カイロン法を利用した高効率的反応場制御に基づく生理活性分子構築法

（課題番号　10640516）

平成１０年度～平成１１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１２年３月

研究代表者　　依田秀実

（静岡大学工学部助教授）

カイロン法を利用した高効率的反応場制御に基づく生理活性分子構築法

（課題番号　10640516）

平成１０年度～平成１１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１２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

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の片方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、応用に関して極めて高い関心が集められている。申請者はすでに天然アミノ酸やC2-軸不斉イミド等から誘導されるキラルユニットを出発物とし、極めて高い立体選択性の出現を可能とした新手法の開発を行い、それを利用して連続不斉中心を有するLignan系薬理、生理機能分子種、および抗菌性の抗生物質群の全合成を行っている。そこで本申請ではこれまでの研究の拡張として、まず第一に近年単離、発見されている化合物群から、種々の強い生理活性（抗腫瘍、抗菌、抗ガン活性等）を有する分子の特徴として注目を集めている、水酸基を有したポリ置換ピロリジン、あるいはインドリジジン系アルカロイド類のまったく新しい構築方法を模索、検討すること。第２に、キラルラクトンを用い、ごく最近単離された植物の病原菌に対する防御反応誘発物質の実践的合成プロセスの開発を行うことを目的としている。

連続不斉中心を有する多置換のアゼチジン、ピロリジン、あるいはインドリジジン系アルカロイドは、その特異な構造と強力な抗腫瘍活性等を持つことから多くの研究者の注目を集めているが、その中で水酸基を有する化合物群は *alkaloidal sugar mimics* として知られ、様々な消化酵素である *glycosidase*に対して協奏的あるいは逆行的に極めて強い阻害活性を示すことが知られている。特に近年注目を集めているインドリジジン系アルカロイドである *lentiginosine*、および*broussonetine*は、強い抗HIVウィルス活性や機能障害治療作用を有している。

一方フラノイド系化合物は、これまでに多くの有用な物質が単離、発見されており、heterocyclesのもっとも典型的な天然物である。このうち、ごく近年に単離、構造決定され、現代病の一つである慢性Ｂ型肝炎の治療に対して効果が期待される*virgatusin*や、*styryllactone*の新しいグループとして、１９９８年に単離された*goniothalesdiol*は、強い白血病の予防効果が期待されている化合

物である。この化合物群は農芸化学的見地からも極めて重要な化合物であり、ほとんど合成報告例がないため先のアルカロイド類を含めて最も簡便かつ高効率的にこれらを得るstrategyの開発は、学問上重要であるばかりでなく新たなBiomaterialsへのスクリーニングを含めた合成手法としても極めて価値の高い研究と考えられる。

このように本申請では異なった種類の生理活性物質を、単糖類や単純な骨格であるジヒドロキシアセトン、あるいは酒石酸を出発物質として用い、

1） 立体選択的にキラルなラクタム類を得、連続不斉中心を持つ複素環化合物群が有した高度な立体化学を制御し、強力な抗HIVウィルス活性や機能障害治療作用を有したアルカロイド系生理活性物質の全合成を主眼とする。

2） 新たな官能基化されたキラルなラクトンを合成中間体として利用し、フラン系化合物が有する極めて立体選択性の高い不斉誘導法を開発すると同時に、優れた生理活性天然物の実践的な構築を目的としている。

一つの分子中にたくさんの反応点のある化合物や、さまざまな立体配置を有したアルカロイドやフラノイド系天然物は、これまでに成就されている化学的手法ではなかなか直接的に構築することが困難であり、これまでの概念を凌ぐ新手法の開発は、新たな今後の機能性あるいは生理活性を有する分子種設計のために十分意義深いと考えられる。

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　Novel Asymmetric Synthesis of an Indolizidine Alkaloid, (+)-Lentiginosine Employing Highly Stereoselective Hydrogenation of α-Hydroxypyrrolidine

第二章　An Efficient and Stereoselective Conversion of Lactones to Substituted Cyclic Ether

第三章　Stereoselective Synthesis of Tetrasubstituted Furan from

Dihydroxyacetone Dimer

第四章　First Total Synthesis of a New Tetrasubstituted Pyrrolidine Alkaloid, Broussonetine C

第五章　First Total Synthsis of Tetrasubstituted Tetrahydrofuran Lignan, (-)-Virgatusin

第六章　Asymmetric Synthesis of Tetrasubstituted Tetrahydrofuran, 2-Epigoniothalesdiol, Employing C2-Symmetrical Imide

この分野の研究は日進月歩極めて早い速度で進行しており、各種不斉反応への応用について詳細に研究されている。しかしながら、まだまだ満足のいく高度な合成手法の開発には至っていない。本研究では、上述した研究の方針により、さらなる選択性の追及と化学的手法による不斉反応の開発と、生理活性天然物の全合成を推す進めようと考えている。一つの分子中にたくさの作用点のある生物化学上の酵素を用いた反応に比し、その数の極めて少ない化学合成分子をいかに上手に構築し、鋭敏な化学的手法を用いてこれを凌ぐか、また、複雑な構造を持つ化合物上で、どのようにしたら期待するような完全なコントロールを行えるか、という観点を含めて、環境に配慮した新しい合成手法の開発は意義深いと考えられる。

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　　カイロン法を利用した高効率的反応場制御に基づく
生理活性分子構築法

課題番号　　１０６４０５１６

研究組織　　研究代表者　　依　田　秀　実

研究経費　　平成１０年度　　２、２００　千円
平成１１年度　　１、１００　千円
合計　　３、３００　千円

研究発表

（1）学会誌等

1. H. Yoda, M. Kawauchi, and K. Takabe
Novel Asymmetric Synthesis of an Indolizidine Alkaloid, (+)-Lentiginosine Employing Highly Stereoselective Hydrogenation of α-Hydroxypyrrolidine.
Synlett, **1998**, 137-138.

2. H. Yoda, M. Mizutani, and K. Takabe
An Efficient and Stereoselective Conversion of Lactones to Subsituted Cyclic Ethers.
Heterocycles, **1998**, *48*, 679-686.

3. H. Yoda, M. Mizutani, and K. Takabe
Stereoselective Synthesis of Trisubstituted Furan from Dihydroxyacetone Dimer.
Synlett, **1998**, 855-856.

4. H. Yoda, T. Shimojo, and K. Takabe
First Total Synthesis of a New Tetrasubstituted Pyrrolidine Alkaloid, Broussonetine C.
Tetrahedron Letters, **1999**, *40*, 1335-1336.

5. H. Yoda, M. Mizutani, and K. Takabe
First Total Synthesis of Tetrasubstituted Tetrahydrofuran Lignan, (-)-Virgatusin.

Tetrahedron Letters, **1999**, *40*, 4701-4702.

6. H. Yoda, Takahiro Shimojo, and Kunihiko Takabe
Asymmetric Synthesis of Tetrasubstituted Tetrahydrofuran, 2-Epigoniothalesdiol, Employing C2-Symmetrical Imide
Synlett, **1999**, 1969-1971.

（2）口頭発表

1. 依田秀実、河内美穂、浅井文人、高部圀彦
光学活性４級ヒドロキシピロリジンの立体選択的脱酸素反応による抗生物質(+)-Lentiginosineの全合成
日本化学会、第７４春季年会、1998.3.27.

2. 依田秀実、下條孝弘、鈴木克美、高部圀彦
光学活性な４級ヒドロキシラクタムの立体選択的脱酸素反応を利用した抗生物質Broussonetine Cの不斉合成研究
日本化学会、第７４春季年会、1998.3.27.

3. 依田秀実、水谷雅人、長野公彦、高部圀彦
環状アセタールの脱酸素反応による置換テトラヒドロフランの立体選択的合成
日本化学会、第７４春季年会、1998.3.27.

4. 依田秀実、河内美穂、高部圀彦
糖のキラリティーを利用する外因性エリシター、Syributin １の全合成
日本化学会、第７４春季年会、1998.3.27.

5．　依田秀実、河内美穂、高部圀彦
インドリジジン系アルカロイド、Lentiginisineおよび外因性エリシター、Syringolide類の不斉全合成
第３５回有機合成化学協会関東支部（埼玉）シンポジウム、1998.5.9.

6．　依田秀実、鈴木克美 、高部圀彦
光学活性カルボニル化合物への求核付加反応を利用した(-)-Slaframineの不斉合成研究
第３５回有機合成化学協会関東支部（埼玉）シンポジウム、1998.5.9.

7．　依田秀実、鈴木克美、高部圀彦
カルボニル化合物へのアセチレン誘導体の求核付加を用いたインドリジジン系アルカロイド、(-)-Slaframineの不斉合成
第２９回中部化学関係学協会支部連合秋季大会、1998.10.4.

8．　依田秀実、浅井文人、高部圀彦
フラノース型アミナールへの求核反応を利用したピロリジジン系アルカロイド、Alexine類の不斉合成
第２９回中部化学関係学協会支部連合秋季大会、1998.10.4.

9．　依田秀実、下條孝弘、高部圀彦
C2-対称イミド誘導体の立体選択的脱酸素反応を利用した抗生物質Broussonetine Cの不斉合成
第２９回中部化学関係学協会支部連合秋季大会、1998.10.4.

１０．日本化学会、第７６春季年会、1999.3.29.
置換テトラヒドロフランの高効率的立体制御法の開発とリグナン系生理活性化合物合成への応用

第２９回中部化学関係学協会支部連合秋季大会、1998.10.4.

１１．依田秀実、下條孝弘、高部圀彦
ピロリジン系抗生物質Broussonetine Cの不斉合成
日本化学会、第７６春季年会、1999.3.29.

１２．依田秀実、木村耕平、水谷雅人、高部圀彦
光学活性３置換フラノリグナン、(-)-Sesaminoneの合成研究
日本化学会、第７６春季年会、1999.3.29.

１３．依田秀実、水谷雅人、高部圀彦
新規４置換フラノリグナン、(-)-Virgatusinの不斉全合成
日本化学会、第７６春季年会、1999.3.29.

１４．依田秀実、水谷雅人、高部圀彦
環状エーテルの高効率的立体制御法の開発とフラノリグナン系生理活性天然物の全合成
有機合成化学協会、関東支部（東京・多摩）シンポジウム、1999.5.7.

１５．依田秀実
ポリヒドロキシアルカロイド系生理活性物質の構築に向けて
第３０回中部化学関係学協会支部連合秋季大会、1999.10.2.
（依頼講演）

１６．依田秀実、浅井文人、加藤秀明、高部圀彦
フラノース型アミナールへの求核反応を用いたAlexine類の不斉合成研究
第３０回中部化学関係学協会支部連合秋季大会、1999.10.3.

１７．　依田秀実、下條孝弘、高部圀彦

C２ー対称化合物の立体選択的官能基化反応を利用する生理活性天然物の全合成研究

第３０回中部化学関係学協会支部連合秋季大会、1999.10.3.

目　次

Chapter 1

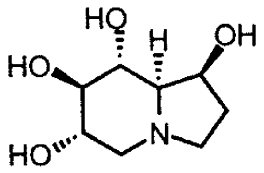
Novel Asymmetric Synthesis of an Indolizidine Alkaloid, (+)-Lentiginosine Employing Highly Stereoselective Hydrogenation of α-Hydroxypyrrolidine

Hidemi Yoda,* Miho Kawauchi, and Kunihiko Takabe

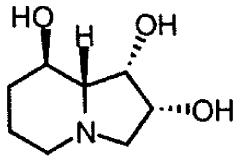
Department of Molecular Science, Faculty of Engineering, Shizuoka University, Hamamatsu 432, Japan

Abstract: An efficient and novel process is described for the asymmetric synthesis of a (*1S,2S,8aS*)-dihydroxyindolizidine alkaloid, (+)-lentiginosine in which the asymmetric deoxygenation of the quaternary α-hydroxypyrrolidine derivative derived from D-xylose is used as a key step.

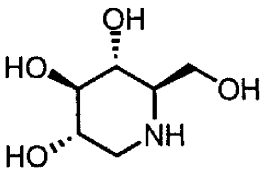
Structurally complex alkaloidal sugar mimics with a nitrogen in the ring have been isolated from plants and microorganisms and inhibit various glycosidases in a reversible and competitive manner.[1] Since such glycosidase inhibitors proved to have the potential to produce antiviral, insect antifeedant, antidiabetic, and anticancer effects, as well as immune modulatory properties, they have held considerable interest in the context of stereoselective heterocyclic synthesis. Noteworthy members among this class of compounds are castanospermine (**1**), swainsonine (**2**) and deoxynojirimycin (**3**) and these have also found use in anticancer, antiviral and antiretroviral research.[2]



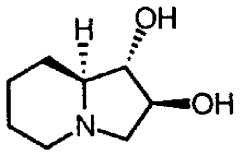
1: Castanospermine



2: Swainsonine



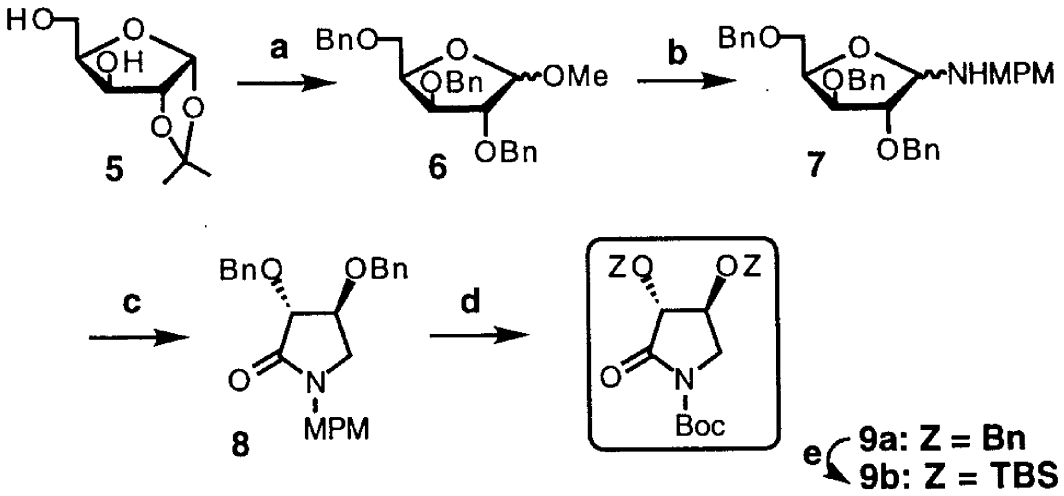
3: Deoxynojirimycin



4: Lentiginosine **Figure 1**

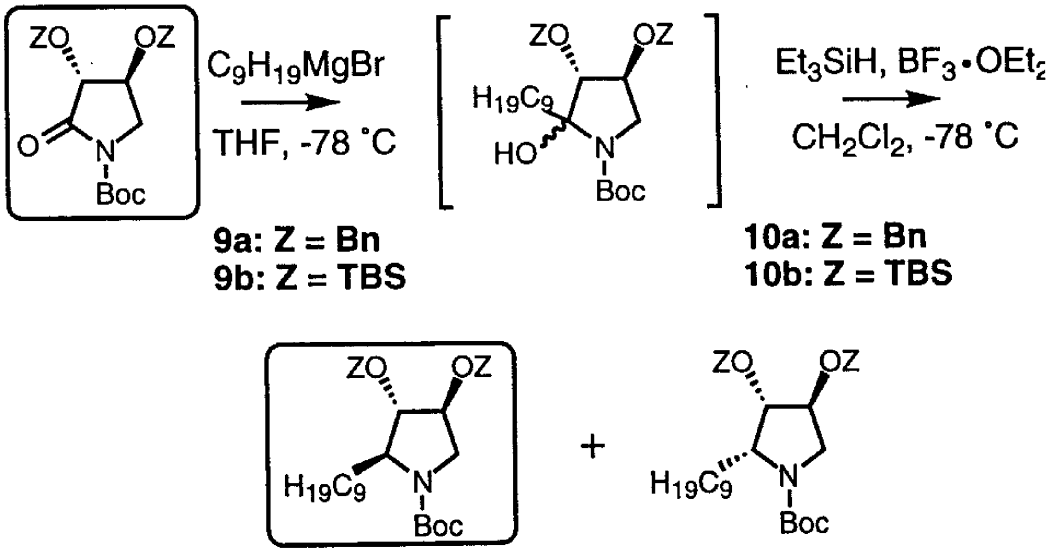
An examination of the structural features of the known such azasugars that act as inhibitors of glycosidases led to the establishment of a general empirical rule starting that a substance should possess at least three hydroxyl groups β to the amino moiety in order to display inhibitory activity.[3] The first compound that violated this rule was lentiginosine (**4**), an alkaloid isolated in 1990 from the spotted locoweed, *Astragalus lentiginosus var. diphysus* and assigned the *trans*-1,2-dihydroxyindolizidine structure.[4] Although we reported the first asymmetric synthesis of (+)-**4**[5] starting from L-tartaric acid, due to impurities present in the natural alkaloid it was not until the inhibitory activities of (+)- and (-)-**4** were investigated in 1995 by Brandi and co-workers that the absolute stereochemistry of the natural **4** was determined unambiguously as shown in Figure 1.[6] In spite of its low degree of hydroxylation, **4** was found to be ca. twice as potent as castanospermine (**1**) also known to inhibit replication of human immunodeficiency virus (HIV),[7] in its inhibition of amyloglucosidases, making this compound the most potent inhibitor of this type of α-glucosidase.[8] In this communication we wish to report our short and novel synthetic strategy based on the reductive deoxgenation of a labile quaternary α-hydroxypyrrolidine derived from D-xylose, which has led to the novel total synthesis of natural (+)-lentiginosine (**4**).

Starting from the commercially available 1,2-*O*-isopropylidene-D-xylofuranose (**5**) as shown in Scheme 1, tribenzylether **6** was obtained through the successive reactions of benzylation and deprotection in CH_3OH followed by benzylation again in high yield. Hydrolysis and amination of **6** with *p*-methoxybenzylamine ($MPMNH_2$) gave the crude aminal **7**,[9] which was subsequently reduced with $LiAlH_4$, leading to the amino alcohol intermediate. This was submitted to oxidative degradation with PCC[9] to provide the optically pure lactam **8** ($[\alpha]D^{25}$+77.5° (c 7.01, $CHCl_3$)) in good yield. Then, **8** was transformed into the desired *N*-Boc lactam **9a** ($[\alpha]D^{26}$+76.2° (c 1.68, $CHCl_3$)) by 2 steps. The bissilylated ether **9b** ($[\alpha]D^{26}$+66.4° (c 1.40, $CHCl_3$)) was also easily prepared through removal of benzyl groups followed by silylation in almost quantitative yield.



Scheme 1. Reagents and conditions: (a) 1, NaH, BnBr, THF; 93%; 2, conc. HCl, MeOH; 93%; 3, NaH, BnBr, THF; 98%; (b) 1, 80%-CH_3COOH, 100 °C; 91%; 2, $MPMNH_2$, benzene-$CHCl_3$, 70 °C, MS 4A; quant.; (c) 1, $LiAlH_4$, THF; 83%; 2, PCC, MS 4A, CH_2Cl_2; 58%; (d) 1, CAN, CH_3CN-H_2O; 81%; 2, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 96%; (e) 1, Pd (black), 4.4% HCOOH-CH_3OH, 40 °C; 96%; 2, TBSCl, imidazole, DMF; 94%.

At first nucleophilic addition with simple nonylmagnesium bromide to **9a** was investigated. The reaction was performed at -78 °C in THF to afford the labile quaternary α-hydroxypyrrolidine derivative **10a** rapidly, which readily underwent the reductive deoxygenation with Et_3SiH in the presence of $BF_3 \cdot OEt_2$[9,10] to lead to the moderately diastereoselective products of **11a** (47%) and **12a** (13%)[11] after separation on silica-gel chromatography. Accompanying formation of the keto-type of compound resulted from the ring-opening reaction was not observed. Furthermore, it became apparent that a change from the benzyl substituents to the larger *t*-butyldimethylsilyl groups in **9** highly enhanced the stereoselectivity (11:1) to yield **11b** (55%) as a predominant product, however, no addition product was observed in the case of the reaction of **9** with the largest triisopropylsilyl groups in any conditions.



9a: Z = Bn
9b: Z = TBS

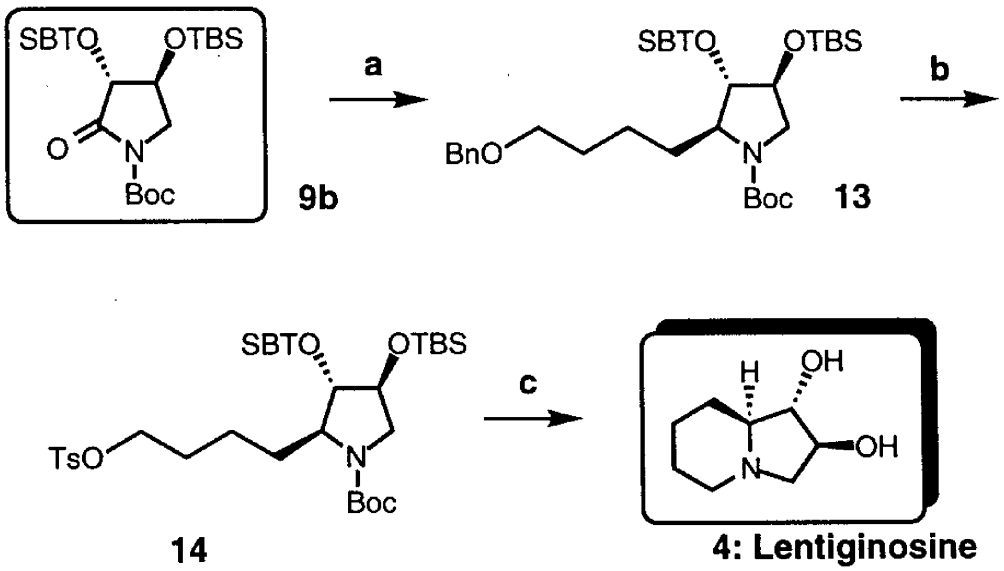
10a: Z = Bn
10b: Z = TBS

11a: Z = Bn (47%) **12a: Z = Bn (13%)**
11b: Z = TBS (55%) **12b: Z = TBS (5%)**

Scheme 2

With these results in hand, the total synthesis of (+)-**4** was accomplished in a short number of steps as follows: Nucleophilic addition of $BnO(CH_2)_4MgBr$ to **9b** followed by the reductive deoxgenation with Et_3SiH-$BF_3 \cdot OEt_2$ provided the pyrrolidine derivative **13** with extremely high stereoselectivity

(98:2 determined by HPLC using Daicel Chiralpak AS). After separation of the major component, the benzyl substituent in **13** ($[\alpha]D^{27}$+6.85° (c 1.78, $CHCl_3$)) was replaced by the leaving group to give the corresponding tosylate **14** ($[\alpha]D^{26}$+7.71° (c 1.34, $CHCl_3$)) in good yield. Finally, **14** was subjected to deprotections with $BF_3 \cdot OEt_2$[12] and in turn cyclization under basic conditions to complete the total synthesis of (+)-lentiginosine (**4**) ($[\alpha]D^{27}$+3.20° (c 1.07, CH_3OH) [lit. $[\alpha]D^{25}$+3.2° (c 0.27, CH_3OH)][6a]) in high yield. The spectral data of the synthetic **4** were completely identical with those of the reported natural[4] and synthetic[5,6] compound.



Scheme 3. Reagents and conditions: (a) 1, $BnO(CH_2)_4MgBr$, THF, -78 °C; 2, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 55% (2 steps); (b)1, Pd (black), 4.4% HCOOH-CH_3OH, 40 °C; 94%; 2, TsCl, pyridine; 70%; (c) $BF_3 \cdot OEt_2$, CH_2Cl_2, -20 ~ 0 °C; 2, KOH, CH_3OH; 74% (2 steps).

In summary, an efficient and novel synthetic pathway from D-xylose to a dihydroxyindolizidine alkaloid, (+)-lentiginosine has been established employing the stereoselective deoxygenation of α-hydroxypyrrolidine as a key step, which will furthermore serve for the synthesis other natural products.

References and Notes

(1) (a) Elbein, A. D. (Inhibitors of the Biosynthesis and Processing of N-linked Oligosaccharide Chains.) *Annu. Rev. Biochem.* **1987**, *56*, 497. (b) Fellows, L. E.; Kite, G. C.; Nash, R. J.; Simmonds, M. S. J.; Scofield, A. M. In *Plant Nitrogen Metabolism*; Poulton, J. E., Romero, J. T., Conn, E. E., Eds.; Plenum: New York, **1989**; pp 395. (c) Legler, G. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 319.

(2) (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215. (b) Liu, P. S.; Hoekstra, W. J.; King, C.-H. R. *Tetrahedron Lett.* **1990**, *31*, 2829.

(3) (a) Elbein, A. D.; Molyneux, R. J. In *Alkaloids*: Chemical and Biological Perspectives; Pelletier, S. W.; Ed.; Wiley: New York, **1987**; Vol. *5*, Chapter 1, pp.1. (b) Howard, A. S.; Michael, J. P. *Alkaloids* (N.Y.) **1986**, *28*, 183. (c) Michael, J. P. *Natural Products Reports* **1990**, 485.

(4) (a) Pastuszak, I.; Molyneux, R. J.; James, L. F.; Elbein, A. D. *Biochemistry* **1990**, *29*, 1886. (b) Molyneux, R. J. *J. Nat. Prod.* **1990**, *53*, 609.

(5) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1455.

(6) (a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Frignoli, R.; Goti, A.; Picasso, S.; Vogel, P. *J. Org. Chem.* **1995**, *60*, 6806. (b) Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949 and the other syntheses are as follows: (c) Gurjar, M. K.; Ghosh, L.; Syamala, M.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871. (d) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398. (e) Giovannini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1995**, *60*, 5706.

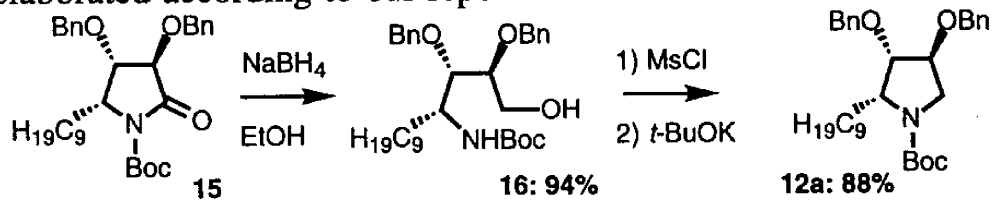
(7) (a) Gruters, R. A.; Neefjes, J. J.; Tersmette, M.; de Goede, R. E. Y.; Tulp, A.; Huisman, H. G.; Miedema, F.; Ploegh, H. L. *Nature* **1987**, *330*, 74. (b) Fleet, G.W. J.; Karpas, A.; Dwek, R. A.; Fellows, L. E.; Tyms, A. S.; Petursson, S.; Namgoong, S. K.; Ramsden, N. G.; Smith, P. W.; Son, J. C.; Wilson, F.; Witty, D. R.; Jacob, G. S.; Rademacher, T. *FEBS Lett.* **1988**, *237*, 128.

(8) Molyneux, R. J.; Pan, Y. T.; Tropea, J. E.; Benson, M.; Kaushal, G. P.; Elbein, A. D. *Biochemistry* **1991**, *30*, 9981.

(9) (a) Yoda, H.; Nakajima, T.; Yamazaki, H.; Takabe, K. *Heterocycles* **1995**, *41*, 2423. (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669. (c) Yoda, H.; Yamazaki, H.; Takabe, K. *Tetrahedron: Asymmetry* **1996**, *7*, 373 and references cited therein.

(10) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531.

(11) The newly created stereogenic centers of **11** and **12** were easily determined to be *S* and *R* respectively as indicated in Scheme 2 based on the observed chemical shift of ^{13}C NMR, since the authentic **12a** was quickly prepared through the successive reactions of reduction and mesylation followed by cyclization from **15**, which was in turn elaborated according to our reported method.[9b]



(12) Yoda, H.; Oguchi, T.; Takabe, K. *Tetrahedron Lett.* **1997**, *38*, 3283.

Chapter 2

AN EFFICIENT AND STEREOSELECTIVE CONVERSION OF LACTONES TO SUBSTITUTED CYCLIC ETHERS

Hidemi Yoda,* Masato Mizutani, and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering,
Shizuoka University,
Hamamatsu 432, Japan

Abstract- A general route to substituted cyclic ethers has been described by using nucleophilic addition of Grignard reagents to lactones in the presence of $CeCl_3$ followed by the Lewis acid-induced deoxygenation of the corresponding hemiketals with Et_3SiH. Stereoselective reduction of the 5-membered adducts to the disubstituted tetrahydrofurans has been also investigated.

Structurally complex tetrahydrofuran and tetrahydropyran units are often found in many natural products[1] including pheromones,[2] polyether antibiotics,[3] and polyene mycotoxins,[4] and there has been increasing interest in the synthesis of such ring systems.[5] Particularly, since tetrahydrofuran derivatives containing chiral 2,3-disubstituents serve as good templates for the convergent construction of antifungal metabolites,[6] further exploitation

of much more convenient stereodefined methods is strongly desired. Although one of the most effective ways to construct these types of compounds is electrophile-induced cyclization[7] of γ, δ-unsaturated alcohols by use of iodine, *N*-bromosuccinimide, mercury(II) acetate, phenylselenenyl chloride, etc., highly stereoselective forms are not readily available.
On the other hand, direct conversion of lactones to cyclic ethers *via* Lewis acid-induced reduction of hemiketal intermediates with Et_3SiH has been studied especially in the carbohydrate area[8] for the synthesis of C-glycosyl compounds, however, little has been known on simpler cyclic systems.[9] The reduction of a hemiketal to a cyclic ether would introduce a new stereogenic center. Thus, in this report we wish to disclose our results concerning the reactions of Grignard reagents with simple lactones in the presence of $CeCl_3$ followed by the Lewis acid-promoted deoxygenation. Stereoselective conversion of the three types of 5-membered lactones to the disubstituted tetrahydrofurans is also presented.

As shown in Table 1, we initially investigated the nucleophilic attack of butylmagnesium bromide to the lactone (**1**) in THF followed by the one-pot deoxygenation of the corresponding hemiketal intemediate (**2**) in CH_2Cl_2 with Et_3SiH in the presence of $BF_3 \cdot OEt_2$[10] after evaporation of the solvent *in vacuo*. Whereas the reaction with Grignard reagent only resulted in the low and non-selective formation of the desired **3** (In this reaction accompanying formation of small amounts of **4** (7%) and **5** (5%) derived from the dialkylation of **1** was also observed.), the reaction in the presence of $CeCl_3$ (1.0 equiv.)[11] afforded **3** as a major product (entry 5). The use of other metal halides such as $MgBr_2$, $SmCl_3$, and $MnCl_2$ (entries 2-4) brought about unsatisfactory results. After detailed investigations the best result was observed under the conditions indicated in entry 6 in 76% isolated yield.

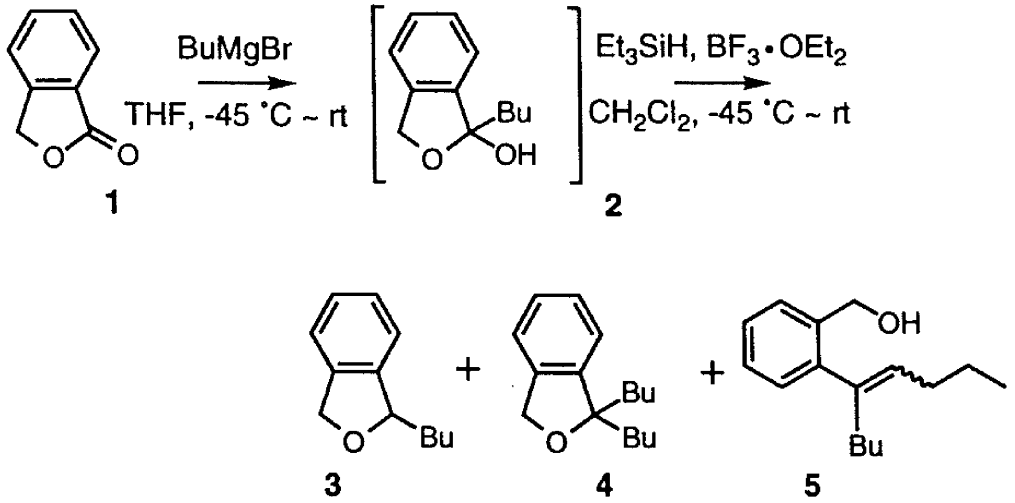


Table 1. Nucleophilic Addition of Grignard Reagents to **1** Followed by the One-pot Deoxygenation.

entry	BuMgBr (equiv.)	additive (equiv.)	Et_3SiH (equiv.)	$BF_3 \cdot OEt_2$ (equiv.)	products (%) a) **3**	**4**	**5**
1	1.2	---	10	10	4	7	5
2	2.4	$MgBr_2$ (1.0)	10	10		--- b)	
3	2.4	$SmCl_3$ (1.0)	10	10		--- b)	
4	2.4	$MnCl_2$ (1.0)	10	10	5	trace	trace
5	2.4	$CeCl_3$ (1.0)	10	10	34	5	4
6	**2.4**	**$CeCl_3$ (2.5)**	**10**	**10**	**76**	trace	trace

a) Isolated yield based on the lactone (**1**). b) Grignard addition was not observed. c) Complex mixture.

Next, we examined the reactions with a variety of lactones under similar conditions in the presence of $CeCl_3$. The results are summarized in Table 2. After nucleophilic addition of Grignard reagents to the lactones (**6**), both

reactions in Method A and Method B (entries 1,2) as well as the reactions with a 5-methyl substituent (entries 4,5) smoothly proceeded to give the substituted cyclic ethers (**8**) in moderate to good yields. In addition, it became apparent that the procedure described here was also applicable to the synthesis of 7-membered cyclic ether (**8e**) (entry 8).

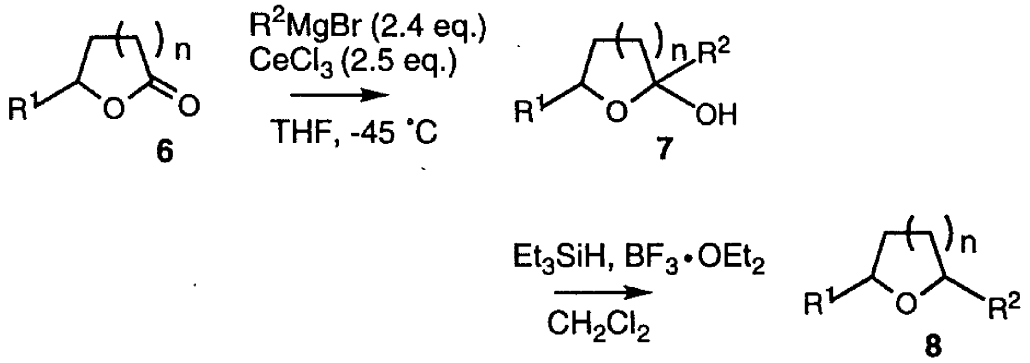


Table 2. Nucleophilic Addition of Grignard Reagents to **6** Followed by the Deoxygenation.

entry	n	lactone (**6**) R^1	R^2	Et_3SiH (equiv.)	$BF_3 \cdot OEt_2$ (equiv.)	temp. (°C)	yield of **8** [c] (%)
1 [a]	1	H	Ph	4	4	-45 ~ rt	50 (**8a**)
2 [b]	1	H	Ph	4	4	-45	48 (**8a**)
3 [b]	1	H	$C_{11}H_{23}$	4	4	-45 ~ rt	49 (**8b**)
4 [a]	1	Me	Ph	10	10	-45 ~ rt	75 [d] (**8c**)
5 [b]	1	Me	Ph	4	4	-45	88 [d] (**8c**)
6 [a]	2	H	Ph	10	10	-45 ~ rt	23 (**8d**)
7 [b]	2	H	Ph	4	4	-45	62 (**8d**)
8 [b]	3	H	Ph	4	4	-45 ~ rt	39 (**8e**)

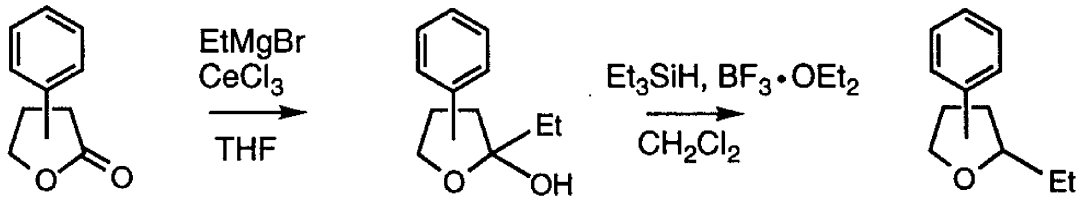
a) Method A; the deoxygenation was performed without extraction after evaporation of THF *in vacuo*.

b) Method B; the deoxygenation was performed after extraction with ether.

c) Isolated yield based on the lactone (**6**).

d) The ratio of the stereoisomers was not determined .

With the above outcome in hand, we turned our attention to the investigations on the relative stereochemistry of the products derived from the reductive deoxygenation of the 5-membered ring lactones (**9**). As shown in Table 3, in the case of the reaction with 3-phenyllactone (**9a**) the Lewis acid-promoted deoxygenation with Et_3SiH proceeded with complete *trans* diastereoselectivity (100 : 0)[12] at low temperature (entry 2). In contrast, a change of the phenyl group to the 4-position on the lactone ring reversely led to the predominant *cis* selectivity (95 : 5) (entry 3 or 4). However, the reaction employing **9c** with 5-phenyl subsituent did not indicate any diastereoselectivity.



9 **10** **11**

Table 3. Stereoselective Deoxygenation of the Substituted 5-Membered Lactones (**9**).

entry	lactone **9** a)	temp. (°C)	yield of **11** b) (%)	*cis* : *trans* c)
1	**9a**	-78 ~ rt	25 (11a)	11 : 89
2	**9a**	**-78 ~ -60**	**23(11a)**	**0 : 100**

3	**9b**	**-78 ~ rt**	**38(11b)**	**95 : 5**
4	**9b**	-78	44 (11b)	95 : 5
5	**9c**	-78 ~ rt	53 (11c)	57 : 43
6	**9c**	-78	53 (11c)	60 : 40

a) **9a**: 3-phenyl-, **9b**: 4-phenyl-, **9c**: 5-phenyllactone.[13]

b) Isolated yield based on the lactone **9** and not optimized.

c) Determined by GC analysis.

Recently Schmitt *et al.* reported the replacement of the hydroxyl group of γ-lactols by the alkyl group of organometallic reagents, where 1,2- and 1,3-induction by a single phenyl substituent leads to *trans* selectivities in the formation of tetrahydrofuran derivatives.[12] They rationalize the observed stereochemical outcome based on the reactivity and stability of the oxocarbenium ion intermediate. In our case, the Felkin-Anh model A derived from the 3-phenyl-substituted lactone (**9a**) is also the thermodynamically preferred conformation rather than B (Figure 1). Since phenyl and ethyl groups on the ring occupy the remotest positions each other owing to the steric repulsion, the attack of Et_3SiH could occur preferentially from the less hindered left-site due to the shielding effect of the ethyl function, leading to the *trans*-selective formation of the product. On the other hand, for the 4-phenyl-substituted lactone (**9b**) the phenyl group strongly hinders the attack from the right-site in the thermodynamically less stable model D. Consequently the reaction also could proceed through the attack to the oxocarbenium ion from the left-site of the more stable model C to give the *cis*-selective product predominantly. In the case of the 5-substituted lactone (**9c**), the phenyl substituent is situated in a rather remote position from the reaction center, expecting no selectivity for the formation of the product.

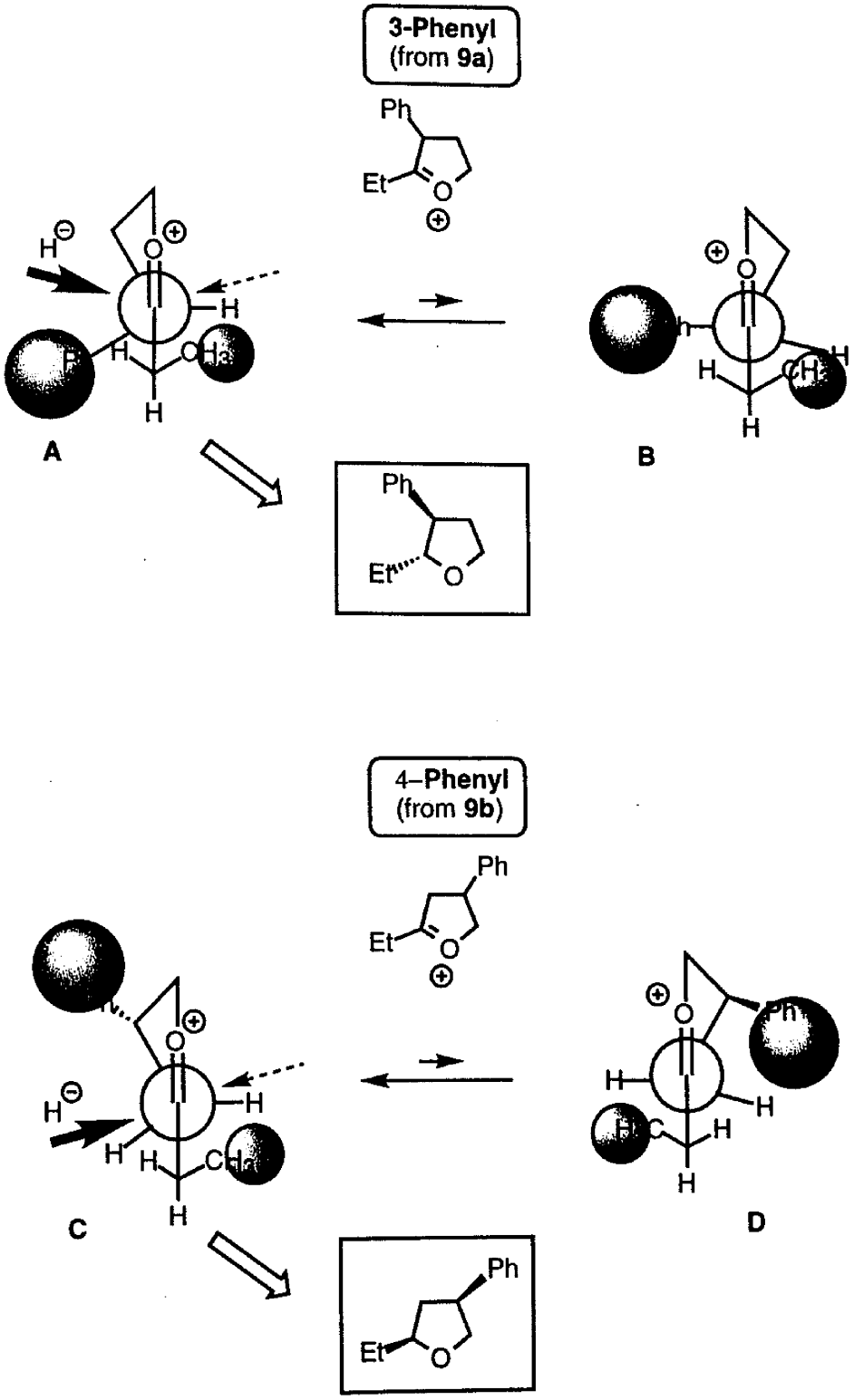


Figure 1. Structure Models of Reaction Intermediate.

In summary, our results demonstrate that the conversion of lactones to cyclic ethers on simpler systems can be achieved in good yield through the nucleophilic addition of Grignard reagents in the presence of $CeCl_3$ followed by the Lewis acid-induced deoxygenation and furthermore an efficient method to control the stereochemistry of the 1,2- and 1,3-positions in the furan rings has been developed. This strategy provides a new synthetic opportunity for the synthesis of biologically active natural products.

EXPERIMENTAL

Ir spectra were recorded on a JASCO Model A-3 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL Model EX-90 spectrometer (operated at 90 and 22.4 MHz, respectively) in $CDCl_3$ referenced to internal tetramethylsilane (TMS) at 0.0 ppm. MS spectra were recorded on a GCMS-QP5050 Shimazu, Japan. Reactions were monitored by TLC using 0.25 mm Merck silica gel 60-F_{254} precoated silica gel plates. Column chromatography was performed on Merck silica gel Kieselgel 60 eluting with the indicated solvent system. Yields refer to chromatographically and spectroscopically (^1H- and ^{13}C-NMR) homogeneous materials. All compounds obtained here are well known and fully characterized.

A TYPICAL PROCEDURE OF METHOD A

2-Phenyltetrahydrofuran (8a): Cerium chloride ($CeCl_3 \cdot 7H_2O$) (0.716 g, 2.90 mmol) was quickly and finely ground to a powder and placed in a flask, which was immersed in an oil bath and heated gradually to 135-140 °C with evacuation (*ca.* 1.0 Torr). After maintenance of the cerium chloride for 1 h, a solution of lactone (**6**) (0.1 g, 1.16 mmol) in THF (6 mL) was

added and stirred for 1 h under nitrogen at rt. Then, the reaction mixture was cooled to -45 °C and phenylmagnesium bromide (1.2 M in THF, 2.4 mL, 2.88 mmol) was added. After the solution was stirred for 1 h at the same temperature, it was concentrated *in vacuo*. The residue was dissolved in 6 mL of CH_2Cl_2 and quickly cooled to -45 °C again. To this solution was added Et_3SiH (1.316 g, 11.32 mmol) and after the mixture was stirred for 5 min, $BF_3 \cdot OEt_2$ (1.689 g, 11.89 mmol) was slowly added. Then, the reaction flask was gradually warmed to rt for 2 h. It was quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by using silica gel column chromatography (20:1 hexane-ethyl acetate) to afford 0.085 g (0.574 mmol, 50%) of the furan (**8a**) as a colorless oil: IR(neat)cm^{-1} 2980, 2870, 1070, 760, 700; ^{1}H-NMR δ 7.70-7.10 (m, 5H, Ph), 4.88 (t, J = 7.2 Hz, 1H, CH_2CH(Ph)O), 4.28-3.75 (m, 2H, OCH_2CH_2), 2.48-1.62 (m, 4H, $OCH_2CH_2CH_2CH$(Ph)); ^{13}C-NMR δ 143.5, 128.3, 127.1, 125.6, 80.6, 68.6, 34.6 26.0; GC-MS m/z 148 (64%, M^+), 147 (78), 105 (100), 77 (48) 42 (51). *Anal.* Calcd for $C_{10}H_{12}O$: C, 81.04; H, 8.16. Found: C, 81.32; H, 8.12.

A TYPICAL PROCEDURE OF METHOD B

2-Phenyltetrahydrofuran (8a): To a suspension of cerium chloride (0.715 g, 2.90 mmol) prepared by the procedure described above in 4 mL of THF was added a solution of lactone (**6**) (0.101 g, 1.17 mmol) in THF (2 mL) and stirred for 1 h under nitrogen at rt. Then, the reaction mixture was cooled to -45 °C and phenylmagnesium bromide (1.2 M in THF, 2.4 mL, 2.88 mmol) was added. After the solution was stirred for 1 h at the same temperature, it was quenched by the addition of water (3 mL) and filtered through a pad of Celite followed by the extraction with ether (3 x 20 mL).

The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil of the crude hemiketal. A solution of the above hemiketal in CH_2Cl_2 (1 mL) was cooled to -45 °C and Et_3SiH (0.541 g, 4.65 mmol) was added. After the mixture was stirred for 5 min, $BF_3 \cdot OEt_2$ (0.66 g, 4.65 mmol) was slowly added. The solution was further stirred for 2 h at the same temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic extracts were dried (Na_2SO_4) followed by the concentration *in vacuo*. The residue was chromatographed (20:1 hexane-ethyl acetate) to give 0.083 g (0.56 mmol, 48%) of the furan (**8a**) as a colorless oil.

2-Butylphthalan (3): colorless oil; IR(neat)cm^{-1} 2960, 2940, 2870, 1460, 1050, 1030, 760; ^{1}H-NMR δ 7.48-7.05 (m, 4H, Ph), 5.36-5.15 (m, 1H, PhC*H*(Bu)O), 5.11 (s, 1H, PhCH_2O), 5.09 (s, 1H, PhCH_2O), 2.08-1.70 (m, 2H, CHCH_2CH$_2$CH$_2$CH$_3$), 1.70-1.16 (m, 4H, CH$_2$CH_2CH_2CH$_3$), 0.95 (t, J = 6.3 Hz, 3H, CH$_2$CH_3); ^{13}C-NMR δ 142.4, 139.5, 127.3, 127.2, 121.1, 120.9, 84.0, 72.4, 36.1, 27.4, 22.8 14.1; GC-MS m/z 176 (3%, M^+), 119 (100), 91 (39), 65 (14). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.68; H, 9.29.

2,2-Dibutylphthalan (4): colorless oil; IR(neat)cm^{-1} 2900, 2850, 1270, 1130, 1050, 720; ^{1}H-NMR δ 7.43-6.93 (m, 4H, Ph), 5.07 (s, 2H, PhCH_2O), 2.08-1.03 (m, 12H, CCH_2CH_2CH_2CH$_3$), 0.83 (t, J = 6.0 Hz, 6H, CH$_2$CH_3). *Anal.* Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.81; H, 10.35.

5-(2'-Hydroxymethylphenyl)-4-nonene (5): colorless oil; IR(neat)cm^{-1} 3600-3000, 2900, 1450, 1020, 730; ^{1}H-NMR δ 7.73-6.90 (m, 4H, Ph), 5.44, 5.33 (2t, J = 7.0, 7.0 Hz, 1H, CC*H*CH$_2$), 4.68, 4.62 (2s, 2H, PhCH_2OH), 2.62-1.98 (m, 5H, CCHCH_2CH$_2$, PhCCH_2CH$_2$, CH$_2$O*H*), 1.98-

0.47 (m, 12H, $CH_2CH_2CH_3$, $CH_2CH_2CH_2CH_3$). *Anal.* Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.59; H, 10.58.

2-Undecyltetrahydrofuran (8b): colorless oil; IR(neat)cm^{-1} 2930, 2850, 1460, 1080; ^{1}H-NMR δ 4.11-3.54 (m, 3H, OCH_2CH_2, $CH_2CH(C_{11}H_{23})O$), 2.10-1.01 (m, 24H, $OCH_2CH_2CH_2CH$-($C_{11}H_{23}$), $CH(CH_2)_{10}CH_3$), 0.88 (t, J = 5.4 Hz, 3H, $(CH_2)_{10}CH_3$); ^{13}C-NMR δ 79.5, 67.6, 35.8, 32.0, 31.5, 29.9, 29.7, 29.4, 26.5, 25.8, 22.8 14.1; GC-MS m/z 226 (0.02%, M^+), 225 (0.08), 71 (100), 55 (8.9), 43 (30). *Anal.* Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.29; H, 13.51.

2-Methyl-5-phenyltetrahydrofuran (8c): colorless oil; IR(neat)cm^{-1} 2980, 1450, 1080, 1030, 760, 700; ^{1}H-NMR δ 7.53-7.09 (m, 5H, Ph), 5.14-4.70 (m, 1H, CH_2CH(Ph)O), 4.52-3.93 (m, 1H, OCH(Me)CH_2), 2.51-1.43 (m, 4H, CH(Me)CH_2CH_2CH(Ph)), 1.34, 1.28 (2d, J = 6.2, 6.2 Hz, 3H, $CHCH_3$); ^{13}C-NMR δ 128.3, 127.1, 127.0, 125.8, 125.5, 81.0, 80.2, 75.9, 35.6, 34.6, 34.2, 33.1, 21.6, 21.3; GC-MS m/z 162 (75%, M^+), 105 (99), 77 (56), 56 (100), 41 (65). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.66; H, 8.58.

2-Phenyltetrahydropyran (8d): colorless oil; IR(neat)cm^{-1} 2950, 2850, 1100, 1060, 1050, 760, 700; ^{1}H-NMR δ 7.68-7.10 (m, 5H, Ph), 4.48-3.96 (m, 2H, OCH_2CH_2), 3.80-3.36 (m, 1H, CH_2CH(Ph)O), 2.10-1.27 (m, 6H, $OCH_2CH_2CH_2CH_2$CH(Ph)); ^{13}C-NMR δ 143.4, 128.2, 127.2, 125.8, 80.1, 68.9, 34.1, 25.9, 24.0; GC-MS m/z 162 (60%, M^+), 161 (54), 105 (100), 77 (53), 41 (51). *Anal.* Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.23; H, 8.81.

2-Phenyloxepane (8e): colorless oil; IR(neat)cm^{-1} 2930, 2850, 1450, 1130, 1040, 750, 700; ^{1}H-NMR δ 7.49-7.15 (m, 5H, Ph), 4.57 (dd, J = 8.4,

4.1 Hz, 1H,CH_2CH(Ph)O), 4.20-3.52 (m, 2H, OCH_2CH_2), 2.28-1.36 (m, 8H, $OCH_2CH_2CH_2CH_2CH_2CH$(Ph)); ^{13}C-NMR δ 144.7, 128.2, 126.8, 125.7, 81.4, 68.7, 37.9, 31.1, 26.8, 25.9; GC-MS m/z 176 (39%, M^+), 107 (53), 105 (100), 79 (44), 42 (65). *Anal.* Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.92; H, 9.03.

2-Ethyl-3-phenyltetrahydrofuran (11a)[12]: colorless oil; IR(neat)cm^{-1} 2840, 1450, 1090, 1060, 1030, 750, 700; ^{1}H-NMR (*trans*-**11a**) δ 7.52-7.01 (m, 5H, Ph), 4.01 (t, J = 7.1 Hz, 2H, CH_2CH_2O), 3.73 (td, J = 6.1, 7.6 Hz, 1H, OCH(Et)CH(Ph)), 2.90 (q, J = 8.4 Hz, 1H, CH(Et)CH(Ph)CH_2), 2.36 (dddd, J = 12.5, 8.5, 7.0, 5.0 Hz, 1H, CH(Ph)CH_2CH_2), 2.11 (dddd, J = 12.5, 9.0, 8.5, 7.5 Hz, 1H, CH(Ph)CH_2CH_2), 1.78-1.36 (m, 2H, $CHCH_2CH_3$), 0.91 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C-NMR (*trans*-**11a**) δ 142.4, 128.6, 127.7, 126.5, 87.5, 67.5, 50.9, 35.8, 26.9, 10.6; ^{13}C-NMR (*cis*-**11a**) δ 142.4, 128.6, 128.1, 126.2, 84.5, 66.8, 47.7, 33.5, 24.3, 10.9; GC-MS (*trans*-**11a**) m/z 176 (16%, M^+), 118 (100), 117 (95), 91 (33); GC-MS (*cis*-**11a**) m/z 176 (10%, M^+), 118 (100), 117 (76), 57 (22).

2-Ethyl-4-phenyltetrahydrofuran (11b)[12]: colorless oil; IR(neat)cm^{-1} 2850, 1460, 1080, 1050, 1020, 750, 700; ^{1}H-NMR (*cis*-**11b**) δ 7.52-7.13 (m, 5H, Ph), 4.34-3.24 (m, 3H, OCH(Et)CH(Ph), CH(Ph)CH_2O), 2.62-2.20 (m, 1H, CH_2CH(Ph)CH_2), 1.90-1.33 (m, 4H, CH(Et)CH_2CH(Ph), $CHCH_2CH_3$), 0.98 (t, J = 7.2 Hz, 3H, CH_2CH_3); ^{13}C-NMR (*trans*-**11b**) δ 142.8, 128.6, 127.2, 126.5, 80.9, 74.6, 44.7, 39.4, 29.0, 10.4; ^{13}C-NMR (*cis*-**11b**) δ 142.8, 128.6, 127.2, 126.5, 81.8, 74.2, 45.6, 40.7, 28.6, 10.4; GC-MS (*trans*-**11b**) m/z 176 (12%, M^+), 147 (52), 117 (80), 104 (65), 91 (100); GC-MS (*cis*-**11b**) m/z 176 (15%, M^+), 147 (74), 117 (98), 104 (59), 91 (100).

2-Ethyl-5-phenyltetrahydrofuran (11c)[12]: colorless oil; IR(neat)cm^{-1}

2850, 1450, 1080, 1060, 1030, 750, 700; ^{1}H-NMR (*trans*-**11c**) δ 7.59-7.12 (m, 5H, Ph), 4.97 (t, *J* = 7.0 Hz, 1H, CH_2CH-(Ph)O), 4.29-3.73 (m, 1H, $OCH(Et)CH_2$), 2.52-1.20 (m, 6H, $CH(Et)CH_2CH_2CH(Ph)$, $CHCH_2CH_3$), 0.96 (t, *J* = 7.3 Hz, 3H, CH_2CH_3); ^{1}H-NMR (*cis*-**11c**) δ 7.59-7.12 (m, 5H, Ph), 4.86 (t, *J* = 6.7 Hz, 1H, $CH_2CH(Ph)O$), 4.29-3.73 (m, 1H, $OCH(Et)CH_2$), 2.52-1.20 (m, 6H, $CH(Et)CH_2CH_2CH(Ph)$, $CHCH_2CH_3$), 0.99 (t, *J* = 7.1 Hz, 3H, $CH2CH_3$); ^{13}C-NMR (*trans*-**11c**) δ 144.0, 128.2, 127.1, 125.8, 81.4, 80.2, 35.4, 31.9, 28.9, 10.4; ^{13}C-NMR (*cis*-**11c**) δ 143.6, 128.2, 127.0, 125.6, 81.3, 80.8, 34.5, 30.9, 28.9, 10.3; GC-MS (*trans*-**11c**) m/z 176 (51%, M^+), 147 (100), 129 (50), 105 (59), 91 (91); GC-MS (*cis*-**11c**) m/z 176 (49%, M^+), 147 (100), 117 (47), 105 (63), 91 (81).

ACKNOWLEDGMENT

We are grateful to Mr. T. Yamada, instrumentation room for chemical analysis, Shizuoka University for measuring the GC-MS spectra.

REFERENCES AND NOTES

1. K. Nakanishi, *Nat. Pro. Chem.*, 1974, **1**, 2.
2. K. Mori, *Tetrahedron*, 1989, **45**, 3233.
3. P. A. Bartlett, *Tetrahedron*, 1980, **36**, 2; T. L. B. Boivin, *ibid.*, 1987, **43**, 3309; M. D. Ruff in '*Polyether Antibiotics: Naturally Occurring Acid Ionophors*,' ed. by I. W. Westley, Marcel Dekker, New York, 1982, Vol. 1, chapter 6.
4. For example see: M. Niwa, T. Endo, S. Ogiso, H. Furukawa, and S. Yamamura, *Chem Lett.*, 1981, 1285; S. Rebuffat, D. Davoust, L. Molho, and D. Molho, *Phytochemistry*, 1980, **19**, 1285.
5. E. D. Mihelich, *J. Am. Chem. Soc.*, 1990, **112**, 8995; S. H. Kang, T. S. Hwang, W. J. Kim, and J. K. Lim, *Tetrahedron Lett.*, 1990, **31**, 5917; J.-C. Harmange and Figadère, *Tetrahedron: Asymmetry*, 1993, **4**,

1711; U. Koert, *Synthesis*, 1995, 115.

6. G. V. Sharma and S. R. Vepachedu, *Tetrahedron*, 1991, **47**, 519 and references cited therein; J. Mulzer, L. Kattner, A. R. Schrecker, C. Schröder, J. Buschmann, C. Lehmann, and P. Luger, *J. Am. Chem. Soc.*, 1991, **113**, 4218.
7. G. Cardillo and M. Orena, *Tetrahedron*, 1990, **46**, 3321.
8. M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976; G. A. Kraus and M. T. Molina, *J. Org. Chem.*, 1988, **53**, 752; E. Ayadi, S. Czernecki, and J. Xie, *Chem. Commun.*, 1996, 347.
9. G. A. Kraus, M. T. Molina, and J. A. Walling, *J. Org. Chem.*, 1987, **52**, 1273.
10. H. Yoda, T. Nakajima, and K. Takabe, *Synlett*, 1997, 911; H. Yoda, T. Nakajima, and K. Takabe, *Tetrahedron Lett.*, 1996, **37**, 5531; H. Yoda, H. Yamazaki, M. Kawauchi, and K. Takabe, *Tetrahedron: Asymmetry*, 1995, **6**, 2669 and references cited therein.
11. T. Imamoto, N. Takiyama, K. Nakamura, T. Hatajima, and Y. Kamiya, *J. Am. Chem. Soc.*, 1989, **111**, 4392.
12. The relative stereochemistry was determined based on the spectral data cited in the following reference; A. Schmitt and H.-U. Reißig, *Chem. Ber.*, 1995, **128**, 871.
13. These substituted lactones were elaborated according to our previous report; H. Yoda, H. Morishita, M. Kudo, T. Katagiri, and K. Takabe, *Chemistry Express*, 1989, **4**, 515.

Chapter 3

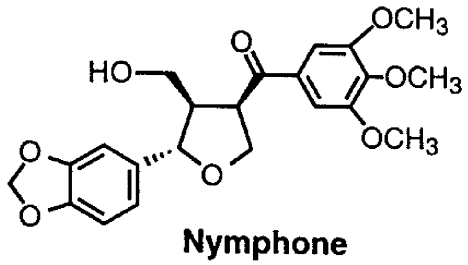
Stereoselective Synthesis of Tetrasubstituted Furan from Dihydroxyacetone Dimer

Hidemi Yoda,* Masato Mizutani, and Kunihiko Takabe

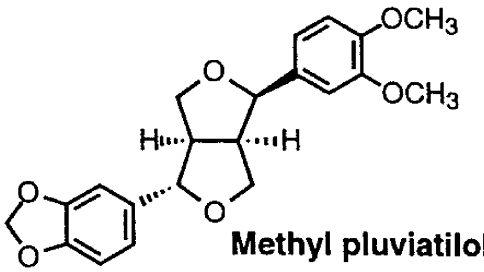
Department of Molecular Science, Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan

Abstract: A convergent route to the stereochemically same tetrasubstituted furan produced as a single stereoisomer has been developed in racemic form featuring the stereoselective hydrogenation of two types of hemiketal derivatives, which were prepared by nucleophilic addition of Grignard reagent in the presence of $CeCl_3$ to the functionalized lactones with γ-stereochemistry different to each other.

Structurally complex tetrahydrofurans feature in many biologically potent natural products such as pheromones,[1] polyether antibiotics,[2] and marine epoxylipids.[3] Due to their interesting activity as well as unique structural characteristics, they have been the subject of an extensive synthetic effort which has culminated in numerous syntheses.[4] In particular, since optically active tetrahydrofuran derivatives with 2,3,4-trisubstituents serve as good templates for the convergent construction of pharmacologically important furanoid lignans (Figure 1),[5] there is a strong desire for the further exploitation of more convenient stereodefined methods.

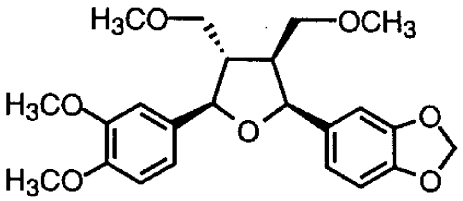


Nymphone



Methyl pluviatilol

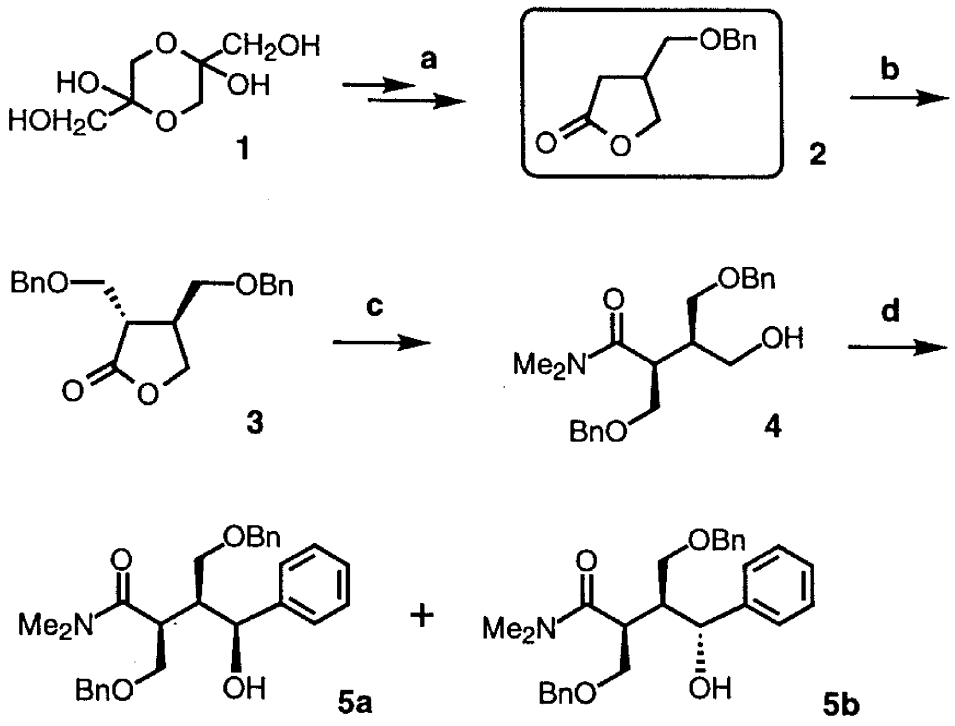
Figure 1



Virgatusin

Recently the direct conversion of lactones to cyclic ethers *via* Lewis acid-induced reduction of hemiketal intermediates, which introduce a new stereogenic center, has been studied. In particular the carbohydrate area has been focussed upon for the synthesis of C-glycosyl compounds,[6] however, little is known of other cyclic systems.[7] In this communication we wish to describe results where two cyclic hemiketals derived from the diastereomeric lactones not only underwent stereoisomerically complete Lewis acid-promoted deoxygenation, but afforded the stereochemically identical tetrasubstituted furan.

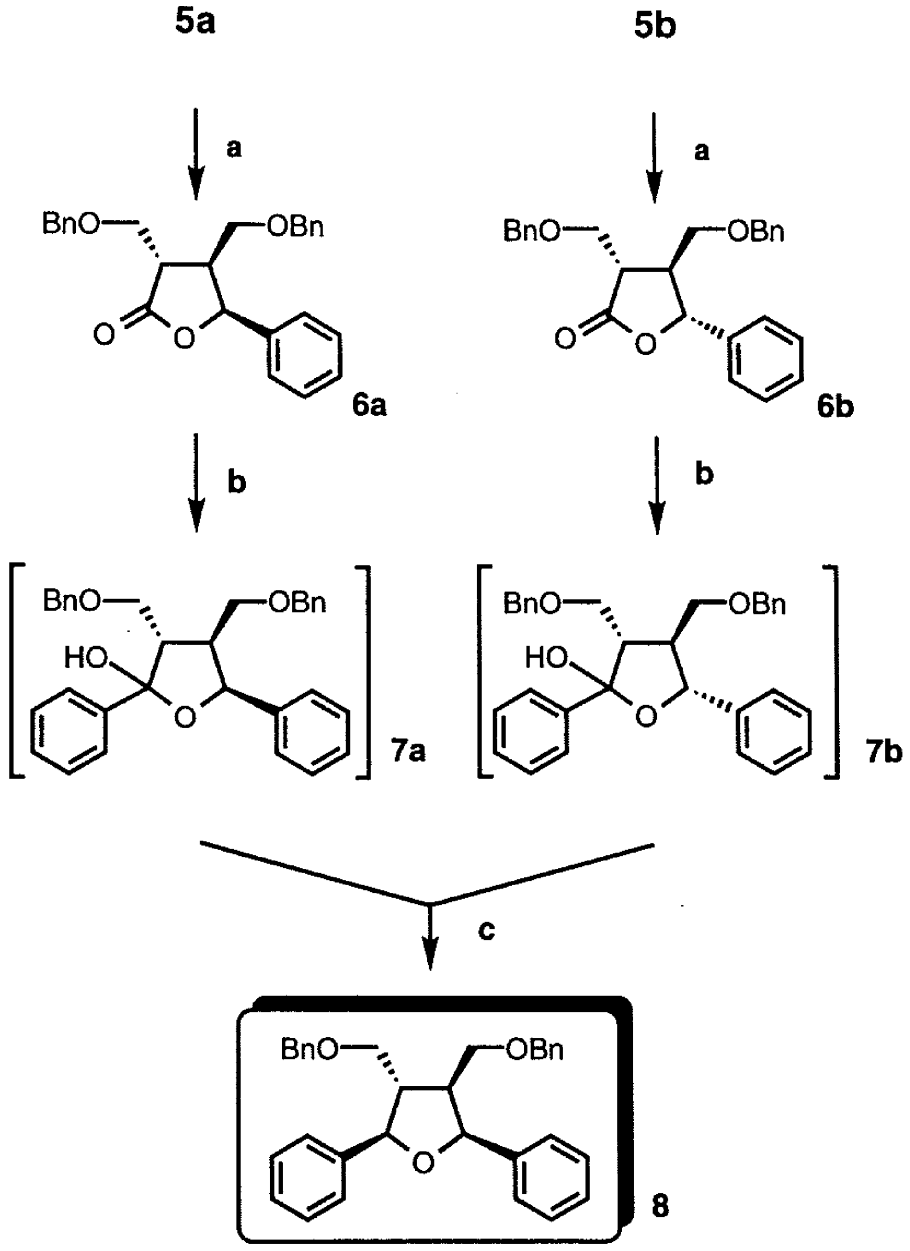
As shown in Scheme 1, γ-lactone **2**,[8] a key compound for the synthesis of furanoid lignans, was prepared from dihydroxyacetone dimer **1** by a 5 step reaction and hydroxymethylated[9] in the presence of HMPA, leading exclusively to the *trans* stereoselective product (98.5:1.5, determined by HPLC). This was benzylated again to give the dibenzyllactone **3** in good yield. For the introduction of a new stereogenic center, aminolysis of **3** opened the lactone to give the amide **4** in high yield. Swern oxidation of **4** thus obtained followed by the nucleophilic addition *in situ* was investigated under various conditions in order to enhance the yield and stereoselectivity. Finally, moderate selectivity (85:15, isolated ratio) was observed to give



Scheme 1. Reagents and conditions: (**a**) **1**, $(CH_3CO)_2O$, Et_3N; 98%; **2**, NaH, $(EtO)_2POCH_2CO_2C_2H_5$, THF; 83%; **3**, H_2SO_4, MeOH, 60 °C; 90%; **4**, Pd/C, H_2, EtOH; 97%; **5**, Ag_2O, BnBr; 81%; (**b**) **1**, LiHMDS, HMPA, $(CH_2O)_n$, THF, -78~-20 °C; 34%; **2**, Ag_2O, BnBr, cat. Bu_4NI; 70%; (**c**) Me_2NH, -20~0°C; 56%; (**d**) **1**, $(COCl)_2$, DMSO, THF then Et_3N, -78~-45 °C; **2**, PhMgBr, THF, 0 °C; 55% (**5a**); 9.8% (**5b**).

syn-**5a**[10] in 55% yield (2 steps) as a predominant product explained in terms of the thermodynamically stable Cram's non-chelation transition model.

Next, we investigated the direct conversion of lactones to the corresoponding tetrahydrofurans *via* Lewis acid-induced reductive deoxygenation. Thus, the trisubstituted lactone **6a** easily obtained from **5a** under acidic conditions in high yield was subjected to reaction with PhMgBr in the presence of CeCl3 as reported previously[11] followed by BF3•OEt2-promoted hydrogenation with Et3SiH[12] of the hemiketal intermediate **7a** at -78 °C (Scheme 2). The reaction proceeded smoothly to provide the deoxgenated tetrasubstituted furan **8**[13] in 64% yield (2 steps) as a sole



Scheme 2. Reagents and conditions: (**a**) *p*-TsOH, benzene, 50 °C; 83% (**6a**); 81% (**6b**); (**b**) PhMgBr, $CeCl_3$, THF, -78 °C; (**c**) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 64% (2 steps) (from **6a**); 81% (2 steps) (from **6b**).

product with complete stereoselectivity. No other stereoisomer or accompanying ring-opening products resulting from side reactions were observed. Further, we attempted the reaction with the minor diastereomer **6b** *via* the hemiketal **7b**. Quite interestingly, a compound whose physical

data are completely identical with the preceding sample **8** was obtained in 81% (2 steps) also as a sole product under the same conditions as above. It is worth noting that in these two sequential reactions employing **6a** and **6b**, the same stereoisomeric compound **8** results and consequently it is unnecessary to separate the diastereomers **5a** and **5b** throughout the entire sequence. Although the reason why such a stereoisomerically complete deoxygenation reaction was accomplished and a stereochemically identical product was obtained are not clear at present,[14] in this case it could proceed through the exclusive attack of Et_3SiH to the oxocarbenium ion intermediate from the opposite side of the γ-phenyl group independent of the other substituents.

This strategy provides a new synthetic opportunity for the synthesis of biologically active tetrasubstituted furanoid natural products such as virgatusin groups shown in Figure 1.

References and notes

(1) Mori, K. *Tetrahedron*, **1989**, *45*, 3233.

(2) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Ruff, M. D. in *Polyether Antibiotics: Naturally Occurring Acid Ionophors*, ed. by Westley, I. W., Marcel Dekker, New York, **1982**, Vol. 1, chapter 6.

(c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (d) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.- K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(3) (a) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609. (b) Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, *63*, 75.

(4) (a) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995. (b) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917. (c) Harmange, J.-C.; Figadère, B. *Tetrahedron:*

Asymmetry **1993**, *4*, 1711. (d) Koert, U. *Synthesis* **1995**, 115. (e) Li, K.; Vig, S.; Uckun, F. M.; *Tetrahedron Lett.* **1998**, *39*, 2063.

(5) (a) Maiti, G.; Adhikari, S.; Roy, S. C. *Tetrahedron Lett.* **1994**, *35*, 6731. (b) Yoshida, S.-I.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 1310. (c) Chen, I.-S.; Chen, J.-J.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1997**, *45*, 991.

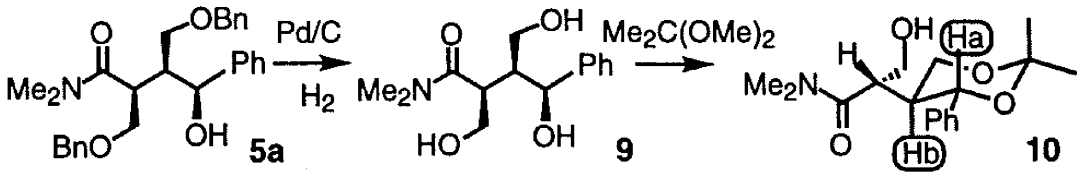
(6) (a) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. (b) Kraus G. A.; Molina, M. T. *J. Org. Chem.***1988**, *53*, 752. (c) Homma, K.; Takenoshita, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1898. (d) Ayadi, E.; Czernecki, S.; Xie, J. *Chem. Commun.* **1996**, 347.

(7) Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, *52*, 1273.

(8) (a) Takabe, K.; Tanaka, M.; Sugimoto, M.; Yamada, T.; Yoda, H. *Tetrahedron: Asymmetry* **1992**, *3*, 1385. (b) Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *J. Org. Chem.* **1997**, *62*, 5215.

(9) Yoda, H.; Nakagami, Y.; Takabe, K. *Tetrahedron: Asymmetry* **1994**, *5*, 169.

(10) The relative stereochemistry of the newly created carbon center in **5a** was proved to be *syn* by the transformation into the acetonide **10**, since the observed vicinal coupling constant ($J_{a,b}$) in **10** was 10.6 Hz, indicating the diaxial relationship.



(11) Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 679.

(12) (a) Yoda, H.; Kawauchi, M.; Takabe, K. *Synlett* **1998**, 137. (b) Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531. (c) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K.

Tetrahedron: Asymmetry **1995**, *6*, 2669 and references cited therein.

(13) Experimental procedure for the synthesis of **8** from **6a**: To a suspension of well-dried cerium chloride (0.10 g, 0.406 mmol)[15] in 2 mL of THF was added a solution of lactone **6** (0.041 g, 0.114 mmol) in THF (1 mL) and stirred for 1 h under nitrogen at rt. Then, the reaction mixture was cooled to -78 °C and phenylmagnesium bromide (1.0 M in THF, 0.40 mL, 0.40 mmol) was added. After the solution was stirred for 2 h at the same temperature, it was quenched by the addition of water (3 mL) and filtered through a pad of Celite followed by the extraction with ether (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give an oil of the crude hemiketal **7a**. A solution of crude **7a** in CH_2Cl_2 (1.2 mL) was cooled to -78 °C and Et_3SiH (0.08 mL, 0.50 mmol) was added. After the mixture was stirred for 5 min, $BF_3 \cdot OEt_2$ (0.07 mL, 0.555 mmol) was slowly added. The solution was further stirred for 2 h at the same temperature and quenched by the addition of saturated aqueous $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic extracts were dried (Na_2SO_4) followed by the concentration *in vacuo*. The residue was chromatographed (15:1 hexane-ethyl acetate) to give 0.034 g (0.073 mmol, 64%) of the tetrasubstituted furan **8** as a colorless oil.

The newly created stereogenic center of **8** was easily determined to be *trans* as indicated based on its ^1H and ^{13}C NMR, since **8** does not possess a C_2-axis of symmetry.

(14) In our previous report[11] it has been demonstrated that the γ-substituent in the lactone ring has no effect on the stereoselectivity in this type of deoxygenation reaction.

(15) Imamoto, T.: Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

Chapter 4

First Total Synthesis of a New Tetrasubstituted Pyrrolidine Alkaloid, Broussonetine C

Hidemi Yoda,* Takahiro Shimojo, and Kunihiko Takabe

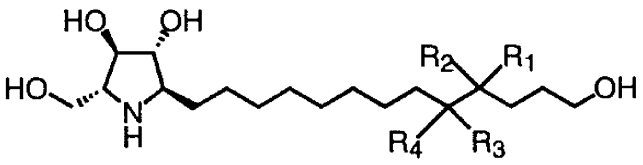
Department of Molecular Science, Faculty of Engineering,
Shizuoka University, Hamamatsu 432-8561, Japan

Abstract: An efficient and stereodefined process is described for the first asymmetric synthesis of a tetrasubstituted pyrrolidine alkaloid, broussoneitne C, as a potent β-galactosidase and β-mannosidase inhibitor by featuring the elaboration through asymmetric deoxgenation of a homochiral C_2-imide and stereoselective reduction of its derivative.

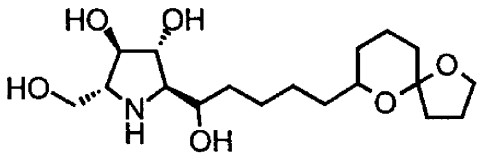
Keywords: Broussonetine C, Pyrrolidine Alkaloid, C_2-imide, Deoxygenation, Tartaric Acid.

Broussonetine C (**1**) and D (**2**) together with several structurally related compounds were first isolated in 1997 by Kusano *et al.*[1] from the branch of *Broussonetia kazinoki* SIEB. (Moraceae) (whose branches, leaves, and fruits have been used as a diuretic, a tonic, and a suppressant for edema in Chinese folk medicine.) These compounds exhibit unique β-galactosidase and β-mannosidase inhibitory activities, while their congeners inhibit other

glycosidases. After structural characterization by the same group based on spectroscopic and chemical methods, these were revealed to be a new class of tetrahydroxylated pyrrolidine alkaloids possessing a 1,2,3,4-tetrasubstituted structure[2] situated in all *trans* positions. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, no report concerning the total synthesis of **1** or **2** has been appeared to date despite those pharmacological activities and interesting structural features. With these considerations in mind, we wish to communicate the details of the first asymmetric synthesis of **1** by means of requisite stereoselective reduction of a hydroxypyrrolidine intermediate elaborated through Lewis acid-promoted deoxygenation of a C_2-imide.

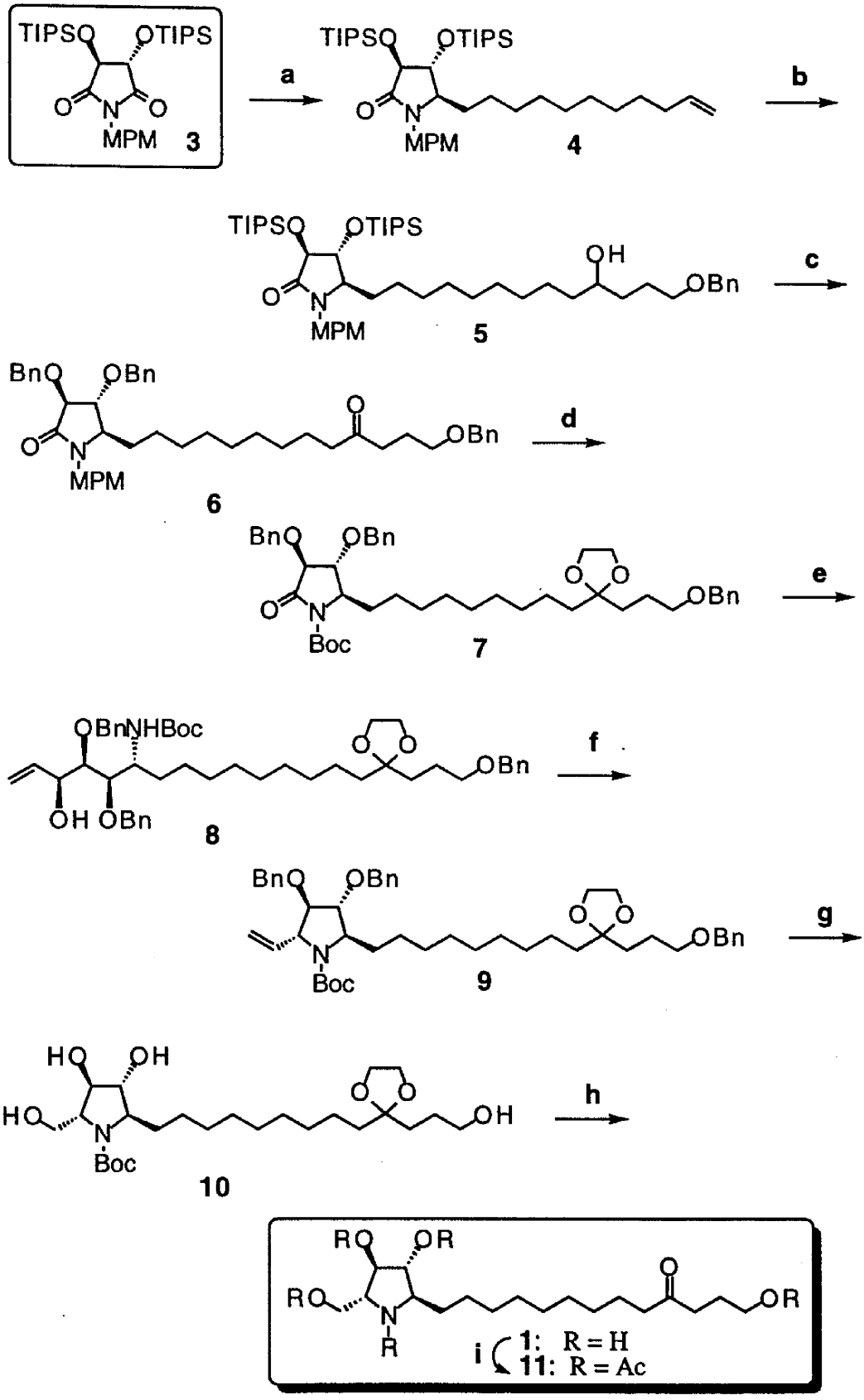


Broussonetine C (1): R_1,R_2=O, R_3=R_4=H
Broussonetine D (2): R_1=R_2=H, R_3,R_4=C



Broussonetine G

TIPS-protected C_2-imide (**3**) obtained from D-tartaric acid[3] was treated with undecenylmagnesium bromide at ambient temperature to give the quaternary α-hydroxylactam intermediate, which underwent subsequently $BF_3 \cdot OEt_2$-promoted reductive deoxgenation with Et_3SiH,[4] leading to the *trans*-substituted lactam **4** exclusively (96% d.e., determined by HPLC using Daicel Chiralpak AS) in 83% yield. After oxidative cleavage of the olefinic part in **4** followed by the coupling reaction with the C_3-unit containing a hydroxyl function, **5** thus obtained was subjected to oxidation with PCC and then exchange of the TIPS-protecting groups to benzylethers to resist changes in pH resulted in the preparation of **6** in high yield. This


TIPSO
OTIPS
MPM
3
a
4
b
OH
OBn
5
c
BnO
6
d
7
e
OBnNHBoc
8
f
9
g
HO
10
h
R
i
1: R = H
11: R = Ac

Scheme 1. Reagents and conditions: (**a**) **1**, undecenylmagnesium bromide, THF, rt; **2**, Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78~-50 °C; 83% (2 steps); (**b**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 99%; **2**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, benzyloxypropylmagnesium bromide, THF, 0 °C; 85% (2 steps); (**c**) **1**, PCC, CH_2Cl_2, MS 4A; 90%; **2**, Bu_4NF, THF; 92%; **3**, BnBr, Ag_2O, CH_3COOEt; 100%; (**d**) **1**, CAN, CH_3CN; 70%; **2**, $HOCH_2CH_2OH$, cat. *p*-TsOH, benzene, reflux; 96%; **3**, $(Boc)_2O$, Et_3N, DMAP, CH_2Cl_2; 100%; (**e**) **1**, vinylmagnesium bromide, THF, -78 °C; **2**, $NaBH_4$-$CeCl_3$, MeOH, -45 °C; 78% (2 steps); (**f**) **1**, MsCl, Et_3N, CH_2Cl_2, **2**, *t*-BuOK, THF; 92% (2 steps); (**g**) **1**, OsO_4, NMO, acetone-H_2O (1:1); 100%; **2**, $NaIO_4$, Et_2O-H_2O (1:1); **3**, $NaBH_4$, MeOH; 92% (2 steps); **4**, Pd (black), 4.4% HCOOH-MeOH; 83%; (**h**) conc. HCl, CH_3COOEt; (**i**) Ac_2O, pyridine, DMAP; 67% (2 steps).

was deprotected and transformed into the *N*-Boc lactam **7** by 2 steps to enhance the nucleophilicity.

The second Grignard addition to **7** easily afforded the labile quaternary α-hydroxypyrrolidine,[5] which was successively subjected to reduction with $NaBH_4$ in the presence of $CeCl_3$ to provide the desired stereoisomer **8**[6] as a sole product fortunately (determined by C^{13} NMR and chiral HPLC analysis). Then, **8** was effected by the reactions of mesylation and cyclization, leading to the homochiral tetrasubstituted pyrrolidine **9** with the desired configurations. The double bond in **9** was cleavaged *via* dihydroxylation and reduced to the primary alcohol. Finally, deprotection of the obtained product was at first performed with Pd (black) due to avoid the acetal formation, affording the debenzylated *N*-Boc ketal derivative **10** of broussonetine C (**1**). Then, removal of the resulted protecting groups in **10** was conducted under acidic conditions to complete the total synthesis of **1**, whose structure was characterized after derivarization to the pentaacetate **11**, $[\alpha]_D^{24}$-21.5 (c 1.21, MeOH).[7]

In summary, the first asymmetric synthesis of natural broussonetine C was achieved in 21% overall yield from C_2-imide. This process will be widely applicable to the synthesis of other broussonetine congeners.

Acknowledgment: This work was supported in part by a Grant-in Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

References and notes

1. (a) Shibano, M.; Kitagawa, S.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 505~508. (b) Shibano, M.; Kitagawa, S.; Nakamura, S.; Akazawa, N.; Kusano, G. *Chem. Pharm. Bull.* **1997**, *45*, 700~705.
2. Shibano, M.; Kitagawa, S.; Kusano, G. Symposium papers, *37th Symposium on the Chemistry of Natural Products*, Tokushima, **1995**, 433-438.
3. (a) Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 3401~3404. (b) Yoda, H.; Shirakawa, K.; Takabe, K. *Chemistry Lett.* **1991**, 489-490.
4. Yoda, H.; Kitayama, H.; Yamada, W.; Katagiri, T.; Takabe, K. *Tetrahedron: Asymmetry* **1993**, *4*, 1451~1454.
5. Yoda, H.; Nakajima, T.; Takabe, K. *Tetrahedron Lett.* **1996**, *37*, 5531~5534.
6. The absolute configuration of the generated stereogenic centre in **8** was easily assigned to be ***S*** based on our previous results.[5]
7. HRMS calcd for $C_{28}H_{46}NO_{10}$ (M^++H^+) 556.3121, found 556.3110. It seems that the compound **11** exists as a mixture of two rotational isomers concerning to the N-Ac bond in analogy with the case of acetylated penaresidins[8] based on its spectra. Further details of these results will be reported and discussed elsewhere.
8. Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97~111.

Chapter 5

First Total Synthesis of Tetrasubstituted Tetrahydrofuran Lignan, (-)-Virgatusin

Hidemi Yoda,* Masato Mizutani, and Kunihiko Takabe

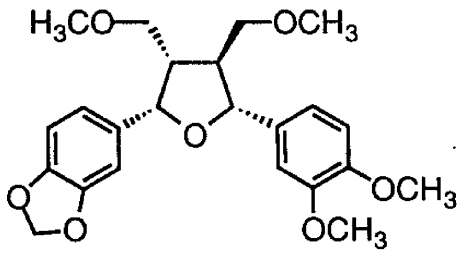
Department of Molecular Science, Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan

Abstract: The first asymmetric total synthesis of (-)-virgatusin, a new furanolignan, isolated from *phyllanthus virgatus*, was accomplished in a stereoselective manner by nucleophilic addition of organolithium reagent to the functionalized lactone elaborated from dihydroxyacetone dimer followed by asymmetric deoxygenation of the hemiketal intermediate.

Keywords: (-)-Virgatusin, Furanolignan, Trisubstituted Lactone, Deoxygenation, Dihydroxyacetone.

Natural lignans display a wide variety of constitution based on phenolic and *O*-heterocyclic substructures, and an equally wide range of biological activities such as antitumor activity, platelet-activating factor (PAF) antagonists, and inhibitory effects on microsomal monooxygenases in insects.[1] The diverse array of these potentially useful characteristics make

them inviting targets for synthesis.[2] In this connection we have also recently reported the total synthesis of two dibenzylbutyrolactone lignans, (-)-hinokinin[3a] and (-)-enterolactone,[3b] employing different synthetic strategies, however, a major sub-group is comprized of tri- and tetrasubstituted tetrahydrofuran groups. Since the synthesis of this type of compounds poses interesting and often unsolved problems of stereocontrol, very few synthetic strategies for the furanolignans have been reported.[4] Herein we wish to describe the first stereoselective total synthesis of (-)-virgatusin (**1**) based on the asymmetric Lewis acid-promoted deoxygenation. **1** first isolated in 1996 by Chen et al.[5] is a new furanolignan with four substituents in the furan ring and is expected as a herbal drug to inhibit the endogenous DNA polymerase of hepatitis B virus (HBV).[6]



1: (-)-Virgatusin

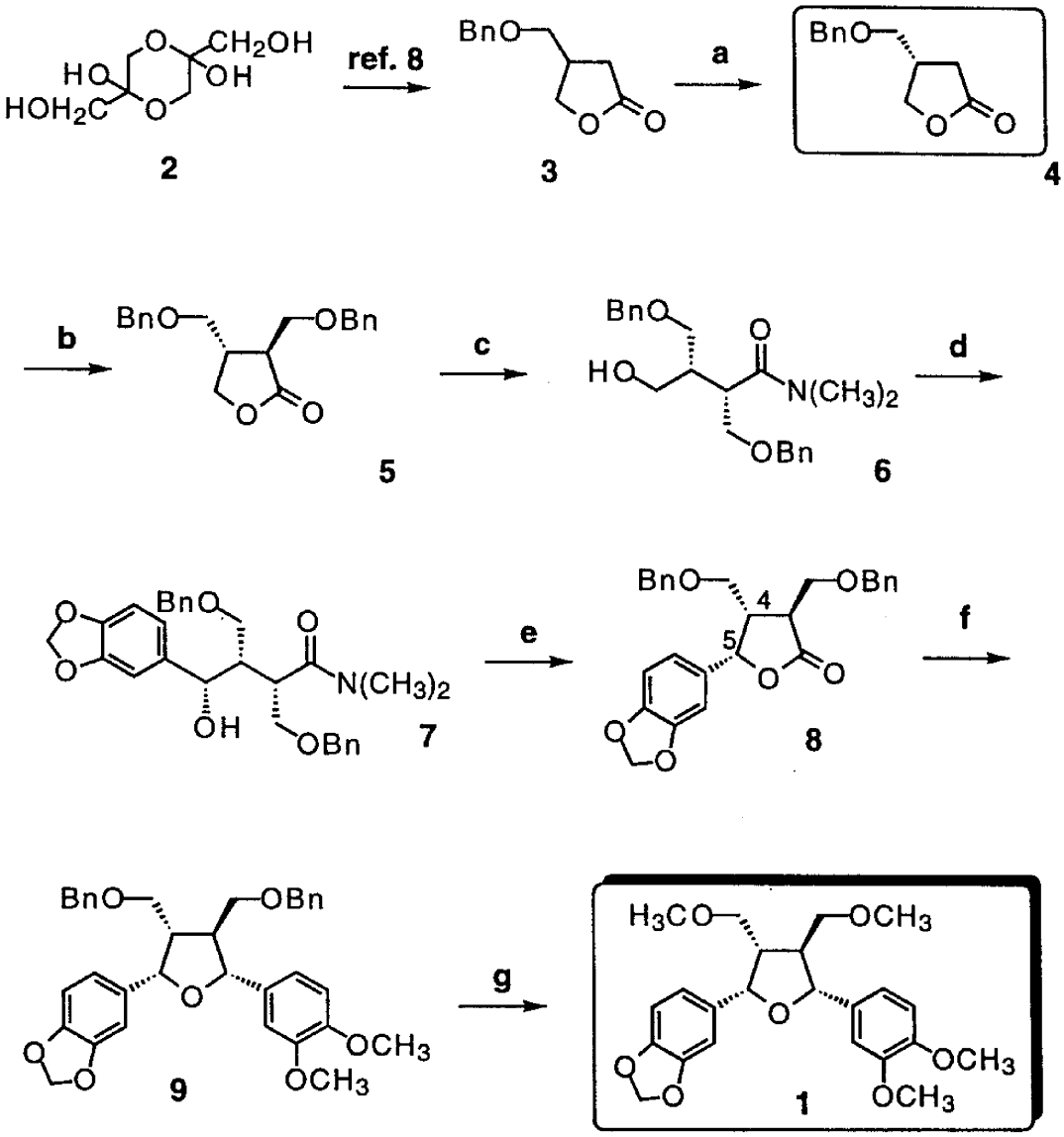
As shown in Scheme 1, the homochiral benzyllactone **4**,[7] an important building block for the terpenoid synthesis,[7a] was easily prepared in an enantiomerically pure form starting from dihydroxyacetone dimer **2**[8] through diastereomer separation with (*R*)-(+)-α-methybenzylamine. Hydroxymethylation of **4** with paraformaldehyde followed by benzylation afforded the dibenzyllactone **5** in 96.4% d.e..[9] After aminolysis of **5** with $(CH_3)_2NH$, amide **6**, thus obtained, was successively subjected to Swern oxidation followed by nucleophilic addition of 3,4-(methylenedioxy)phenylmagnesium bromide *in situ*, leading to the amide alcohol **7** predominantly (80:20 isolated diastereomer ratio)[10] explained in terms of the Cram's non-chelation transition model. This was then cyclized

under acidic conditions to give the key trisubstituted lactone **8**. Careful treatment of **8** with 3,4-dimethoxyphenyllithium reagent at -78 °C provided the labile hemiketal intermediate, which was readily effected by $TiCl_4$-induced deoxygenation with Et_3SiH[11] at low temperature to lead cleanly to the tetrasubstituted furanolignan derivative **9** as a single stereoisomer in 80% yield from **8** with the desired configuration.[12] Accompanying formation of the other stereoisomer was not observed in this reaction.

Finally, **9** was methylated effectively with NaH-CH_3I after deprotection of the benzyl groups to complete the total synthesis of (-)-virgatusin (**1**), $[\alpha]_D^{25}$-12.5 (c 0.51, CH_2Cl_2) [natural **1**, $[\alpha]_D^{25}$-12.7 (c 0.5, CH_2Cl_2)[5]]. The spectral data of the synthetically produced **1** (viscous oil) were completely identical with those of the reported natural product.[5]

In summary, this work constitutes the first synthesis of the natural furanolignan, (-)-virgatusin, and verifies the structure proposed in the literature for this compound.

Acknowledgment:: This work was supported in part by a Grant-in Aid for Scientific Research from the
Ministry of Education, Science, Sports, and Culture of Japan.



Scheme 1. Reagents and conditions: (**a**) **1**, (***R***)-(+)-α-methylbenzylamine, MeOH, 60 °C; **2**, *p*-TsOH, benzene, 50 °C; 21% (2 steps; diastereomer separation followed by cyclization); (**b**) **1**, LiHMDS, HMPA, $(CH_2O)_n$, THF, -78~-20 °C; 35%; **2**, Ag_2O, BnBr, cat. Bu_4NI; (**c**) Me_2NH, -20~0°C; 46% (2 steps); (**d**) **1**, $(COCl)_2$, DMSO, THF then Et_3N, -78~-45 °C; **2**, 3,4-(methylenedioxy)phenylmagnesium bromide, THF, 0 °C; 55% (2 steps); (**e**) *p*-TsOH, benzene, 50 °C; 87%; (**f**) **1**, 3,4-dimethoxyphenyllithium, Et_2O, -78 °C; **2**, Et_3SiH, $TiCl_4$, CH_2Cl_2, -78 °C; 80% (2 steps); (**g**) **1**, Pd (black), 4.4% HCOOH-MeOH; 93%; **2**, NaH, CH_3I, THF; 80%.

References and notes

1. (a) Ward, R. S. *Tetrahedron*, **1990**, *46*, 5029~5041. (b) Ward, R. S. *Nat. Prod. Rep.* **1993**, *10*, 1-28 and references cited therein.
2. For recent examples: (a) Gaboury, J. A.; Sibi, M. P. *J. Org. Chem.* **1993**, *58*, 2173~2180. (b) van Oeveren, A.; Jansen, J. F. G. A.; Feringa, B. L. *J. Org. Chem.* **1994**, *59*, 5999~6007. (c) Bode, J. W.; Doyle, M. P.; Protopopova, M. N.; Zhou, Q.-L. *J. Org. Chem.* **1996**, *61*, 9146~9155.
3. (a) Yoda, H.; Naito, S.; Takabe, K.; Tanaka, N.; Hosoya, K. *Tetrahedron Lett.* **1990**, *31*, 7623~7626. (b) Yoda, H.; Kitayama, H.; Katagiri, T.; Takabe, K. *Tetrahedron* **1992**, *48*, 3313~3322.
4. (a) Stevens, D. R.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 633~637 (b) Mitra, J.; Mitra, A. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1285~1286 (c) Maiti, G.; Adhikari, S.; Roy, S. C. *J. Chem. Soc., Perkin Trans. 1* **1995**, 927~929.
5. Huang, Y.-L.; Chen, C.-C.; Hsu, F.-L.; Chen, C.-F. *J. Nat. Prod.* **1996**, *59*, 520~521.
6. Thyagarajan, S. P.; Subramanian, S.; Thirunalasundari, T.; Venkateswaran, P. S.; Blumberg, B. S. *Lancet* **1988** *1*, 764~766.
7. (a) Takabe, K.; Tanaka, M; Sugimoto, M.; Yamada, T.; Yoda, H. *Tetrahedron: Asymmetry* **1992**, *3*, 1385~1386. (b) Mazzini, C.; Lebreton, J.; Alphand, V.; Furstoss, R. *J. Org. Chem*, **1997**, *62*, 5215~5218.
8 Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855~856.
9. The d.e. was determined by chiral HPLC using Daicel chiralpak AD after derivatization to the amide **6**.
10. Stereochemistry of the new stereocentre was assigned based on our previous results,[8] and observed chemical shift (C5-H) and coupling constant ($J_{4,5}$ = 8.4 Hz) after lactonization to **8** according to the

following reference; Marino, J. P.; de la Pradilla, R. F. *Tetrahedron Lett.* **1985**, *26*, 5381~5384.

11. Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 679~686.

12. The absolute configuration of the generated stereogenic centre was determined unambiguously based on its spectral data of synthetic (-)-**1**.

Chapter 6

Asymmetric Synthesis of Tetrasubstituted Tetrahydrofuran, 2-Epigoniothalesdiol, Employing C_2-Symmetrical Imide

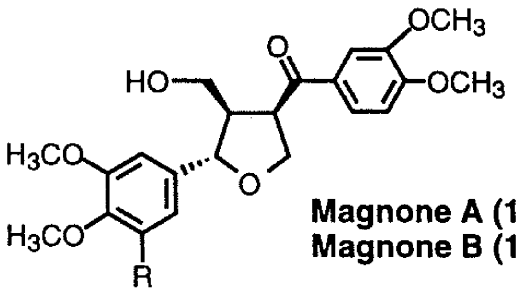
Hidemi Yoda,* Takahiro Shimojo, and Kunihiko Takabe

Department of Molecular Science, Faculty of Engineering, Shizuoka University, Hamamatsu 432-8561, Japan

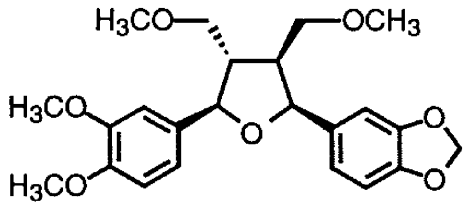
Abstract: An efficient and stereodefined process is described for the preparation of a 3,4-dihydroxy-2,5-disubstituted tetrahydrofuran ring with the contiguous stereogenic centers and the asymmetric synthesis of 2-epigoniothalesdiol is also reported by featuring the elaboration of the functionalized homochiral lactone derived from C_2-imide.

Tetrahydrofuran backbone is among the most common heterocyclic unit found in natural products and structurally complex ones feature in many biologically potent compounds such as pheromones,[1] polyether antibiotics,[2] and marine epoxylipids.[3] Due to their interesting activity as well as unique structural characteristics, they have been the subject of an extensive synthetic effort which has culminated in numerous syntheses.[4] Noteworthy members among this class of compounds are optically active tetrahydrofuran derivatives with tri- and tetrasubstituents serving as good templates for the construction of pharmacologically important furanoid

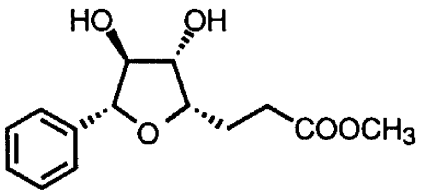
groups and exhibiting various degrees of potency and specificity (Figure 1).[5] In this connection we have also recently reported a novel and stereoselective conversion of lactones to polysubstituted cyclic ethers,[6a,b] and the first total synthesis of (-)-virgatusin (**2**).[6c]



Magnone A (1a): R = H
Magnone B (1b): R = OCH_3



Virgatusin (2)

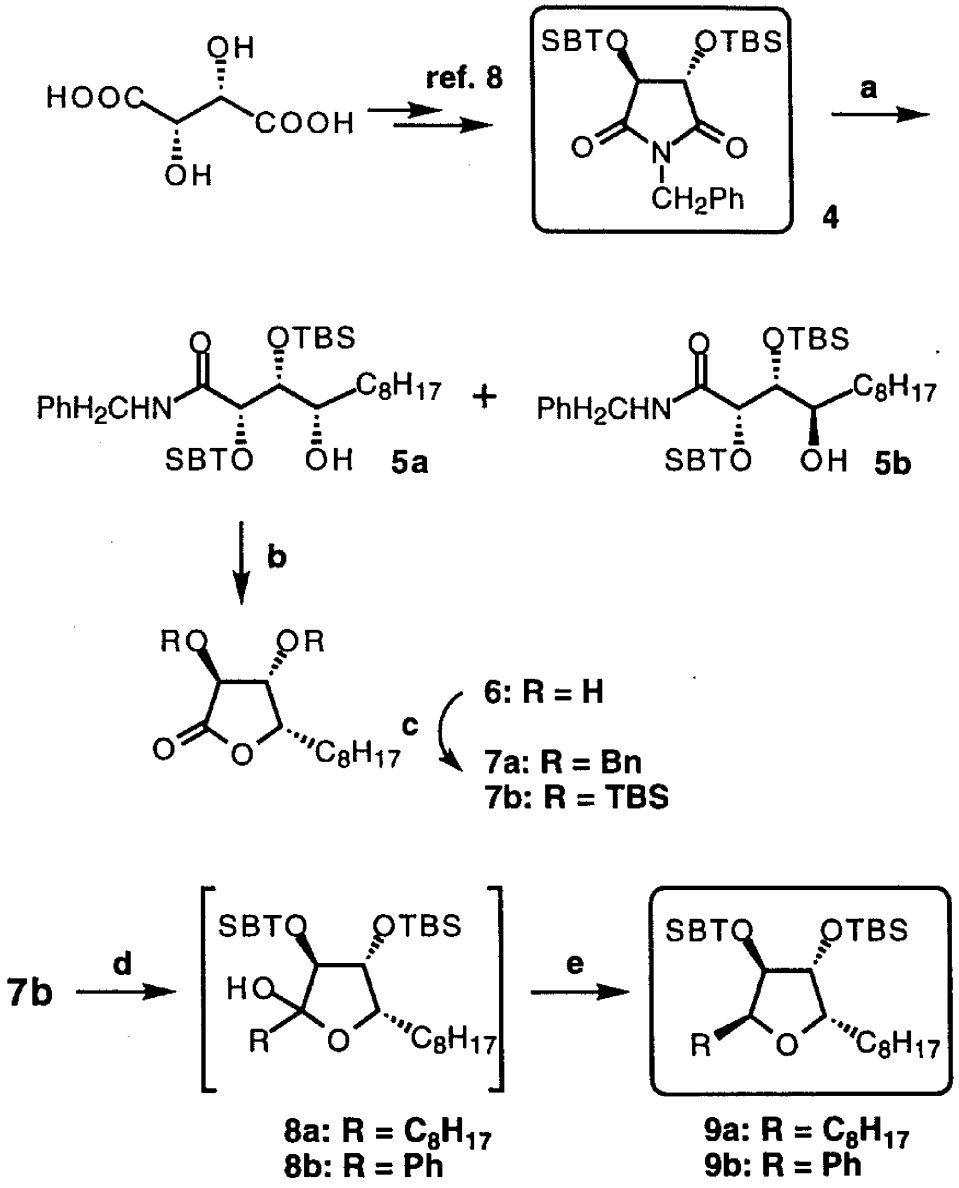


Goniothalesdiol (3)

Figure 1

On the other hand, dihydroxylated tetrahydrofuran, goniothalesdiol (**3**), isolated in 1998 from the bark of the Malaysian tree *Goniothalamus borneensis* (Annonaceae) is revealed to have significant cytotoxicity against P388 mouse leukemia cells and insecticidal activities,[5c] and a new addition to the styryl-type lactone series.[7] In particular the preparation of unnatural epimers and other structural analogs of this styryllactone groups has genarated much interest since the biological activity of these molecules varies substantially with the number, position and stereochemistry of the functional groups into the furan skeleton. In this communication we wish to report our efficient synthetic strategy based on the completely stereoselective hydrogenation of a ketal derivative derived from C_2-imide which has led to the synthesis of 2-epimer of the natural product, goniothalesdiol (**3**).

As shown in Scheme 1, *N*-benzyl-C2-imide **4** obtained from D-tartaric acid was treated with octylmagnesium bromide followed by reduction of



Scheme 1. Reagents and conditions: (**a**) **1**, $C_8H_{17}MgBr$, THF, 0 °C; **2**, $NaBH_4$, EtOH; 67% (**5a**) (2 steps); trace (**5b**) (2 steps) ; (**b**) 10% HCl-dioxane (1 : 1), 80 °C; 95%; (**c**) BnBr-Ag_2O, CH_3COOEt; 51% (**7a**); TBSCl, imidazole, DMF; 97% (**7b**); (**d**) **1**, $C_8H_{17}MgBr$, $CeCl_3$, THF, -78 °C (**8a**); PhMgBr, $CeCl_3$, THF, -78 °C (**8b**); **2**, Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 64% (**9a**) (2 steps); 66% (**9b**) (2 steps).

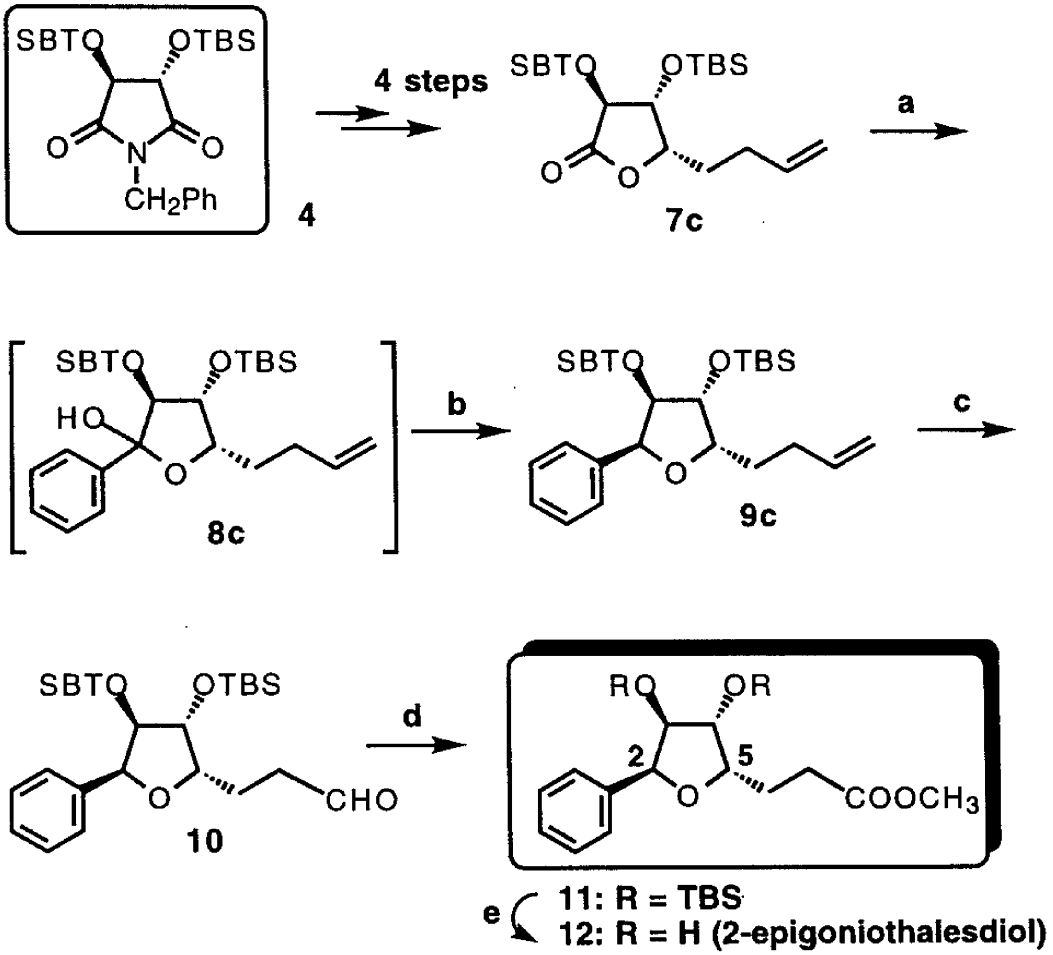
the α-hydroxylactam intermediate with $NaBH_4$, leading to the corresponding hydroxyamide **5a** in 67% yield with exclusive stereoselectivity.[8] Accompanying formation of the other stereoisomer **5b** was observed in mere trace amounts after isolation using silica gel column chromatography. Then, **5a** was cyclized under acidic conditions to give the dihydroxylactone **6**. Whereas the use of BnBr-Ag_2O for the protection of the dihydroxyl functions in **6** brought about unsatisfactory racemization at C-5 in **7a**, the reaction with TBSCl-imidazole in DMF provided the disilylated compound **7b** as a single isomer (determined by ^{13}C NMR) in almost quantitative yield.

Next, we investigated the direct conversion of **7b** to the corresponding substituted tetrahydrofuran *via* Lewis acid-induced reductive deoxygenation. Thus, **7b** was subjected to reaction with the second Grignard reagents (alkyl- and arylmagnesium bromide) at -78 °C in the presence of $CeCl_3$ as reported previously,[6] followed by $BF_3 \cdot OEt_2$-promoted hydrogenation with Et_3SiH[9] of the hemiketal intermediates **8** at the same temperature. The reactions in both cases proceeded within 10 minutes to afford the deoxygenated tetrasubstituted furans **9a** and **9b**,[10] respectively, in good yields with complete stereoselectivity (determined by ^{13}C NMR and HPLC analysis). No other stereoisomer or ring-opened diol type product resulting from the attack of excess Grignard reagent was observed.

With above stereochemical outcome in hand, we turned our attention to the asymmetric synthesis of 2-epigoniothalesdiol. As summarized in Scheme 2, the homochiral lactone **7c**, $[\alpha]_D^{30}$ -62.2 (c 1.45, EtOH), with a butenyl side chain was easily and stereoselectively prepared according to the above method in an enantiomerically pure form from **4** in 65% yield (4 steps). Treatment of **7c** with phenylmagnesium bromide at -78 °C in the presence of $CeCl_3$ furnished the labile hemiketal intermediate **8c**, which was readily effected by $BF_3 \cdot OEt_2$-induced deoxygenation with Et_3SiH at the same temperature with care (the use of excess Et_3SiH partially hydrogenated the

olefinic part in **8c** as well as the deoxygenation reaction of the hemiketal skeleton.), to lead cleanly to the tetrasubstituted furan **9c**, $[\alpha]_D^{28}$ +46.0 (c 1.05, EtOH), also as a sole stereoisomer (determined by ^{13}C NMR) in 91% yield. Then, the double bond in **9c** was cleavaged *via* dihydroxylation with OsO_4 to the aldehyde **10**. This was successively oxidized with bromine in MeOH[11] to the methyl ester **11**, $[\alpha]_D^{30}$ +36.9 (c 0.57, EtOH), in 83% yield, followed by final deprotection of the silyl groups to complete the total synthesis of (-)-2-epigoniothalesdiol (**12**),[12] $[\alpha]_D^{24}$ -23.4 (c 1.33, EtOH), in 29% overall yield from C_2-imide **4**.

In summary, this work constitutes the first asymmetric synthesis of 2-epigoniothalesdiol from D-tartaric acid based on the stereoselective Lewis acid-promoted hydrogenation, and verifies the structure proposed in the literature for this natural product, since no report concerning the total synthesis of goniothalesdiol has been appeared to date.



Scheme 2. Reagents and conditions: (**a**) PhMgBr, $CeCl_3$, THF, -78 °C; (**b**) Et_3SiH, $BF_3 \cdot OEt_2$, CH_2Cl_2, -78 °C; 91% (2 steps); (**c**) **1**, OsO_4, NMO, acetone-H_2O (1 : 1); 99%; **2**, $NaIO_4$, Et_2O-H_2O (1 : 1); (**d**) Br_2, $NaHCO_3$, MeOH-H_2O (9 : 1); 83% (2 steps); (**e**) cat. *p*-TsOH, MeOH; 60%.

Acknowledgment: This work was supported in part by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

References and notes

(1) Mori, K. *Tetrahedron*, **1989**, *45*, 3233.

(2) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Ruff, M. D. in *Polyether Antibiotics: Naturally Occurring Acid Ionophors*, ed. by Westley, I. W., Marcel Dekker, New York, **1982**, Vol. 1, chapter 6. (c) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (d)

Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330.

(3) (a) Capon, R. J.; Barrow, R. A.; Skene, C.; Rochfort, S. *Tetrahedron Lett.* **1997**, *38*, 7609. (b) Capon, R. J.; Barrow, R. A. *J. Org. Chem.* **1998**, *63*, 75.

(4) (a) Mihelich, E. D. *J. Am. Chem. Soc.* **1990**, *112*, 8995. (b) Kang, S. H.; Hwang, T. S.; Kim, W. J.; Lim, J. K. *Tetrahedron Lett.* **1990**, *31*, 5917. (c) Harmange, J.-C.; Figadère, B. *Tetrahedron: Asymmetry* **1993**, *4*, 1711. (d) Koert, U. *Synthesis* **1995**, 115. (e) Li, K.; Vig, S.; Uckun, F. M.; *Tetrahedron Lett.* **1998**, *39*, 2063.

(5) (a) Yoshida, S.-I.; Ogiku, T.; Ohmizu, H.; Iwasaki, T. *J. Org. Chem.* **1997**, *62*, 1310. (b) Chen, I.-S.; Chen, J.-J.; Duh, C.-Y.; Tsai, I.-L. *Phytochemistry* **1997**, *45*, 991.(c) Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. T.; Pereira, J. T.; Goh, S.-H. *Tetrahedron* **1998**, *54*, 2143.

(6) (a) Yoda, H.; Mizutani, M.; Takabe, K. *Heterocycles* **1998**, *48*, 679.

(b) Yoda, H.; Mizutani, M.; Takabe, K. *Synlett* **1998**, 855. (c) Yoda, H.; Mizutani, M.; Takabe, K. *Tetrahedron Lett.* **1999**, *40*, 4701.

(7) (a) Geran, R. I.; Greenberg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep.* **1972**, *3*, 1. (b) Talapatra, S. K.; Basu, D.; Deb, T.; Goswani, S.; Talapatra, B. *Indian J. Chem., Sect. B* **1985**, *24*, 29. (c) Mukai, C.; Hirai, S.; Hanaoka, M. *J. Org. Chem.* **1997**, *62*, 6619. (d) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493 and references cited therein.

(8) (a) Yoda, H.; Shirakawa, K.; Takabe, K. *Tetrahedron Lett.* **1991**, *32*, 6771. (b) Yoda, H.; Shirakawa, K.; Takabe, K. *Chemistry Lett.* **1991**, 489.

(9) (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.

(10) Stereochemistry of the newly created carbon center in **9** was unambiguously determined to be *S* based on its spectral data of synthetic (-)-**12**.

(11) (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.

(12) ^{1}H and ^{13}C NMR data ($CDCl_3$) for **12**. ^{1}H NMR δ 0.89 (6H, br t, J = 4.4 Hz), 1.07-2.00 (12H, m), 1.48 (9H, s), 3.61-4.20 (4H, m), 4.50 (2H, s), 4.62 (2H, d, J = 2.0 Hz), 7.29 (5H, s), 7.31 (5H, s). ^{13}C NMR δ 13.9, 22.4, 22.7, 28.1, 28.3, 28.4, 29.7, 34.0, 58.3, 61.2, 71.6, 72.2, 79.0, 83.6, 84.7, 127.5, 127.6, 127.9, 128.2, 128.3, 137.7, 138.1, 155.1.