Ag_2O; DMF; 92%; (**b**) **1**, CAN, CH_3CN-H_2O (9:1); 93%; **2**, $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, 0 °C; quant.; **3**, Pd (black), 4.4% HCOOH-MeOH, 45 °C; quant.; **4**, TBDPSCl, imidazole, CH_2Cl_2; 94%; (**c**) **1**, $NaBH_4$, MeOH, 0 °C; **2**, CH_2=$CHCH_2SiMe_3$, BF_3•OEt_2, CH_2Cl_2, -78 °C; 72%; (**9a**) (two steps); $MPMO(CH_2)_2CH$=$CHCH_2SiMe_3$, BF_3•OEt_2, CH_2Cl_2, -78 °C; 47%; (**9b**) (two steps); (**d**) **1**, DDQ, CH_2Cl_2-H_2O (11:1), 0 °C; 90%; **2**, CBr_4, PPh_3, CH_2Cl_2; 96%; (**e**) **1**, OsO_4, NMO, acetone-H_2O, 0 °C; **2**, $NaIO_4$, ether-THF-H_2O (1:1:2); 88% (two steps); **3**, Br_2, $NaHCO_3$, MeOH-H_2O (9:1); 89%; (**f**) **1**, Bu_4NF, THF, 0 °C; 87%; **2**, 3-(*p*-benzyloxy-*m*-methoxyphenyl)propanoic acid, EDCI, DMAP, CH_2Cl_2; 0 °C; 70%; (**g**) **1**, BF_3•OEt_2, CH_2Cl_2; -15 °C; **2**, $NaHCO_3$, H_2O; 85% (two steps); (**h**) H_2, Pd/C, CH_3COOEt; 58% (amphorogynine A (**1**)); 26% (1-epi-amphorogynine A (6-epi-amphrogynine B)) (**14**).



Reagents and conditions: **(a)** **1**, TBDMSCl, imidazole, DMF; **2**, $NaBH_4$, MeOH; **3**, Ac_2O, pyridine, DMAP; **4**, CH_2=$CHCH_2SnBu_3$, $MgBr_2$, toluene; quant. (four steps); **(b)** **1**, conc. HCl, MeOH; **2**, BnBr, Ag_2O, CH_3COOEt; 58% (two steps); **3**, CAN, CH_3CN-H_2O (9:1); **4**, TBDMSCl, imidazole, DMF; **5**, $(Boc)_2O$, Et_3N, DMAP; 64% (three steps); **(c)** **1**, $NaBH_4$, MeOH; **2**, BzCl, Et_3N, CH_2Cl_2; **3**, Bu_4NF, THF; 71% (three steps); **(d)** **1**, Im_2CS, THF, 40 °C; **2**, Bu_3SnH, AIBN, toluene, 70 °C; 38% (two steps); **3**, K_2CO_3, MeOH; **4**, MsCl, Et_3N, CH_2Cl_2; **5**, *t*-BuOK, THF; 68% (three steps).

Scheme 2



Scheme 3

Chapter 4

First total synthesis of a new sesquiterpenoid natural product, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone

Hidemi Yoda,* Kazuhide Maruyama and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Abstract

An efficient and stereodefined process is described for the first preparation of a new prenyl-benzoylfuranone type sesquiterpenoid, (±)-3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone. The synthetic strategy is based on nucleophilic addition of organometallic reagents to the functionalized ketoamides elaborated from dihydroxyacetone dimer for the stereoselective construction of the key quaternary carbon center in the target compound.

3-(2,4-dihydroxybenzoyl)-4,5-dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone (**1**) together with two structurally related furanyl-substituted compounds, **2** and **3**, was isolated in 1999 by Kojima and coworkers[1] from the roots of *Ferula ferulioides* (STEUD.) KOROVIN (Umbelliferae), which grows in Bulgan Somon of Hovd City, Mongolia (Figure 1). Closely related new sesquiterpene phenylpropanoids, pallidones, were also isolated in 2000 from the roots of *Ferula pallida* (Umbelliferae).[2] These natural products have been used as a traditional medicine for the treatment of spasm[1] for a long time and were revealed to be a new class of prenyl-benzoylfuranone type sesquiterpenoid derivatives possessing contiguous three stereogenic centers along with a quaternary carbon in the lactone ring after structural characterization by the same group based on comprehensive spectral analysis. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, no report has been appeared to date despite those pharmacological activities and attractive structural features. The central feature of this communication is to report the details of the first and expeditious route from dihydroxyacetone dimer for the stereoselective construction of the tetrasubstituted lactone ring with a quaternary

---

Keywords: sesquiterpenoid; benzoylfuranone; nucleophilic addition; terpene lactone; dihydroxyacetone

carbon center and the total synthesis of (±)-3-(2,4-dihydroxybenzoyl)-4,5- dimethyl-5-(4,8-dimethyl-3(*E*),7(*E*)-nonadien-1-yl)tetrahydro-2-furanone natural product (**1**).

Figure 1

As shown in Scheme 1, the protected mono-terpene lactones **5**, key starting compounds for the synthesis of these terpenoids, were easily prepared from dihydroxyacetone dimer **4** according to our reported procedure.[3] Aminolysis of **5** with Me2NH opened the lactone ring to give amide alcohols **6** in high yields. Initial experiments have been performed with **6a** in expectation of the stereoselective construction of the quaternary carbon center. Swern oxidation of **6a** followed by the nucleophilic addition of methyl- or pentenyl Grignard reagent in situ gave the amide alcohol **7** and **8**,[4] as a predominant product,[5] respectively. After oxidation with PCC, we were delighted to find that the second alternating Grignard addition to the ketone intermediates in the presence of $CeCl_3$[6] could effect these reactions to afford the desired products **9a** and **9b** in a reverse stereoselective manner[7] at the quaternary center (the former; **9a**:**9b** = 92:8 and the latter; **9a**:**9b** = 7:93, determined by HPLC). These compounds were smoothly cyclized to the corresponding trisubstituted lactones **10a** and **10b**, respectively. Stereochemical results thus obtained can be easily explained in terms of the thermodynamically more stable Cram's non-chelation transition model.[4]

Scheme 1

With the above stereochemical outcome in hand, we turned our attention to the total synthesis of (±)-**1**. To begin with, successive treatment of **6a** with Swern oxidation reagents, homogeranylmagnesium bromide elaborated from geraniol in six steps,[8] and PCC, followed by the addition of the second methylmagnesium bromide as described

above afforded the amide alcohol **12a** through **11a** as a predominant product with moderate stereoselectivity (**12a**: **13a** = 87:13, determined by HPLC) (Scheme 2). After investigation with three types of mono-protected amide alcohols **6**, a surprising enhancement in stereoselectivity was finally observed upon employing **6c** with the largest TBDPS(*t*-butyldiphenylsilyl) group, leading to the desired isomer **12c** as the single product (determined by HPLC and ^{13}C NMR analysis). Cyclization of **12c** under mild conditions gave the trisubstituted lactone **14** in 76% yield without silyl-deprotection. **14** thus obtained was effected by coupling reaction with 2,4-dimethoxybenzaldehyde in the presence of LiHMDS at low temperature to produce the 3,4-*trans*-adduct **15** alone,[9] including the almost equivalent of stereoisomers at the benzyl position[4] (determined by ^{13}C NMR). Then, **15** was submitted to PCC oxidation again followed by deprotection with Bu_4NF to provide the lactone alcohol **16** in moderate yield. Whereas the deoxygenation reaction of the primary alcohol in **16** with phenylchlorothionoformate[10] or thiocarbonyldiimidazole[11] gave inseparable mixtures, use of Et_3B-Bu_3SnH[12] in the presence of O_2 at 0 °C after bromination of the hydroxyl group with CBr_4-PPh_3 dramatically changed the results and brought about the desired deoxgenated product **17** in satisfactory yield. Finally, **17** was subjected to deprotection with Me_3SiI to complete the total synthesis of (±)-**1**. The spectral data of synthesized **1** were completely identical with those of the reported natural compound.[1]

Scheme 2

In summary, this work constitutes the first synthesis of the naturally occurring prenyl-benzoylfuranone type of sesquiterpenoid through stereoselective construction of the tetrasubstituted lactones containing a quaternary carbon center from mono-terpene lactones and verifies the structure proposed in the literature for this compound.

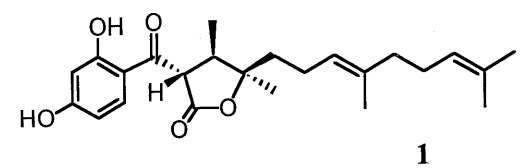
Acknowledgments

This work was supported in part by a Grant-in-Aid (No. 13640530) for Scientific

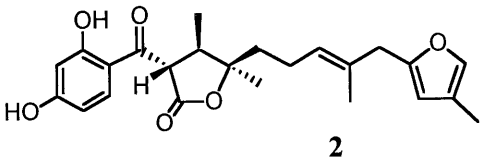
Research from Japan Society for the Promotion of Science.

References

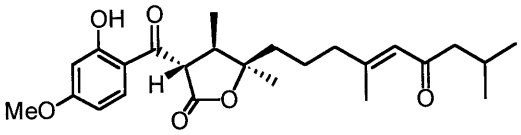
1. Kojima, K.; Isaka, K.; Ondognii, P.; Zevgeegiin, O.; Davgiin, K.; Mizukami, H.; Ogihara,Y. *Chem. Pharm. Bull.* **1999**, *47*, 1145-1147.
2. (a) Su, B.-N.; Takaishi, Y.; Honda, G.; Itoh, M.; Takeda,Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2000**, *63*, 436-440; (b) Su, B.-N.; Takaishi, Y.; Honda, G.; Itoh, M.; Takeda,Y.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.* **2000**, *63*, 520-522.
3. (a) Yoda, H.; Mizutani, M.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 4701-4702; (b) Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855-856.
4. Yoda, H.; Kimura, K.; Takabe, K. *Synlett* **2001**, 400-402.
5. The ratio of these two diastereomers was not determined.
6. Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, 111, 4392-4398.
7. The relative stereochemistry was unambiguously determined based on its spectral data of synthetic **1**.
8. (a) Trost, B. M.; Miller, C. H. *J. Am. Chem. Soc.* **1975**, 97, 7182-7183; (b) Mandai, T.; Hara, K.; Nakajima, T.; Kawada, M.; Otera, J. *Tetrahedron Lett.* **1983**, *24*, 4993-4996.
9. The *trans*-structure was ascertained after completion of the total synthesis of **1** based on its spectral data.
10. Sharma, R.; Marquez, V. E. *Synth. Commun.* **1994**, *24*, 1937-1945.
11. Rasmussen, J. R.; Slinger, C. J.; Kordish, R. J.; Newman-Evans, D. D. *J. Org. Chem.* **1981**, *46*, 4843-4846.
12. Oshima, K.; Uchimoto, K. Yuki Gosei Kagaku Kyokaishi **1989**, *47*, 40-52 and references cited therein.



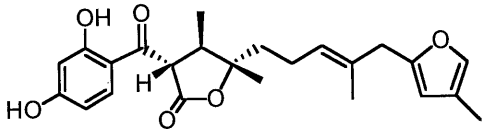
1



2

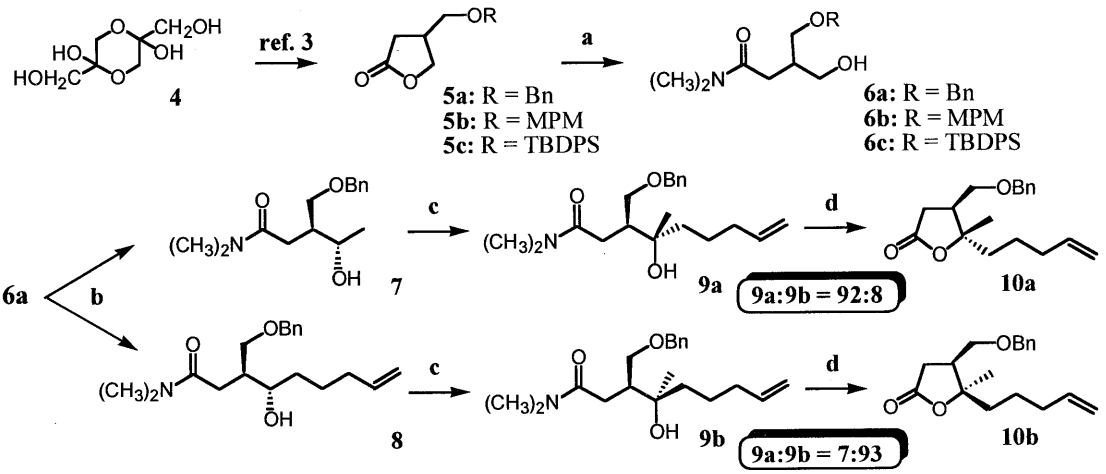


Pallidone G

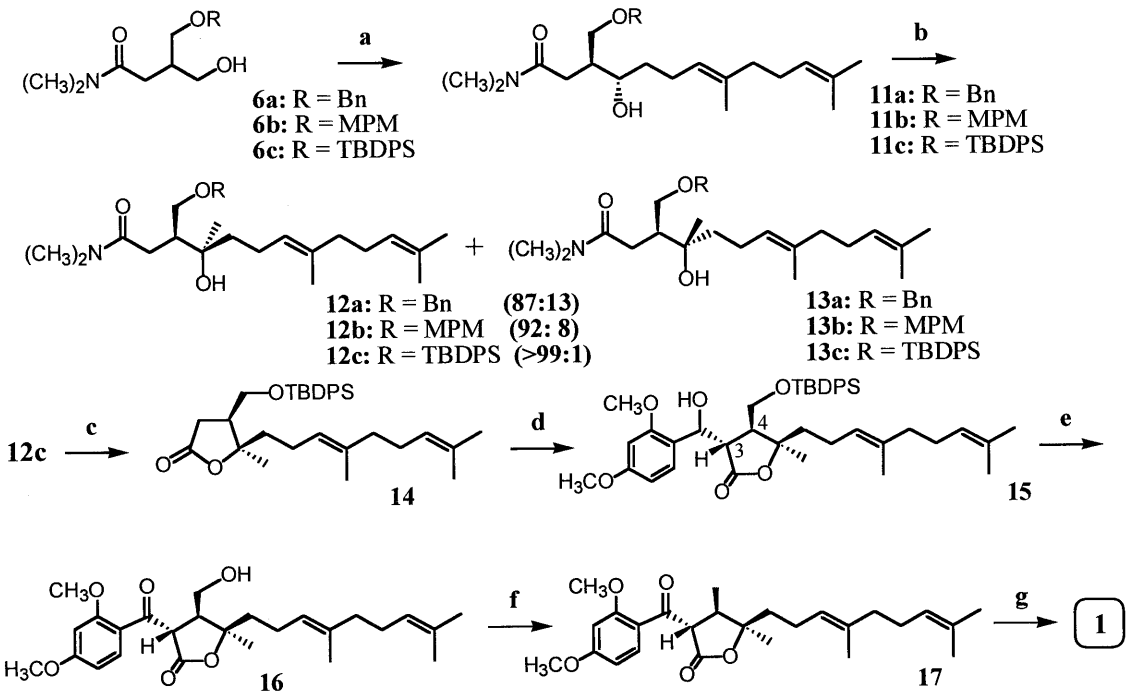


3

Figure 1



Scheme 1. *Reagents and conditions:* (**a**) Me_2NH, THF; 86% (**6a**); 90% (**6b**); 92% (**6c**); (**b**) (i) $(COCl)_2$, DMSO, THF, then Et_3N, -78 ~ -45 °C; (ii) methylmagnesium bromide, THF, 0 °C; 62% (**7**) (two steps); pentenylmagnesium bromide, THF, 0 °C; 54% (**8**) (two steps); (**c**) (i) PCC, CH_2Cl_2; (ii) pentenylmagnesium bromide, THF, $CeCl_3$, -78 °C; 53% (**9a**) (two steps); methylmagnesium bromide, THF, $CeCl_3$, -78 °C; 43% (**9b**) (two steps); (**d**) *p*-TsOH, benzene, 50 °C; 77% (**10a**); 68% (**10b**).



Scheme 2 . *Reagents and conditions:* (**a**) (i) $(COCl)_2$, DMSO, THF, then Et_3N, -78 ~ -45 °C; (ii) homogeranylmagnesium bromide, THF, 0 °C ; 48% (**11a**); 50% (**11b**); quant. (**11c**) (two steps, respectively); (**b**) (i) PCC, CH_2Cl_2; (ii) methylmagnesium bromide, THF, $CeCl_3$, -78 °C; 50% (**12a**); 70% (**12b**); 76% (**12c**) (two steps, respectively); (**c**) *p* -TsOH, benzene, 50 °C; 76%; (**d**) LiHMDS, 2,4-dimethoxybenzaldehyde, THF, -78 °C; quant.; (**e**) (i) PCC, CH_2Cl_2; (ii) TBAF, THF; 40% (two steps); (**f**) (i) CBr_4, PPh_3, CH_2Cl_2; 62%; (ii) Et_3B, Bu_3SnH, O_2, CH_2Cl_2; 66%; (**g**) Me_3SiI, $CHCl_3$, -20 °C; 88%.

Chapter 5

Lewis acid-promoted tandem desulfurization and hydroxylation of γ-phenylthio-substituted lactams: novel synthetic strategy of isoindolobenzazepine alkaloid, chilenine

Hidemi Yoda,* Kei-ichi Inoue, Yasuaki Ujihara, Nobuyuki Mase and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering, Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Abstract

Treatment of a variety of alicyclic and aromatic γ-phenylthio-substituted lactams with Lewis acids such as cuprous or cupric halides in aqueous solution at rt was found to undergo novel tandem desulfurization and hydroxylation reactions to generate γ-hydroxylated lactams without the ring-opened products in exremely high yields, respectively. This process was further applied to the total synthesis of an isoindolobenzazepine alkaloid, chilenine, by featuring the elaboration of the functionalized phthalimide derivative.

Due to their well documented and useful structural features for the synthesis of biologically active compounds, there has been increasing interest in the utilization of γ-phenylthio-substituted lactams as crucial and key intermediates. Thus, a number of efficient techniques to utilize such compounds have been accomplished and many advantageous reports have appeared for C-C bond formation, e. g., thionium/*N*-acyliminium ion cyclization cascade,[1a] Lewis acid-mediated allylation,[1b] intramolecular radical cyclization,[1c] direct replacement of the sulfur group by the alkyl function employing organo-zinc reagents,[1d] and successive alkylation-desulfurization sequence for the introduction of the alkyl side chain[1e] together with the well known desulfurization protocol.[1f,g] In this connection recent disclosures from this laboratory have demonstrated SmI_2-promoted tandem desulfurization and high *erythro*-selective coupling reactions of aromatic lactams with carbonyl compounds.[2] Although significant progress, thus, has been made in advancing the versatility of sulfur-substituted lactams, the lack of studies concerning the reactivity toward simple Lewis acids is surprising except the lactol type of compounds.[3] Herein we wish to report our successful efforts for the development of novel Lewis acid-mediated tandem reaction of phenylthio-substituted alicyclic and aromatic lactams in aqueous media, leading to the γ-hydroxylated products, whose process was further applied to the convenient total synthesis of isoindolobenzazepine natural product, chilenine.

Initial experiments have been performed on tandem desulfurization and hydroxylation reactions of simple γ-phenylthio-substituted alicyclic lactams **1** in the presence of a variety of Lewis acid-additives such as $MgBr_2$, $SmCl_3$, or $CeCl_3$ in aqueous solution (CH_3CN-H_2O = 9:1) at ambient temperature. The reactions, however, did not proceed under any conditions and recovered the starting material **1**. Next, we examined the same type of reactions employing another Lewis acids. The results from our servey are summarized in Table 1. Whereas the reactions with $FeCl_3$ and CuI gave the desired hydroxylated product **2**, but in low yield, respectively (entries 1,2), use of CuCl or CuBr had a dramatic effect on the rate and smoothly brought about the taget compound **2** in almost quantitative yields (entries 6-8) under these mild and readily available conditions. We were delighted to find that the same beneficial results were again obtained in reaction employing quaternary substituted phenylthiolactams containing aliphatic and aromatic alkyl side chains (entries 9,10) by replacement of the solvent system from CH_3CN-H_2O (9:1) to 1,4-dioxane-H_2O (2:1) without by-products such as ring-opened ketoamides derived from **2**.

Table 1

As shown in Table 2, we further found that the use of β-substituted and α,β-disubstituted g-phenylthiolactams **3** (entries 1,2) as well as the aromatic one (entry 3) underwent convenient reactions to afford the corresponding desulfurized hydroxylactams in quite high yields, respectively. In addition, it will be particularly of interest to note that a variety of both sterically more hindered and unstable quaternary hydroxy-substituted lactams **4** with β- or α,β-disubstituents[4a-f] could be obtained again under these conditions (entries 4-9) irrespective of their structures.

Thus, this procedure is applicable for the production of a wide range of γ-hydroxylated lactam derivatives and provides an easily accessible alternative to the existing synthetic method of these types of compounds, since, to the best of our knowledge, one approach

to the direct preparation of γ-hydroxylactams **2** or **4** through nucleophilic addition of organometallic reagents to cyclic imides has been demonstrated.[4]

Table 2

In light of the above outcome, we turned our attention to the development of novel and convenient synthetic method of isoindolobenzazepine alkaloid, chilenine (**5**),[5] whose structure incorporating the 3*H*-3-benzazepine moiety and equally an isoindolinone ring system is architecturally sophisticated and possesses the real and potential biological properties.[6] As summarized in Scheme 1, the functionalized imide **6** obtained from 3,4-dimethoxy-2-ethoxycarbonylbenzoic acid and bromopiperonal based on our reported method,[6f] was reduced with DIBAL-H[7] at low temperature to provide the hydroxylactam intermediate, which was quickly treated with thiophenol under acidic conditions, leading to the phenylthiolactam **7** in 61% yield (two steps) regioselectively (96:4, determined by ^{1}H NMR). When the deprotection of the MPM-group in **7** was performed by the use of DDQ, the desired aldehyde derivative **8** could be obtained directly. This was successively effected by intramolecular cyclization reaction under basic conditions to provide the corresponding product **9** possessing the benzazepine structure. Although the oxidation of the hydroxyl function in **9** with PCC or Swern-oxidation reagents gave inseparable mixtures, use of TPAP (tetrapropylammonium perruthenate)[8] in the presence of NMO brought about the desired ketone **10** in satisfactory yield without the sulfur-oxidized compound. Finally, **10** was subjected to the tandem desulfurization and hydroxylation reactions with CuBr in aqueous media at ambient temperature to complete the total synthesis of chilenine **5** in 83% isolated yield. The spectral data of synthesized **5** were completely identical with those of the reported natural substance.[5a]

Scheme 1

In summary, we have disclosed herein the instructive example of the Lewis acid-mediated tandem reaction of desulfurization and hydroxylation in aqueous solution, whose process found application in the novel synthetic strategy of a structurally sophisticated and biologically important isoindolobenzazepine alkaloid and will be widely applicable to the synthesis of other fused alkaloidal natural products such as new antitumor antibiotics, UCS 1025 series[9] containing a quaternary hydroxyl group α to the nitrogen.

Acknowledgments

This work was supported in part by a Grant-in-Aid (No. 15550031) for Scientific Research from the Japan Society for the Promotion of Science.

References

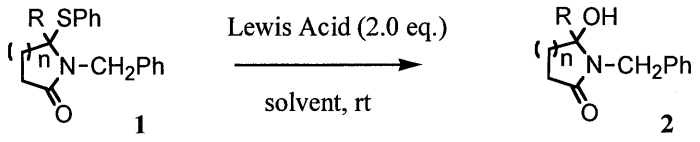
1. For example; (a) Padwa, A.; Waterson, A. G. *Tetrahedron* **2000**, *56*, 10159-10173; (b) Ostendorf, M.; Van der Neut, S.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem.* **2000**, 105-113; (c) Hunter, R.; Richards, P. *Tetrahedron Lett.* **2000**, *41*, 3755-3758; (d) Huang, P. Q.; Tang, X.; Chen, A. Q. *Synth. Commun.* **2000**, *30*, 2259-2268; (e) Luzzio, F. A.; Zacherl, D.-A. P. *Tetrahedron Lett.* **1998**, *39*, 2285-2288; (f) Huang, P. Q.; Zheng, X.; Wang, S. L.; Ye, J. L.; Jin, L. R.; Chen, Z. *Tetrahedron: Asymmetry* **1999**, *10*, 3309-3317; (g) Luzzio, F. A.; Zacherl, D.-A. P.; Figgs, W. D. Tetrahedron Lett **1999**, *40*, 2087-2090.
2. Yoda, H.; Ujihara, Y.; Takabe, K. *Tetrahedron Lett.* **2001**, *42*, 9225-9228.
3. Hitherto copper-mediated tandem desulfurization and hydroxylation reactions employing α-phenylthio-substituted derivatives of cyclic ethers to the original lactols was only reported. For example; (a) Martin-Lomas, M.; Flores-Mosquera, M.; Chiara, J. Eur. *J. Org. Chem.* **2000**, 1547-1562; (b) Motawia, M. S.; Marcussen, J.; Moeller, B. L. *J. Carbohydrate Chem.* **1995**, *14*, 1279-1294; (c) Chernyak, A. Y.;

Antonov, K. V.; Kochetkov, N. K. Bioorganicheskaya Khimiya 1989, 15, 1113-1127; (d) Hiroi, K.; Nakamura, H.; Anzai, T. *J. Am. Chem. Soc.* **1987**, *109*, 1249-1250; (e) Takano, S.; Sato, N.; Akiyama, M.; Ogasawara, K. *Heterocycles*, **1985**, *23*, 2859-2872.

4. (a) Schuch, C. M.; Pilli, R. A. *Tetrahedron:Asymmetry* **2002**, *13*, 1973-1980; (b) Yoda, H.; Shimojo, T.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 1335-1336 and references cited therein; (c) Huang, P. Q.; Wang, S. L.; Zheng, H.; Fei, X. S. *Tetrahedron Lett.* **1997**, *38*, 271-272; (d) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531-5534; (e) Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451-1454; (f) Yoda, H.; Morishita, H.; Kudo, M.; Katagiri, T.; Takabe, K. *Chem. Express* **1989**, *4*, 515-518; (g) Tanis, S. P.; Dixon, L. A. *Tetrahedron Lett.* **1987**, *28*, 2495-2498; (h) Wrobel, J. T.; Cybulski, J.; Dabrowski, Z. *Synthesis* **1977**, 686-688.
5. (a) Fajardo, V.; Elango, V.; Cassels, B. K.; Shamma, M. *Tetrahedron Lett.* **1982**, *23*, 39-42; (b) Valencia, E.; Freyer, A. J.; Shamma, M.; Fajardo, V. *Tetrahedron Lett.* **1984**, *25*, 599-602; (c) Valencia, E.; Weiss, I.; Firdous, S.; Freyer, A. J.; Shamma, M. Urzua, A.; Fajardo, V. *Tetrahedron* **1984**, *40*, 3957-3962.
6. (a) Weinstock, J.; Hieble, J. P.; Wilson, J. W. *Drugs Future* **1985**, *10*, 645-651; (b) Csende, F.; Szabo, Z.; Stajer, G. *Heterocycles* **1993**, *36*, 1809-1821; (c) Epsztajn, J.; Grzebak, R.; Jozwiak, A. *Synthesis* **1996**, 1212-1216; (d) Marchalin, S.; Decroix, B. *Heterocycles* **1995**, *41*, 689-696; (e) Daich, A.; Marchalin, S.; Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1998**, *39*, 9187-9190 and recent synthetic examples, see: (f) Yoda, H.; Nakahama, A.; Koketsu, T.; Takabe, K. *Tetrahedron Lett.* **2002**, *43*, 4667-4669; (g) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414-2421; (h) Fuchs, J. R.; Funk, R. L. *Org. Lett.* **2001**, *3*, 3923-3925; (i) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491-1499; (j) Ruchirawat, S.; Sahakitpichan, P. *Tetrahedron Lett.* **2000**, *41*, 8007-8010; (k) Koseki, Y.; Kusano, S.; Sakata, H.; Nagasaka, T. *Tetrahedron Lett.* **1999**, *40*, 2169-2172; (l) Rodríguez, G.; Castedo, L.; Domínguez, D.; Saá, C.

Tetrahedron Lett. **1998**, *39*, 6551-6554; (m) Ishibashi, H.; Kawanami, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 817-821; (n) Rodríguez, G.; Cid, M. M.; Saá, C. Castedo, L.; Domínguez, D. *J. Org. Chem.* **1996**, *61*, 2780-2782 and references cited therein.

7. Reduction of **6** with $NaBH_4$ in MeOH afforded the reverse regioselective product predominantly (78:22, determined by ^1H NMR). It is not clear at present which effect (stereoelectronic or steric effect) would be more predominant on this regioselectivity.
8. Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639-666. Agatsuma, T.; Akama, T.; Nara, S.; Matsumiya, S.; Nakai, R.; Ogawa, H.; Otaki, S.; Ikeda, S.-I.; Saitoh, Y.; Kanda, Y. *Org. Lett.* **2002**, *4*, 4387-4390 and references cited therein.

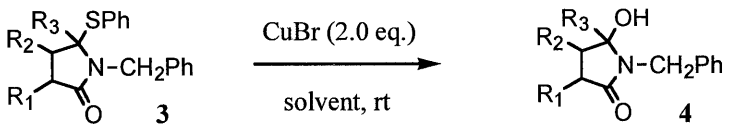


Entry	n	R	Lewis acid	Conditions[a]	Time (d)	Yield (%)[b]
1	1	H	$FeCl_3$	A	1	36
2	1	H	CuI	A	1	8
3	1	H	CAN	A	1	81
4	1	H	$CuBr_2$	A	1	65
5	1	H	$CuCl_2$	A	1	>99
6	1	H	CuCl	A	1	>99
7	1	H	CuBr	A	1	>99
8	2	H	CuBr	A	1	>99
9	1	$CH_3(CH_2)_3$	CuBr	B	0.1	84[c]
10	1	C_6H_5	CuBr	B	0.1	97[c]

[a]Conditions A performed in CH_3CN-H_2O (9:1) and conditions B performed in 1,4-dioxane-H_2O (2:1), respectively.

[b]Isolated yield.

[c]Reactions under conditions A gave the corresponding ring-opened ketoamides as a main product derived from the quaternary hydroxylactams **2** in 23% (R: butyl) and 53% (R: phenyl) yields, respectively.



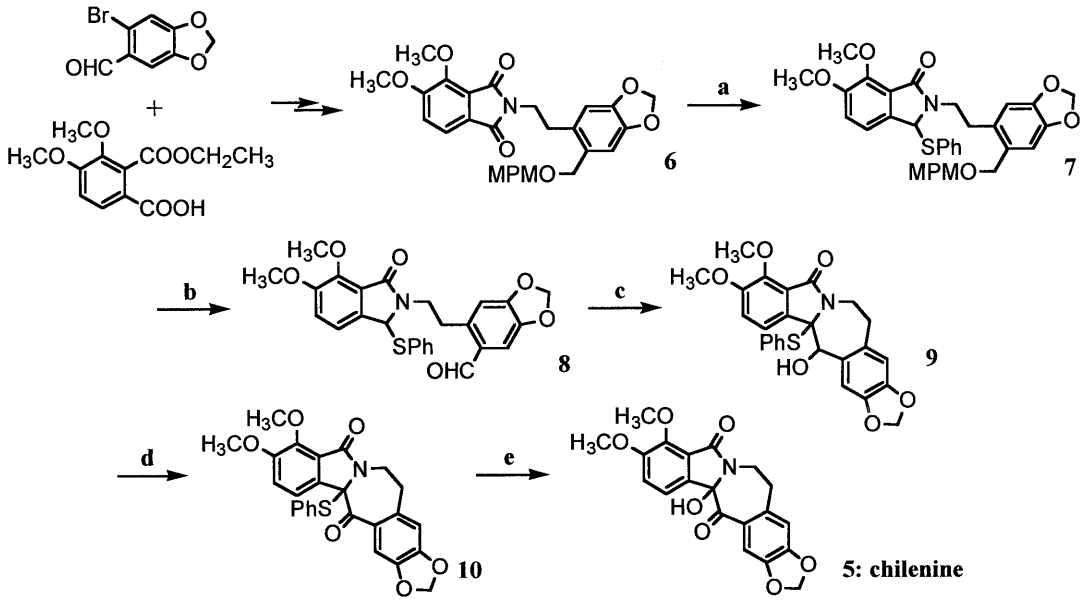
Entry	R_1	R_2	R_3	Conditions[a]	Time (d)	Yield (%)[b]
1	H	OBn	H	A	3	>99[d]
2	OBn	OBn[c]	H	A	1	>99[d]
3	-C_6H_4-		H	A	1	98
4	H	OBn	$CH_3(CH_2)_3$	B	1	92[d]
5	H	OBn	C_6H_5	B	1	90[d]
6	OBn	OBn[c]	$CH_3(CH_2)_3$	B	1	86[d]
7	OBn	OBn[c]	C_6H_5	B	1	98[d]
8	-C_6H_4-		$CH_3(CH_2)_3$	A	0.1	>99
9	-C_6H_4-		C_6H_5	A	0.1	>99

[a]Conditions A performed in CH_3CN-H_2O (9:1) and conditions B performed in 1,4-dioxane-H_2O (4:1), respectively.

[b]Isolated yield.

[c]*d.l*-Tartaric acid-derived lactam **3** was used.

[d]Unfortunately, these reactions resulted in the almost non-stereoselective formation of **4** except the case of entry 1, which indicated the moderate *trans*-selectivity (*cis*:*trans* (to the β-OBn group) = 16:84, isolated ratio).



Scheme 1. *Reagents and conditions*: (**a**) **1**, DIBAL-H, THF, -78℃; **2**, PhSH, BF_3OEt_2, CH_2Cl_2; 61% (two steps); (**b**) DDQ, CH_2Cl_2-H_2O (10:1); 97%; (**c**) LiHMDS, HMPA, THF, -78~0℃; 65%; (**d**) TPAP, NMO, CH_2Cl_2; 78%; (**e**) CuBr, CH_3CN-H_2O (1:1); 83%

Chapter 6

Novel and stereoselective asymmetric synthesis of an amino sugar analogue, furanodictine A

Hidemi Yoda,* Yuji Suzuki and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

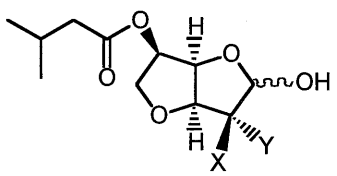
Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Keywords: furanodictine; 3,6-anhydrosugar; amino alcohol; arabinofuranose.

Abstract

A novel and efficient strategy is described for the asymmetric synthesis of the first 3,6-anhydrosugar to be isolated from natural sources, furanodictine A. The synthetic process is based on requisite stereodefined manipulation of the functionalized amino alcohol obtained through nucleophilic addition of vinyl Grignard reagent to the aminal incorporating the D-arabinofuranose-derived skeleton in a complete stereoselective manner.

Furanodictine A (**1**) and B (**2**) were first isolated in 2001 by Oshima and co-workers from a methanol extract of the multicellular fruit body of *Dictyostelium discoideum*[1] in a research to clarify the diversity of secondary metabolites of *Dictyostelium* cellular slime molds and to explore biologically active substances that could be useful in the development of novel drugs (Figure 1). These natural products are unambiguously known to possess the ability to cause neuronal differentiation of rat pheochromocytoma (PC-12) cells and revealed to be the first 3,6-anhydrosugars to be isolated from natural sources after structural characterization by the same group based on comprehensive spectral analysis.[1] Their structural complexity coupled with diverse and potentially useful characteristics as an antitumor agent described above would make them inviting targets for synthesis. In spite of these attractive features, to the best of our knowledge, only one approach concerning the total synthesis of these compounds has appeared to date,[1] since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol.



X=H, Y=NHAc: Furanodictine A (1)
X=NHAc, Y=H: Furanodictine B (2)

Figure 1

With these considerations in mind, the central feature of this communication is to disclose the details of a novel and convenient route for the stereoselective construction of furanodictine A (**1**) possessing real and potential pharmacological properties and the attractive 3,6-anhydrosugar structure

In formulating the synthetic plan for **1**, we recognized that the absolute configurations at C(3), C(4) and C(5) are the same as the configurations at the corresponding centers C(2), C(3) and C(4) of D-arabinofuranose (**I**) as shown in Figure 2. Particularly the furanyl part in **1** would be constructed through nucleophilic intramolecular cyclization of the hydroxyl group of C(2) in the acyclic form of D-arabinose. Further we envisioned that the stereogenic center of C(2) α to the nitrogen would originate from the nucleophilic addition to the aminal derivative of (**I**), allowing the synthesis of amino alcohol (**II**). Meanwhile, construction of the bicyclic furano-lactol structure in furanodictine A (**1**) would have to be independently set in a chemo- and regioselective cyclization reaction of the corresponding α-amino aldehyde intermediate (**III**).

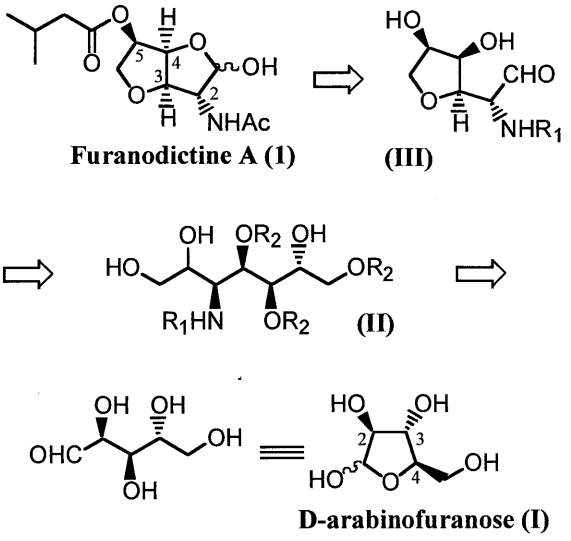
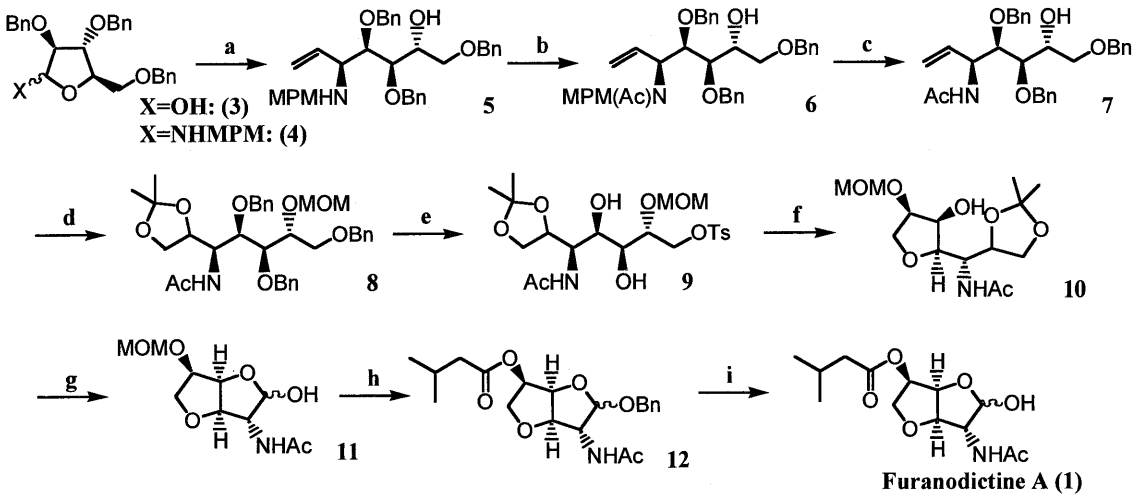


Figure 2

The results from our survey are summarized in Scheme 1. To begin with, the

functionalized amino alcohol **5** with desired contiguous stereogenic centers was prepared from commercially available 2,3,5-tri-*O*-benzyl-β-D-arabinofuranose (**3**) through successive amination and extremely stereoselective addition of vinyl magnesium bromide[2] (>99% de, determined by HPLC) at low temperature in good yield. Then, *N*-acetylation was performed with acetyl chloride under acidic conditions to avoid racemization of the vinyl group α to the nitrogen[3] and the product was in turn submitted to hydrolysis to provide the corresponding alcohol **6**. Due to the lability of the final bicyclic furano-lactol structure under acidic deprotection conditions,[4] the MPM (*p*-methoxybenzyl) group in **6** was in advance removed at this stage to give the acetoamide **7**, $[\alpha]_D^{28}$-22.4° (c 1.17, $CHCl_3$). This was then subsequently effected by reactions of dihydroxylation with OsO_4, chemoselective acetonide formation and MOM-protection, leading to the benzylether **8** in 84% yield (three steps). Three benzyl protecting groups in **8** were easily removed under mild conditions such as treatment with H_2 on Pd/C in almost quantitative yield, followed by the regioselective mono-tosylation in the presence of cat. Bu_2SnO[5] to afford the tosylate **9**. Treatment of **9** with K_2CO_3 in methanol brought about the regioselectively cyclized tetrahydrofuran derivative **10** in 96% yield. We were then delighted to find that the use of $NaIO_4$ as an oxidative cleavage reagent to the aldehyde intermediate could effect the reaction smoothly to lead to the corresponding desired bicyclic product **11** in satisfactory yield.[6] After protection of the hydroxyl group in **11** with benzyl bromide to resist changes in pH, replacement of the MOM group by the desired isovaleric acid ester function in the presence of EDCI {1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride} was subsequently effected to produce *O*-benzyl furanodictine A (**12**) in high yield. Finally, **12** was subjected to deprotection under mild conditions with H_2 on Pd/C again to compete the total synthesis of the natural type of **1**, $[\alpha]_D^{27}$+132.6° (c 0.72, $CHCl_3$) {natural **1**, $[\alpha]_D^{25}$+100.4° (c 0.233, $CHCl_3$)[1] and synthetic **1**, $[\alpha]_D^{25}$+118.5° (c 0.437, $CHCl_3$)[1]},[7] in 87% yield



Scheme 1. *Reagents and conditions*: (a) vinylmagnesium bromide, THF, -78 to -40℃; 62%; (b) **1**, CH_3COCl, CH_2Cl_2; **2**, K_2CO_3, MeOH; 50% (two steps); (c) CAN (diammmonium cerium(IV) nitrate), MeOH; 49%; (d) **1**, cat. OsO_4, NMO, acetone-H_2O (1:1); 99%; **2**, 2,2-dimethoxypropane, cat. *p*-TsOH, acetone; 90%; **3**, MOMCl, (*i*-Pr)$_2$NEt, CH_2Cl_2; 94%; (e) 1, H_2, Pd/C, MeOH; 97%; 2, TsCl, Bu_2SnO, Et_3N, CH_2Cl_2; 79%; (f) K_2CO_3, MeOH; 96%; (g) **1**, cat. conc. HCl, MeOH; 82%; **2**, $NaIO_4$, ether-H_2O (1:1); 92%; (h) **1**, BnBr, Ag_2O, CH_3COOEt; 77%; **2**, cat. conc. HCl, MeOH; 78%; **3**, isovaleric acid, EDCI, DMAP, CH_2Cl_2; 94%; (i) H_2, Pd/C, CH_3COOEt; 87%

In sammary, this process involves no separation of stereoisomers and was substantially performed under ambient conditions through entire sequence until furanodictine A was synthesized. Further it constitutes a new synthetic strategy and, in addition, represents a short and easily accessible pathway to furanodictine natural product.

Acknowledgments

This work was supported in part by a Grant-in-Aid (No. 15550031) for Scientific Research from the Japan Society for the Promotion of Science

References

9. Kikuchi, H.; Saito, Y.; Komiya, J.; Takaya, Y.; Honma, S.; Nakahata, N.; Ito, A.; Oshima, Y. *J. Org. Chem.* **2001**, *66*, 6982-6987.

10. (a) Lay, L.; Nicotra, F.; Paganini, A.; Pangrazio, C.; Panza, L. *Tetrahedron Lett.* **1993**, *34*, 4555–4558; (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron : Asymmetry* **1995**, *6*, 2669–2672; (c) Yoda, H.; Uemura, T.; Takabe, K. *Tetrahedron Lett.* **2003**, *44*, 977-979.

11. Partial racemization at this center was observed under basic acetylation conditions employing Ac_2O, Et_3N and cat. DMAP in CH_2Cl_2

12. Initial experiments have been performed on the synthesis of the target compound **1** without removal of the MPM group, however, in this case the desired product could not be isolated at the final MPM-deprotection reaction stage and, instead, the reaction resulted in the production of an inseparable mixture.

13. (a) Martinelli, M. J.; Vaidyanathan, R.; Khau, V. V. *Tetrahedron Lett.* **2000**, *41*, 3773-3776; (b) Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447-450.

14. The ratio of the two anomers (α:β = 6.2:1) was easily determined by ^{1}H NMR, since the observed coupling constant corresponding to the α-anomer was 4.8 Hz, indicating the *cis*-relationship and the other β-one has no coupling constant.

15. Synthesized furanodictine A in this report was a mixture {α:β = 3.9:1 (natural; α:β = 7:1)[1]} of the two anomers.

Chapter 7

Studies toward a synthesis of trilobatin B, a lignan from the liverwort *Bazzania trilobata*: asymmetric construction of the tetrahydrofuran segment

Hidemi Yoda,* Yuka Nakaseko and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University
Johoku 3-5-1, Hamamatsu 432-8561
Japan

Tel: +81 53 478 1150
Fax: +81 53 478 1150
E-mail: tchyoda@ipc.shizuoka.ac.jp

Keywords: trilobatin; substituted tetrahydrofuran; Horner-Emmons reaction; xylose; glucuronolactone.

Abstract

A novel and stereocontrolled process is described for the asymmetric synthesis of the tetrahydrofuran segment of a 2,3-dicarboxy-6,7-dihydroxy-1-(3',4'-dihydroxyphenyl)-1,2-dihydronaphthalene mono-ester, trilobatin B, a lignan from the liverwort *Bazzania trilobata*. The key *cis*-substituted lactone ring was constructed in a stereoselective manner by Horner-Emmons reaction followed by the subsequent tandem Michael addition and cyclization of two types of lactol intermediates elaborated from natural sources.

Substituted tetrahydrofurans feature in many biologically potent natural products such as annonaceous acetogenins,[1] macrolides,[2] cytotoxic polyethers,[3] marine toxins,[4] pheromones,[5] and epoxylipids.[6] To fully exploit the opportunities offered by these compounds requires access to synthetic methodology capable of targeting chiral substituted tetrahydrofurans. In this conncetion many strategies have been explored in developing synthetic routes to these compounds and the natural products themselves. However, most methods were concerned with the construction of 2,5-disubstituted furans, while few focused on tri- and tetrasubstituted ones,[7] although the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol. We have recently succeeded in the development of novel and stereoselective asymmetric syntheses of biologically active tri-[8a,b] and tetrasubstituted[8c,d] furan-type of natural products through elaboration of commercially available materials based on new routes exploited in this laboratory. On the other hand, new interesting lignans such as trilobatin A (**1**), methyl ester derivative of **1** (**2**) and trilobatin B (**3**) containing a polysubstituted tetrahydro-pyran or furan skeleton were recently isolated from the liverwort *Bazzania trilobata* in a research for the genus *Bazzania* with its several hundred species distributed in the tropics and subtropics, which represents one of the four European species, that grow in dense, widespread pads on forest ground, boggy soil and trunks (Fig. 1).[9]

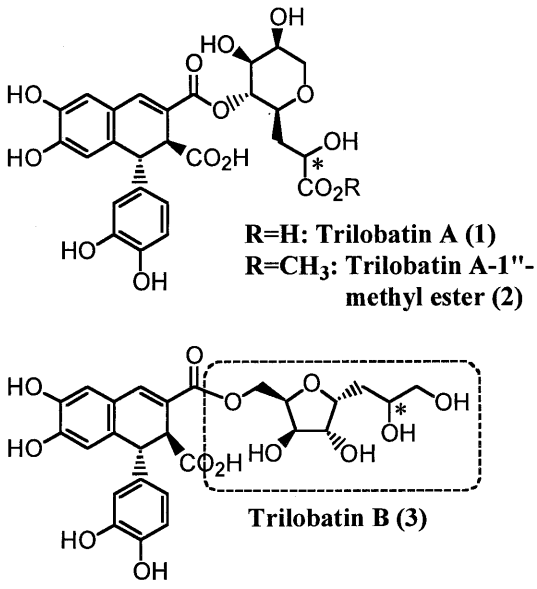
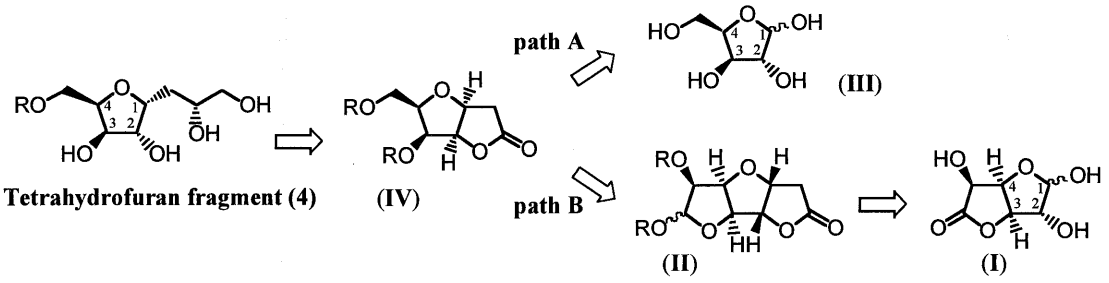


Figure 1

The structural and stereochemical complexity of these secondary metabolites with respect to the heterocyclic moiety coupled with their diverse and potentially useful characteristics would make them hereafter inviting targets for synthesis. In this communication we wish to report the details of a novel route for the stereoselective construction of the requisite tetrasubstituted tetrahydrofuran segment of trilobatin B (**3**) from two natural sources.

In formulating the synthetic plan for the core segment **4**, we recognized that nucleophilic addition of an organometallic reagent to the lactone (**IV**) followed by its transformation could undergo the desired reaction, allowing the synthesis of the target **4** (Fig. 2). In this case, D-xylofuranose (**III**) would be selected as one of the starting material, since the absolute configurations at C(2), C(3) and C(4) in **4** are the same as the configurations at the corresponding centers C(2), C(3) and C(4) of (**III**) (path A). Meanwhile, the tricyclic lactone (**II**), which would have to be set in an asymmetric transformation of the corresponding commercially available D-glucuronolactone (**I**), could be independently regarded as an another precursor of **4** (path B).

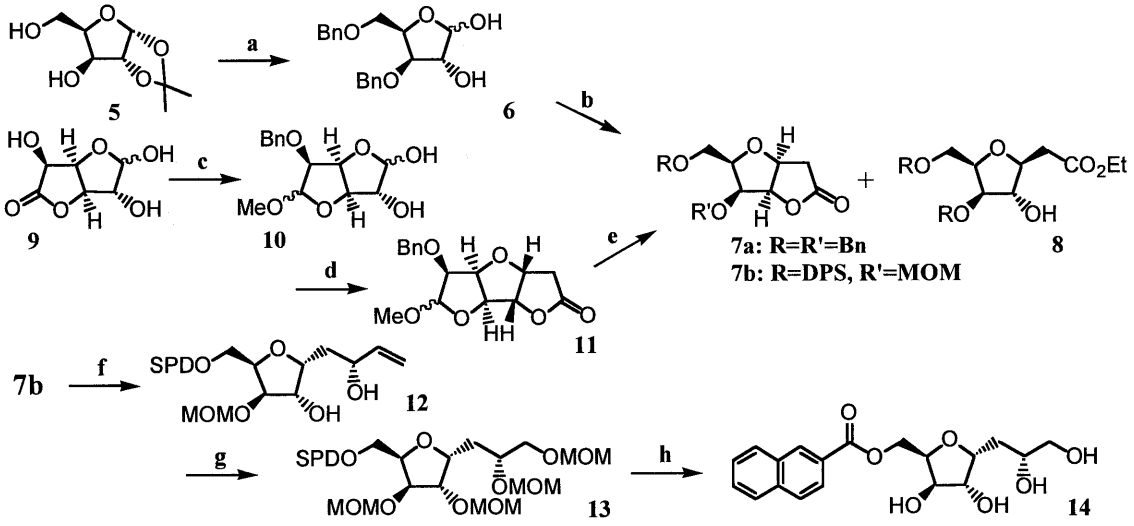


To begin with, an attempt to synthesize the crucial intermediate furanolactone **7a** based on path A is outlined in Scheme 1. Regioselectively benzyl-protected D-xylofuranose **6** obtained from reactions of benzylation and deacetalization of commercially available 1,2-*O*-isopropylidene-D-xylofuranose (**5**) was effected with ethyl diethylphosphonoacetate in the presence of base at low temperature to afford the desired *cis*-fused **7a**, $[\_]_D^{24}$+12.8° (c 1.06, MeOH), fortunately in moderate yield through a three-step sequence such as Horner-Emmons reaction, Michael addition and intramolecular cyclization, but disappointingly accompanied with the *trans*-furanoester **8** (2.8:1, isolated ratio).[10]

In light of the above outcome, we next focused our research on the reaction employing the same type of the bicyclic lactol derivative **10** under these Horner-Emmons reaction conditions (Scheme 1). This compound was easily prepared from readily available and inexpensive D-glucuronolactone (**9**) through a seven-step sequence in 55% overall yield as follows; thus, three hydroxyl groups of **9** were successively protected by the reactions of acetonide formation and benzylation with Ag_2O followed by exchange of the acetonide protecting group to the TBS ethers, giving the corresponding bis-TBS product.[8d] This was then submitted to the following reactions of DIBAL-H reduction, protection of the resulting hydroxyl function with CH_3I and finally desilylation to provide the desired lactol precursor **10** smoothly. Whereas treatment of **6** with ethyl diethylphosphonoacetate gave the separable mixture of the two compounds **7a** and **8** as mentioned above, we were delighted to find that the use of **10** brought about, in turn, the desired tricyclic lactone **11** as the single as well as the sole

product in 87% isolated yield (as the anomer mixture) under the same reaction conditions. This high stereoselective performance compared with that of the analogous compound **6** would be attributed simply to the steric demand of the tricyclic core.

With these results in hand, **11** was further transformed into the desired bicyclic lactone **7b** by the routine reaction sequence of hydroxylation under acidic conditions, reduction of the corresponding lactol with $NaBH_4$ and regioselective protection of the secondary hydroxyl group with MOMCl via the TBS-ether. This was then subjected to the reactions of oxidative cleavage after hydrogenation, reduction again and protection of the primary alcohol with DPSCl, providing the *cis*-fused **7b**, $[\alpha]_D^{26}$+13.8° (c 1.03, MeOH). Then, **7b** thus obtained was effected with vinylmagnesium bromide at low temperature to afford the labile hemiketal intermediate, which was readily treated with $NaBH_4$ in the presence of $CeCl_3$ at -40 °C, leading to the corresponding vinyl alcohol **12**, $[\alpha]_D^{27}$-9.91° (c 0.54, MeOH), surprisingly with complete stereoselectivity (determined by ^{13}C NMR analysis). No other stereoisomer was observed in this reaction.[11] After protection with MOMCl of **12**, the olefinic part was then cleavaged via dihydroxylation to give the aldehyde, which was successively subjected to reduction and MOM-protection again, leading to the tetramethoxymethyl ether **13**, $[\alpha]_D^{27}$-15.9° (c 0.55, MeOH). Finally, **13** was effected by deprotection of DPS group with Bu_4NF and esterification with 2-naphthoic acid (the similar framework of the natural product, trilobatin B (**3**)) in the presence of EDCI (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride) and DMAP,[12] followed by deprotection of the resulting tetramethoxymethyl ether to accomplish the synthesis of trilobatin B derivative **14**, $[\alpha]_D^{26}$+32.3° (c 0.085, MeOH).



Scheme 1. *Reagents and conditions*: (a) **1**, NaH, BnBr, cat. Bu_4N, THF; 98%; **2**, 1.8% HCl, 1,4-dioxane, 80°C; 85%; (b) **1**, NaH, $(EtO)_2POCH_2CO_2Et$, THF, -78 to -17°C; **2**, cat. *p*-TsOH, benzene, 50°C; 39% (two steps) (**7a**); 14% (two steps) (**8**); (c) **1**, acetone, H_2SO_4; **2**, BnBr, Ag_2O, CH_3CO_2Et; **3**, TFA, THF; **4**, TBSCl, imidazole, DMF; **5**, DIBAL-H, THF, -78 to 0°C; **6**, *t*-BuOK, CH_3I, cat. Bu_4NI, THF, -78 to -40°C; **7**, Bu_4NF, THF, 0°C; 55% (seven steps); (d) NaH, $(EtO)_2POCH_2CO_2Et$, THF, -78 to -17°C; 87%; (e) **1**, 5% HCl, 1,4-dioxane, 80°C; 94%; **2**, $NaBH_4$, *i*-PrOH, 0°C; 92%; **3**, TBSCl, Et_3N, CH_2Cl_2; 98%; **4**, $(i\text{-}Pr)_2NEt$, MOMCl, CH_2Cl_2; **5**, 1.8% HCl, MeOH; 97% (two steps); **6**, Pd/C, H_2, CH_3CO_2Et; quant.; **7**, $NaIO_4$, Et_2O-H_2O (1:1), 0°C; **8**, $NaBH_4$, THF, 0°C; **9**, DPSCl, imidazole, CH_2Cl_2; 86% (three steps) (7b); (f) **1**, vinylmagnesium bromide, $CeCl_3$, THF, -78°C; **2**, $NaBH_4$, $CeCl_3$, MeOH, -40°C; 53% (two steps); (g) **1**, $(i\text{-}Pr)_2NEt$, MOMCl, CH_2Cl_2; 90%; **2**, cat. OsO_4, NMO, acetone; quant.; **3**, $NaIO_4$, Et_2O-H_2O (1:1), 0°C; **4**, $NaBH_4$, MeOH, 0°C; **5**, $(i\text{-}Pr)_2NEt$, MOMCl, CH_2Cl_2; 88% (three steps); (h) **1**, Bu_4NF, THF, 0°C; 91%; **2**, 2-naphthoic acid, EDCI, DMAP, CH_2Cl_2, 0°C; quant.; **3**, 10% HCl, MeOH; 98%

In summary, this work constitutes the first asymmetric synthesis of the tetrahydrofuran segment of the natural lignan product, trilobatin B, based on a stereoselectively tandem reaction sequence via Horner-Emmons reaction,

stereoselective Michael addition and intramolecular cyclization and will be widely applicable to the synthesis of other chiral tetrahydrofuran-containing natural products.

Acknowledgments

This work was supported in part by a Grant-in-Aid (No. 15550031) for Scientific Research from the Japan Society for the Promotion of Science.

References and notes

1. (a) Zeng, L.; Ye, Q.; Oberlies, N. H.; Shi, G.; Gu, Z.-M.; He, K.; McLaughlin, J. L. *Nat. Pro. Rep.* **1996**, *13*, 275; (b) Cavé, A.; Figadère, B.; Laurens, A.; Cortes, D. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Eds.; Springer-Verlag: Wien, New York, **1997**, Vol. *70*, pp 81.
2. (a) Bauer, I.; Maranda, L.; Young, K. A.; Shimizu, Y.; Huang, S. *Tetrahedron Lett.* **1995**, *36*, 709; (b) Sakai, R.; Rinehart, K. L. *J. Nat. Prod.* **1995**, *58*, 773; (c) Wipf, P.; Lim, S. *J. Am. Chem. Soc.* **1995**, *117*, 558.
3. (a) Matsuo, Y.; Suzuki, M.; Masuda, M. *Chem. Lett.* **1995**, 1043; (b) Morte, M. *Tetrahedron Lett.* **1997**, *38*, 3137; (c) Koert, U. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 298.
4. Faulkner, D. J. *Nat. Prod. Rep.* **1997**, *14*, 259.
5. Seki, T.; Satake, M.; Mackenzie, L.; Kaspar, H. F.; Yasumoto, T. *Tetrahedron Lett.* **1995**, *36*, 7093.
6. (a) Boukouvalas, J.; Fortier, G.; Radu, I.-I. *J. Org. Chem.* **1998**, *63*, 916; (b) Fernández de la Pradilla, R.; Montero, C.; Priego, J.; Martínez-Cruz, L. A. *J. Org. Chem.* **1998**, *63*, 9612; (c) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609; (d) Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, *63*, 75; (e) Capon, R. J.; Barrow, R. A.; Rochfort, S.; Jobling, M.; Skene, C.; Lacey, E.; Gill, J. H.; Friedel, T.; Wadsworth, D. *Tetrahedron* **1998**, *54*, 2227; (f)

Wang, Z.-M.; Shen, M. *J. Org. Chem.* **1998**, *63*, 1414; (g) Mori, Y.; Sawada, T.; Furukawa, H.; *Tetrahedron Lett.* **1999**, *40*, 731 and references cited therein. (a) Stevens, D. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 633; (b) Mitra, J.; Mitra, A. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1285; (c) Maiti, G.; Adhikari, S.; Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 927; (d) Yoshida, S.-I.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 1310; (e) Chen, I.-S.; Chen, J.-J.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1997**, *45*, 991; (f) Gar_ia, C.; Martín, T.; Martín, V. S. *J. Org. Chem.* **2001**, *66*, 1420; (g) Chakraborty, T. K.; Das, S.; Raju, T. V. *J. Org. Chem.* **2001**, *66*, 4091; (h) Gadikota, R. R.; Callam, C. S.; Lowary, T. L. *J. Org. Chem.* **2001**, *66*, 9046.