新しい分子素子を用いた生理活性物質の超効率的精密合成

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緒言

現在では有機合成化学の発展により複雑な構造が組み立てられるようになっているが、目的物にたどり着くまでに非常に手間がかかるのが常である。研究のスピードが要求される現代において、できる限り無駄を省いて目的物を得ることが必須であり、それを実現するためには方法論と合成経路の工夫の両輪が働かなければならない。本研究はこの課題に答えるべく、ある程度の大きさと官能基配列を有する天然生理活性物質を合成するための極めて効率的ルートを実現するための方法論と合成経路考案を実践したものである。すなわち、部分構造を短段階で作り上げる方法論と部分構造を効率よく接続する戦略を提示することを目的とした。

研究組織

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平成17年度	2，200，000	0	2，200，000
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研究成果による工業所有権の出願・取得状況

特になし。

研究成果

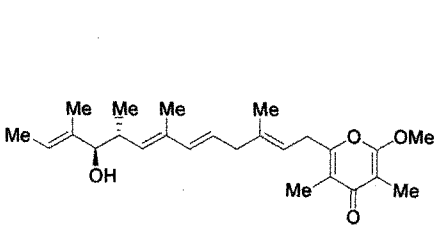
次ページ以降に添付する。

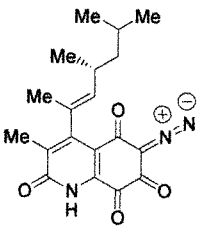
概要

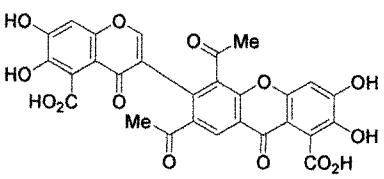
標的化合物の全合成においては、(1) 切断する場所の特定と接続戦略、と (2) 部分構造の合成法、の２つが合成経路の効率化に非常に大きく影響する。

天然生理活性物質

本研究では鎖状ポリケチドと含芳香族多環式化合物の２種類の化合物群を対象に、それぞれその全構造の構築戦略と部分構造の迅速な構築法を確立し、超効率的なポリケチド化合物の全合成を実践した。本研究において以下の化合物の全合成を達成した。


アクチノピロンA


ラグナマイシン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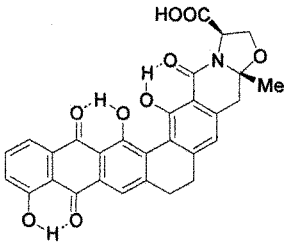
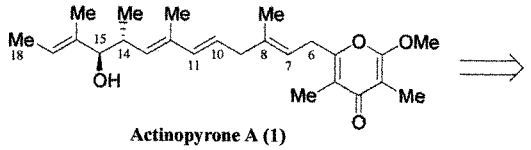
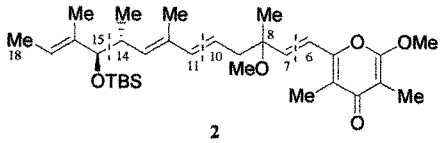

TMC-66

1. 抗ピロリ菌活性物質アクチノピロン A の全合成

アクチノピロン A は 1986 年に冠動脈拡張作用と抗真菌作用をもつ物質として *Streptomyces pactum* から単離されたポリプロピオネートである。その後、*Helicobacter pylori* に対して顕著な抗菌活性を示すことが見出され、毒性の低さと併せて注目を集めている。しかしながらアクチノピロン A は室温で半減期２週間と不安定であり、その立体配置すら不明であった。我々は本化合物の絶対立体配置の決定、および多様な類縁体構築を可能にする効率的で融通性のある合成経路の確立を目指し、全合成研究に着手した。


Actinopyrone A (1)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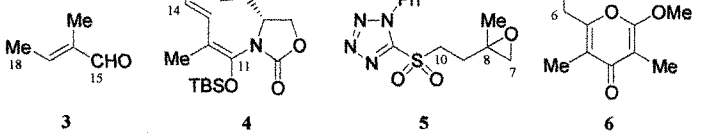
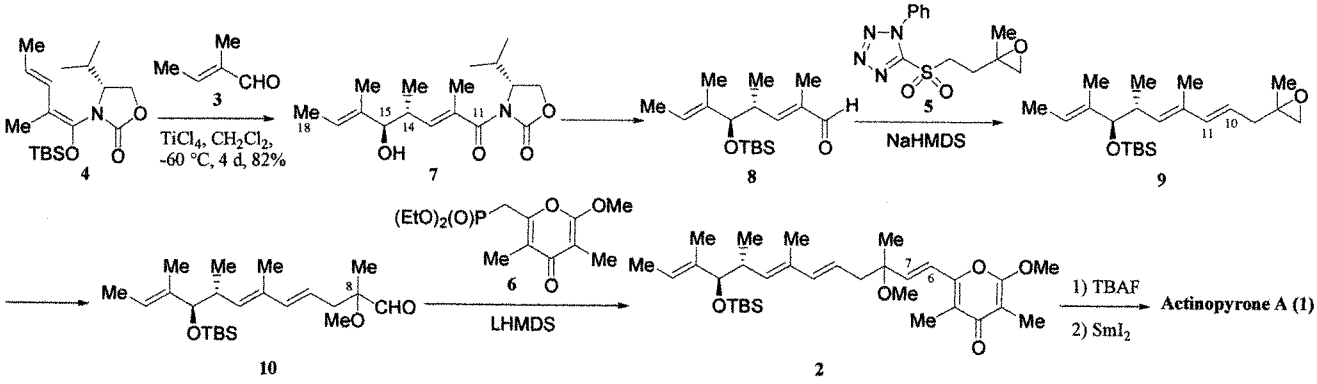

3 4 5 6



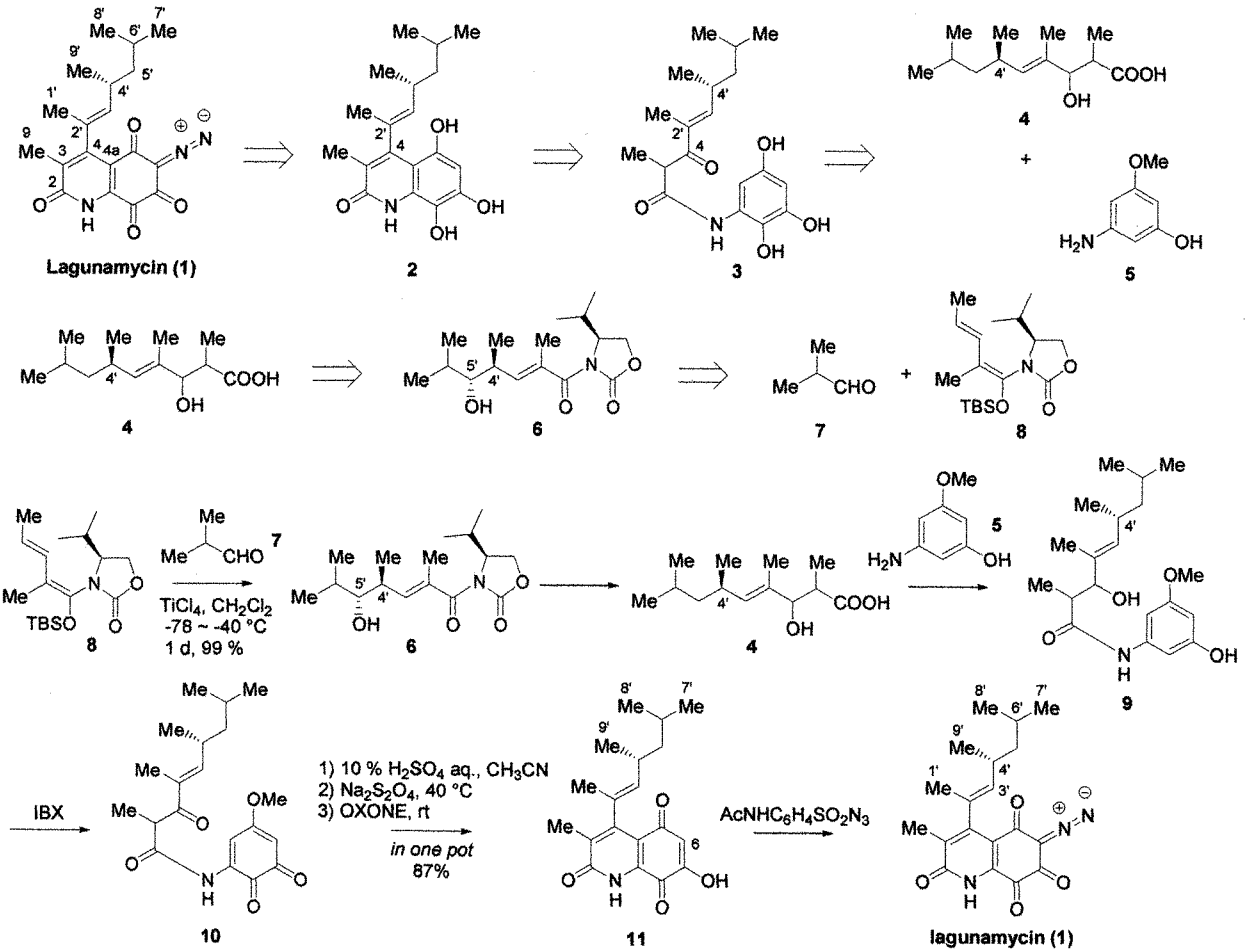
4 7 8 9 10 2

アクチノピロンAの不安定要因は本分子の両翼にある断続された共役系によるものと考えられる。この点を考慮して、C15の水酸基の保護とC6-C8部分をピロン環と共役化した化合物**2**を合成中間体とし、合成終盤においてC15の水酸基の脱保護とC6-C8部分の非共役化を行って全合成を達成することとした。

実際の合成は**3**→**4**→**5**→**6**の方向に順次伸張するルートによって全合成を達成した。すなわち、我々が開発した遠隔不斉誘導法を用いてC11-C18を一挙に構築することから合成を開始した。その後順次**5**と**6**を導入して安定な保護体**2**へと導いた。最後に脱O-シリル化と還元的非共役化を行い、アクチノピロンAの不斉全合成を達成した。得られた**1**の各種スペクトルデータが専攻後も含めて天然のものと一致したことより、アクチノピロンAの絶対立体配置が(14*R*,15*R*)と決定された。

2. IL-5阻害物質ラグナマイシンの全合成

ラグナマイシンは1993年に*Streptomyces* sp. AA0310から単離されたIL-5阻害活性と抗菌性をもつ化合物である。非常に特徴的な構造を持つ化合物であり、ジアゾ基を含むテトラオキソキノリン環に不斉炭素を含む脂肪鎖が付いている。構造決定はNMRと化合物の分解によって行われたのであるが、複雑なNMRスペクトルが得られることから、側鎖の回転異性体の存在が考えられていた。しかし、これについては証明されていなかった。また、側鎖C4'の立体化学も不明であった。我々は、ラグナマイシンの構造と生理活性に興味を持ち、絶対立体配置の解明と回転異性化を検証すべく、全合成に着手した。



まず、ラグナマイシンの不安定性の原因となるジアゾ基を除去した化合物 **2** を前駆体として考えた。側鎖とキノリン環のつながり部分 C4-C2'はたいへん混み合っているため、あらかじめこの部分の結合を持つ化合物 **3** に対する Knorr 縮合によってラグナマイシンの骨格を構築することとした。**3** は、ポリプロピオネート鎖 **4** とアニリン **5** を縮合した後酸化することによって得ることとした。**5** は市販品から容易に得られる既知物質であり、**4** は遠隔不斉誘導反応によって合成することとした。

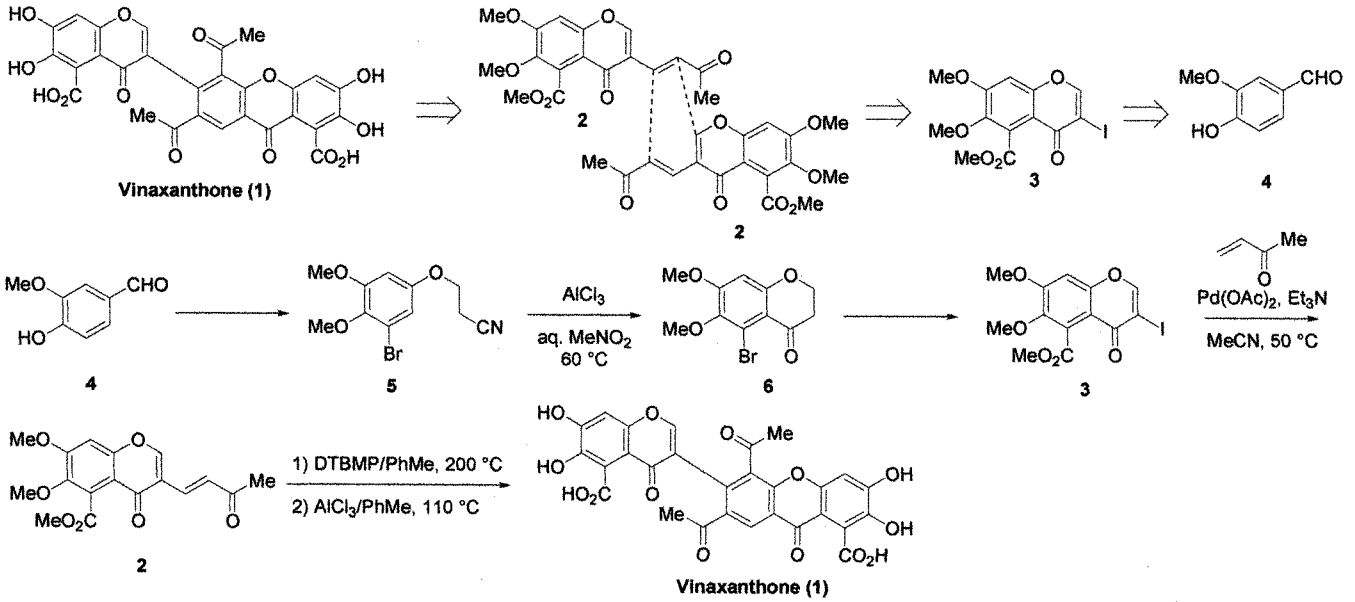
側鎖部は遠隔不斉誘導法を用いて短段階で合成した。すなわち、ビニルケテン *N,O*-アセタール **8** とイソブチロアルデヒド **7** とのビニロガス向山アルドール反応により、アンチ付加体 **6** を単一異性体として定量的に得た。これを **4** へと導き、アニリン **5** と縮合させた。縮合体 **9** に対して、IBX 酸化により芳香環部と側鎖部を同時に酸化してオルトキノン **10** とした。**10** に対して、(1)加水分解による O-Me 結合の切断および(2)還元による求核性の高いヒドロキノンの生成、(3)Knorr 縮合、(4)パラキノンへの酸化、の 4 段階をワンポットで行い、高収率で **11** を得た。**11** のジアゾ化によってラグナマイシンの全合成を達成した。**1** は天然物と各種スペクトルデータが一致し、同じ旋光度を示したことから、ラグナマイシンの絶対立体配置が確立された。

また、**1** と **11** の加熱条件下での NMR スペクトルの比較から、ラグナマイシンには回転異性体が存在することを証明した。

3. セマフォリン 3A 阻害物質ビナキサンソンの全合成

切断された中枢神経が再生できないのは、セマフォリンというたんぱく質によって伸張が抑制されるためである。しかし近年、ビナキサンソンやその類縁体がセマフォリン 3A を阻害することが発見され、再生医療の観点から注目を集めている。ビナキサンソンは酸化度の高いクロモンが 2 量化した構造をとる。われわれはビナキサンソンの特異な構造と有用な生理活性に注目し、全合成研究に着手した。

合成計画としては、酸化度の高いクロモン **2** を合成終盤で 2 量化させる合成経路を考えた。また、単量体 **2** はバニリン **4** から合成することとした。



バニリンを出発原料としてエーテル **6** を合成し、分子内 Friedel-Crafts 反応によってクロモン骨格を構築した。**6** にメトキシカルボニル基とヨウ化ビニル基を導入して **3** とした後、Heck 反応によって単量体 **2** を合成した。**2** を Diels-Alder 反応により二量化したのち、脱 O-メチル化を行

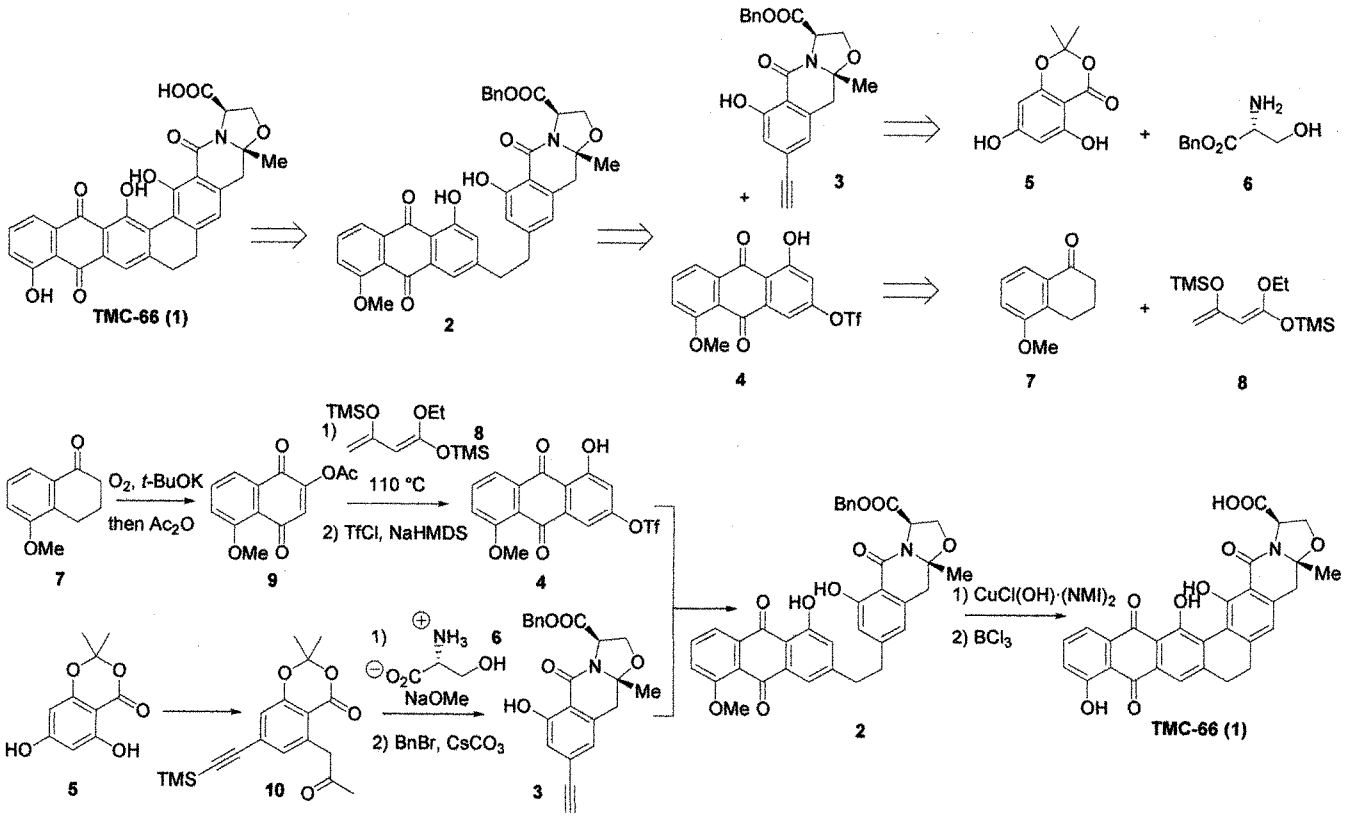
い、ビナキサンソンの全合成を達成した。

4. エンドセリン変換酵素阻害剤 TMC-66 の全合成

TMC-66 は 1999 年にエンドセリン変換酵素阻害剤として *Streptomyces* sp. A5008 より単離・構造決定された多環式化合物である。2 箇所の不斉中心を持つオキサゾリン環を含む 7 つの環が連なる特異な構造をしており、絶対立体配置は不明であった。我々はこの特異な構造と生理活性に興味を持ち、全合成に着手した。

合成計画としては、同等な大きさのフラグメント **3** と **4** をつないで **2** とした後、分子内酸化的カップリングによって真ん中の環を構築することによって全体の骨格を組み上げることとした。フラグメント **3** と **4** は市販の **5** および **6**、**7**、そして 1 段階で合成できるジエン **8** から短段階で得ることを目論んだ。

実際に、フラグメント **4** は **7** から 3 段階で、フラグメント **3** は **5** から 3 段階で得られる **10** に対して **6** との縮合とベンジル化を行うことによって単一異性体として得た。これらを園頭反応で接続した後、$CuCl(OH)\cdot(NMI)_2$ を用いて位置選択的酸化的カップリングを行い、TMC-66 の全合成を達成した。得られた化合物は各種スペクトルが文献のものと一致し、旋光度の符号も同じであることから、TMC-66 の絶対立体配置を図のように決定した。



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The first total synthesis and structural determination of actinopyrone A

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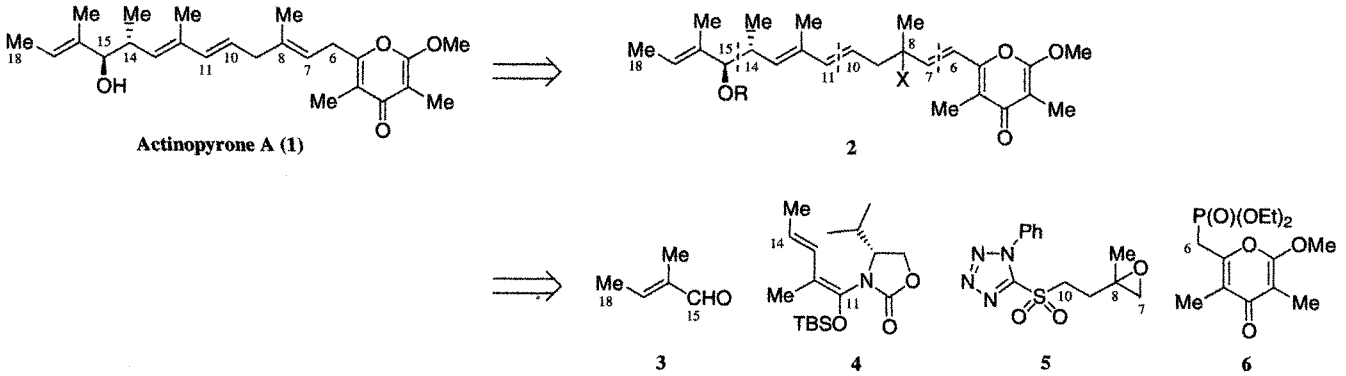
Abstract—Actinopyrone A (**1**) has been synthesized by using our developed remote stereoinduction, Kocienski olefination, Horner–Wadsworth–Emmons olefination, and reductive de-conjugation of the vinylpyrone. A concise method of O-methylation to obtain the γ-pyrone has also been established.

Actinopyrone A (**1**) was isolated from *Streptomyces pactum* S12538 as a relatively unstable compound possessing coronary vasodilating activity and antimicrobial activity.[1] Later, it was found to exhibit potent anti-*Helicobacter pylori* activity.[2]

In addition to multi-bioactivity, little toxicity makes actinopyrone A (**1**) to be an attractive candidate of a drug for chemotherapy. However, instability of **1** makes it difficult to promote further research and even the absolute structure has not been disclosed yet. Thus, the synthesis of actinopyrone A (**1**) has been required to be established. Herein, we present the first total synthesis of actinopyrone A (**1**), which is applicable to a variety of derivatives.[3]

Our synthetic plan is shown in Scheme 1. To avoid instability of actinopyrone A (**1**), the conjugated pyrone **2** was set up as the precursor. The precursor **2** would be subjected to the reductive de-conjugation of the conjugated pyrone moiety in the final stage of the synthesis. The conjugated pyrone **2** might be synthesized by



Scheme 1. Retrosynthetic analysis of actinopyrone A (**1**).

Keywords: Actinopyrone A; Total synthesis; Structural determination; Remote stereoinduction; 4-Pyrone; Reductive de-conjugation.
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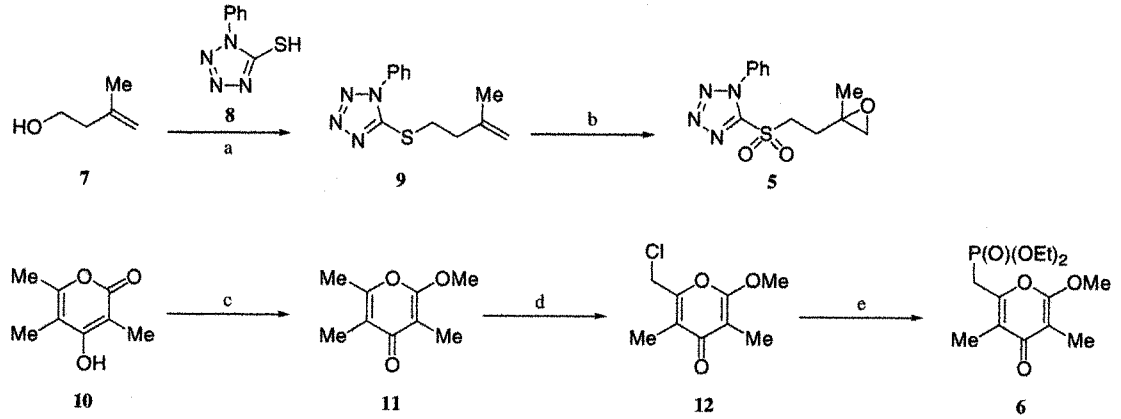
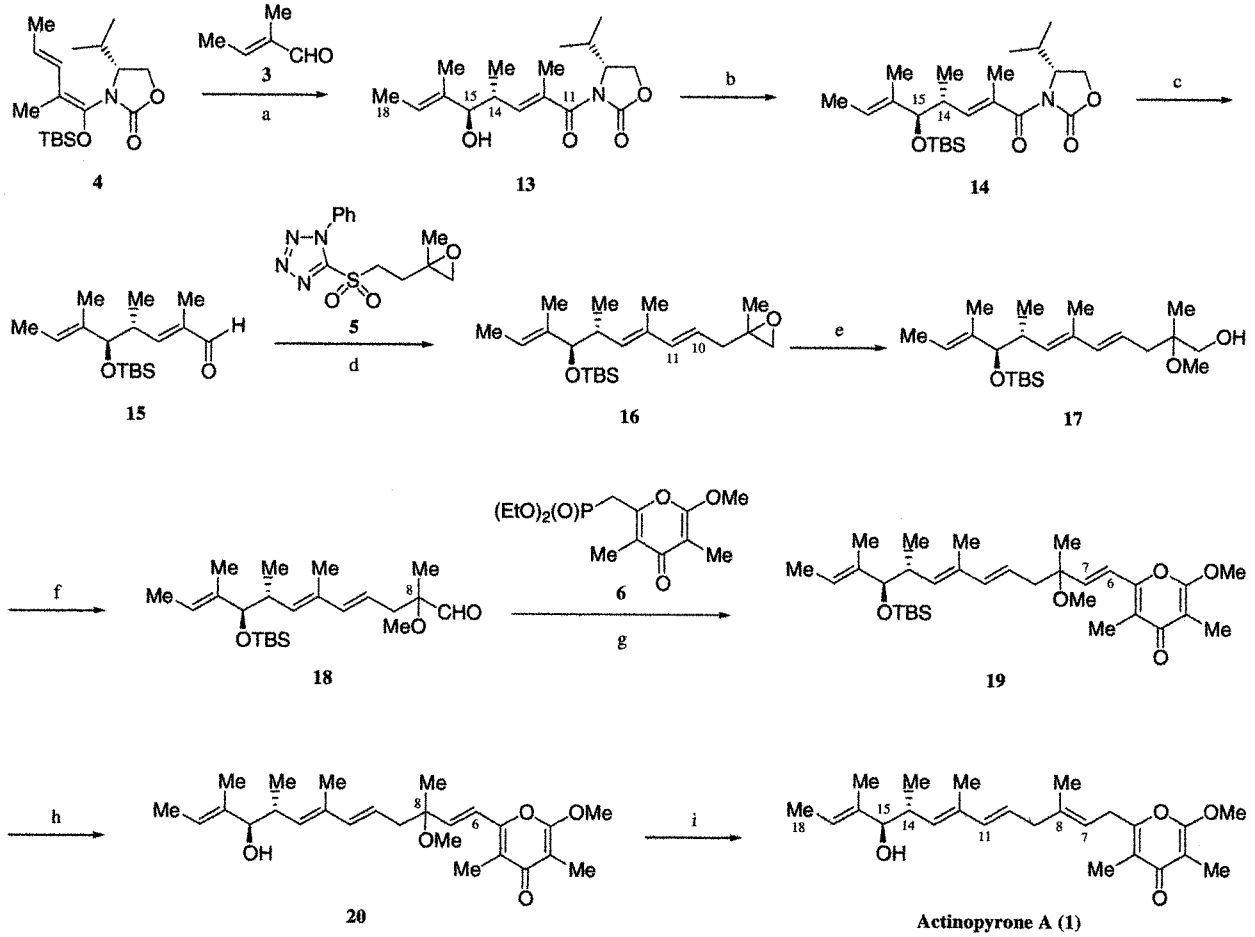
connection of the compounds **3**–**6**. The chiral centers C14 and C15 should be constructed by our developed methodology using the chiral vinylketene *N*,*O*-acetal **4**,[4] which was prepared from D-valine.

Compounds **5** and **6** were synthesized from **7** and **10**, respectively (Scheme 2). The commercially available **7** was converted to tetrazole **9** under Mitsunobu conditions. Both olefin and sulfide of **9** were oxidized to give epoxy-sulfone **5** by treatment with *m*-CPBA in the presence of $NaHCO_3$.[5,6] On the other hand, during the synthesis of the γ-pyrone moiety **6**, we found a concise and economical method of methylation to convert 4-hydroxy-2-pyrone to 2-methoxy-4-pyrone. Treatment of the



Scheme 2. Reagents and conditions: (a) DEAD, PPh_3, THF, rt, 2 h, 92%; (b) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 4 d, 87%; (c) $CaCO_3$, Me_2SO_4, acetone, 50 °C, 3 d, 56%; (d) LHMDS, NCS, THF, 0 °C, 1 h, 67%; (e) $P(OEt)_3$, 140 °C, 6.5 h, 80%.



Scheme 3. Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2, −60 °C, 4 d, 82%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h, 93%; (c) DIBAL, CH_2Cl_2, −78 °C, 1 h, 68%; (d) NaHMDS, DME, −60 to 0 °C, 18 h; (e) CSA, MeOH, 0 °C, 1 h, 67% (two steps); (f) SO_3·Py, DMSO, Et_3N, rt, 30 min, 94%; (g) LHMDS, THF, −78 to 0 °C, 5.5 h, 96%; (h) CSA, MeOH, rt, 18 h, 70%; (i) SmI_2, 2-propanol, THF, −78 to −20 °C, 30 min, 70%.

known α-pyrone **10**[7] with calcium carbonate and dimethylsulfate in acetone at 50 °C promoted 2-O-methylation to give γ-pyrone **11**[8] as a major product. The regioselectivity of the O-methylation was 2-O-methylation/4-O-methylation = 3:1.[9] The isolated yield of γ-pyrone **11** (56%) is comparable to the yield under conditions with $MeSO_3F$ (53%).[10] The regioselective chlorination of γ-pyrone **11** to obtain chloromethylpyrone **12** was realized with lithium hexamethyldisilazide and NCS, and followed by substitution with triethylphosphite to afford phosphonate **6**.[6,11]

The total synthesis of actinopyrone A (**1**) was accomplished as shown in Scheme 3. Stereoselective construction of C11–C18 unit **13** was achieved by our remote stereocontrol methodology.[4] Coupling of silyl dienolate **4**[4c] and tiglic aldehyde **3** in the presence of $TiCl_4$ gave C14–C15 *anti*-adduct **13** as a single isomer. Protection of **13** as the TBS ether afforded the crystalline **14**, of which stereochemistry was determined to be the (14*R*,15*R*)-isomer by X-ray crystallography as expected from our previous works.[4,12] The chiral auxiliary of **14** was removed to give aldehyde **15** by treatment with DIBAL at −78 °C.[4b] The aldehyde **15** was converted to triene **16** (10,11-*E*:10,11-*Z* = 93:7) by Kocienski's method[5] using sulfone **5**. The epoxide **16** was transformed under the acidic conditions to primary alcohol **17**, which was separated from 10,11-*Z*-isomer by silica gel column chromatography. The alcohol **17** was submitted to oxidation to afford aldehyde **18**. The pyrone moiety was introduced by Horner–Wadsworth–Emmons reaction of **18** with phosphonate **6** to afford the stable vinylpyrone **19**. De-O-silylation of **19** under the acidic conditions proceeded in good yield to provide **20** (**2**: R = H, X = OMe). The final and key step was settled. Treatment of the vinylpyrone **20** with SmI_2[13] in the presence of 2-propanol promoted the reductive de-conjugation to give actinopyrone A (**1**) accompanied with the 7,8-*Z*-isomer in the ratio of 88:12. These isomers were easily separated by silica gel column chromatography to isolate **1** in 70% yield. The synthetic **1** was identical in all respects with the natural product including the optical rotation (synthetic **1**: $[\alpha]_D^{25}$ +31.3 (*c* 0.43, CH_2Cl_2), natural: $[\alpha]_D^{26}$ +30.8 (*c* 0.42, CH_2Cl_2)).[6] Thus, the absolute structure of actinopyrone A (**1**) was determined to be (14*R*,15*R*)-configuration. We also synthesized the enantiomer of actinopyrone A showing the opposite optical rotation ($[\alpha]_D^{23}$ −31.7 (*c* 0.43, CH_2Cl_2)) by starting from the enantiomer of **4**[4c] derived from L-valine.

In conclusion, the first total synthesis and structural determination of actinopyrone A (**1**) were accomplished by coupling of four units (**3**, **4**, **5**, and **6**) and reductive de-conjugation of the vinylpyrone **20**. This route is applicable to synthesize a variety of analogs of actinopyrones to produce anti-*H. pylori* drugs.

Acknowledgments

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6. Selected data; Compound **5**: prisms recrystallized from 2-propanol, mp 88.3–88.7 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (3H, s), 2.21 (1H, ddd, *J* = 14.4, 10.8, 5.4 Hz), 2.32 (1H, ddd, *J* = 14.4, 10.8, 5.6 Hz), 2.66 (1H, d, *J* = 4.0 Hz), 2.71 (1H, d, *J* = 4.0 Hz), 3.75 (1H, ddd, *J* = 14.8, 10.8, 5.4 Hz), 3.83 (1H, ddd, *J* = 14.8, 10.8, 5.6 Hz), 7.56–7.64 (3H, m), 7.65–7.73 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0, 28.9, 52.1, 53.3, 54.8, 125.1, 129.8, 131.5, 133.0, 153.3; MS (FAB^+) *m/z* 295 $[M+H]^+$, HRMS (FAB^+) calcd for $C_{12}H_{15}O_3N_4S_1$ $[M+H]^+$ 295.0865, found 295.0863. Anal. Calcd for $C_{12}H_{14}O_3N_4S_1$: C, 48.97; H, 4.79; N, 19.04. Found: C, 48.92; H, 4.78; N, 18.91; IR (KBr) 3072, 3056, 2981, 2967, 2927, 1949, 1348, 1324, 1155, 894, 765, 694. Compound **6**: prisms recrystallized from diisopropyl ether, mp 70.0–70.4 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32 (6H, t, *J* = 7.1 Hz), 1.85 (3H, s), 1.98 (3H, d, *J* = 3.7 Hz), 3.14 (2H, d, *J* = 22.0 Hz), 3.99 (3H, s), 4.08–4.17 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 10.4 (d, *J* = 3 Hz), 16.5 (d, *J* = 6 Hz), 30.1 (d, *J* = 140 Hz), 55.7, 62.6 (d, *J* = 6 Hz), 99.8, 120.8 (d, *J* = 9 Hz), 149.4 (d, *J* = 12 Hz), 162.3, 180.4 (d, *J* = 3 Hz); MS (FAB^+) *m/z* 305 $[M+H]^+$, HRMS (FAB^+) calcd for $C_{13}H_{22}O_6P_1$ $[M+H]^+$ 305.1154, found 305.1158; IR (KBr) 2985, 2967, 2927, 1672, 1602, 1463, 1328, 1253, 1238, 1020, 977, 792. Compound **18** (the value in bracket is data of the isomer at C8 position): ^1H NMR (400 MHz, $CDCl_3$) δ −0.09 (3H, s), −0.07 (3H, s), 0.75 (3H, d, *J* = 6.9 Hz), 0.80 (9H, s), 1.21 [1.22] (3H, s), 1.55 (3H, s), 1.58 (3H, d, *J* = 6.7 Hz), 1.71 (3H, s), 2.33–2.52 (2H, m), 2.55–2.66 (1H, m), 3.32 (3H, s), 3.62 (1H, d, *J* = 8.0 Hz), 5.20 (1H, d, *J* = 10.1 Hz), 5.31 (1H, q, *J* = 6.7 Hz), 5.41 (1H, dt, *J* = 15.3, 7.5 Hz), 6.09 (1H, d, *J* = 15.3 Hz), 9.58 [9.59] (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.1, −4.8, 10.79 [10.81], 12.9 [13.0], 17.4, 17.47 [17.49], 18.1, 25.7, 37.3, 38.0 [38.2], 51.89 [51.93], 82.35 [82.39], 83.5 [83.6], 118.9, 121.29 [121.32], 132.7,136.70 [136.73], 137.1, 139.5 [139.6], 205.0 [205.1]; MS (FAB^+) *m/z* 393 $[M-H]^+$, 365 $[M-CHO]^+$,

363 $[M-OMe]^+$; HRMS (FAB^+) calcd for $C_{23}H_{41}O_3Si_1$ $[M-H]^+$ 393.2825, found 393.3827; IR (KBr) 3031, 2956, 2929, 2856, 2829, 2800, 2701, 1737, 1471, 1461, 1247, 1079, 1056, 860, 836, 773. Compound **20**: (the value in bracket is data of the isomer at C8 position): ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, $J = 6.9$ Hz), 1.35 (3H, s), 1.60–1.68 (7H, m), 1.81 (3H, s), 1.87 (3H, s), 2.05 (3H, s), 2.44 (2H, d, $J = 7.2$ Hz), 2.68 (1H, ddq, $J = 9.6$, 9.1, 6.9 Hz), 3.246 [3.252] (3H, s), 3.63 (1H, d, $J = 9.1$ Hz), 3.998 [4.001] (3H, s), 5.26 (1H, d, $J = 9.6$ Hz), 5.49 (1H, q, $J = 6.2$ Hz), 5.53–5.63 (1H, m), 6.13 [6.14] (1H, d, $J = 15.7$ Hz), 6.36 (1H, d, $J = 16.0$ Hz), 6.50 [6.51] (1H, d, $J = 16.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 9.6, 10.5, 13.1, 13.2, 17.4, 22.16 [22.23], 36.8, 43.5 [43.6], 50.5, 55.3, 77.2, 82.8, 99.6, 119.1, 119.49 [119.52], 122.4 [122.5], 123.6, 134.08 [134.14], 135.49 [135.53], 135.6, 138.0 [138.1], 140.0, 151.2, 161.7, 181.0; MS (FAB^+) m/z 431 $[M+H]^+$; HRMS (FAB^+) calcd for $C_{26}H_{39}O_5$ $[M+H]^+$ 431.2797, found 431.2769; IR (KBr) 3423, 3029, 2971, 2925, 2863, 2829, 1666, 1631, 1602, 1577, 1465, 1417, 1376, 1336, 1259, 1168, 968. Actinopyrone A (**1**) (synthetic): $[\alpha]_D^{25}$ +31.3 (c 0.43, CH_2Cl_2) [natural $[\alpha]_D^{26}$ +30.8 (c 0.42, CH_2Cl_2)] ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, $J = 6.9$ Hz), 1.63 (3H, d, $J = 6.0$ Hz), 1.64 (3H, s), 1.67 (1H, br), 1.73 (3H, s), 1.81 (3H, s), 1.84 (3H, s), 1.96 (3H, s), 2.68 (1H, ddq, $J = 9.6$, 9.1, 6.9 Hz), 2.80 (2H, d, $J = 6.9$ Hz), 3.31 (2H, d, $J = 7.3$ Hz), 3.63 (1H, d, $J = 9.1$ Hz), 3.92 (3H, s), 5.24 (1H, d, $J = 9.6$ Hz), 5.26 (1H, t, $J = 7.3$ Hz), 5.49 (1H, q, $J = 6.0$ Hz), 5.56 (1H, dt, $J = 15.5$, 6.9 Hz), 6.10 (1H, d, $J = 15.5$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.9, 9.9, 10.5, 13.1, 13.2, 16.6, 17.4, 30.0, 36.9, 42.9, 55.2, 82.8, 99.3, 118.0, 118.1, 123.6, 125.6, 133.8, 135.57, 135.61, 136.4, 138.0, 156.9, 162.1, 181.0; MS (FAB^+) m/z 401 $[M+H]^+$, HRMS (FAB^+) calcd for $C_{25}H_{37}O_4$ $[M+H]^+$ 401.2692, found 401.2673; IR (KBr) 3407, 3023, 2958, 2923, 2863, 1666, 1587, 1463, 1378, 1326, 1251, 1164.

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The first total synthesis and structural determination of lagunamycin

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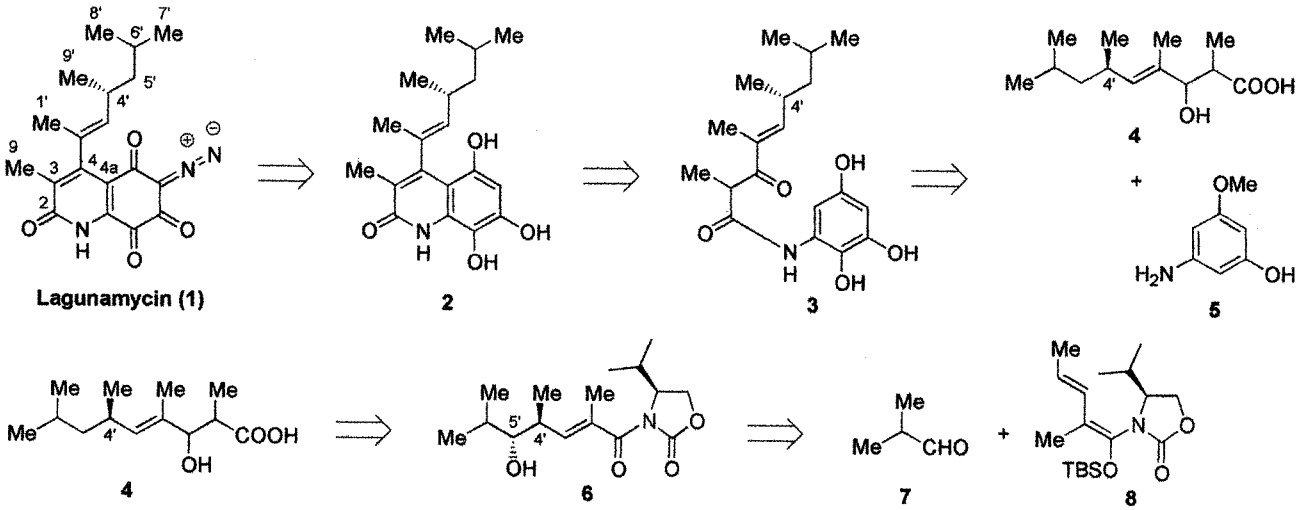
Abstract—Lagunamycin (**1**) has been synthesized by using our developed remote stereoinduction, Knorr condensation, periodinane oxidation, and diazonation. This enantioselective synthesis determined the absolute configuration of lagunamycin. Existence of rotational conformers was confirmed by NMR studies.

Lagunamycin (**1**), a metabolite isolated from the culture filtrate of *Streptomyces* sp. AA0310 showed inhibitory activity against 5-lipoxygenases and antibacterial activity against Gram-positive bacteria.[1a] The structure of lagunamycin (**1**) has been elucidated to possess the diazotetraoxoquinoline skeleton attaching the branched alkyl chain as shown in Figure 1 by a combination of NMR studies and chemical degradations.[1b] The complexity of NMR spectra of lagunamycin (**1**) has been believed to be the result from the rotational isomers caused by the bulky side chain against the 9-methyl group attaching on quinoline plane.[1b] Interested in the structure and bioactivities, we embarked on the synthetic studies on lagunamycin (**1**). Herein, we present the first total synthesis and structural determination of lagunamycin (**1**).

Our retrosynthetic analysis is shown in Scheme 1. The diazo group would be introduced in the final step and oxygenated quinoline moiety could be synthesized from



Scheme 1. Retrosynthetic analysis of lagunamycin.

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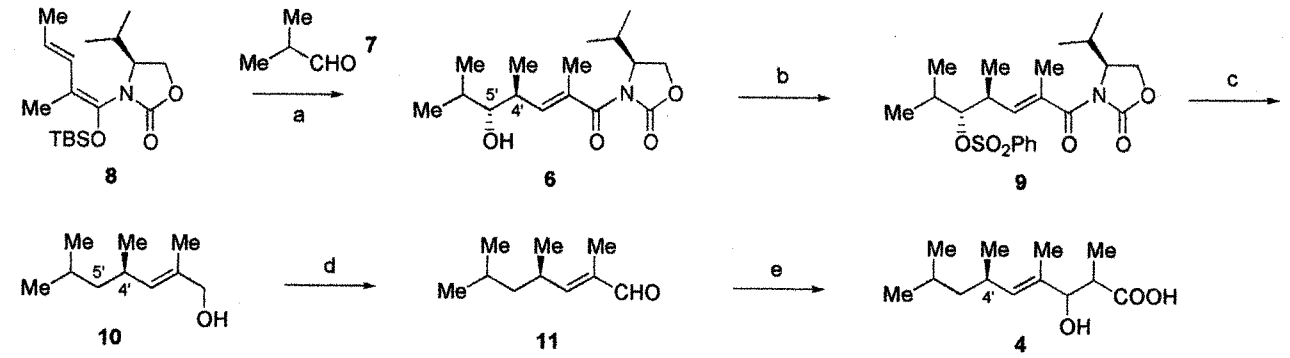
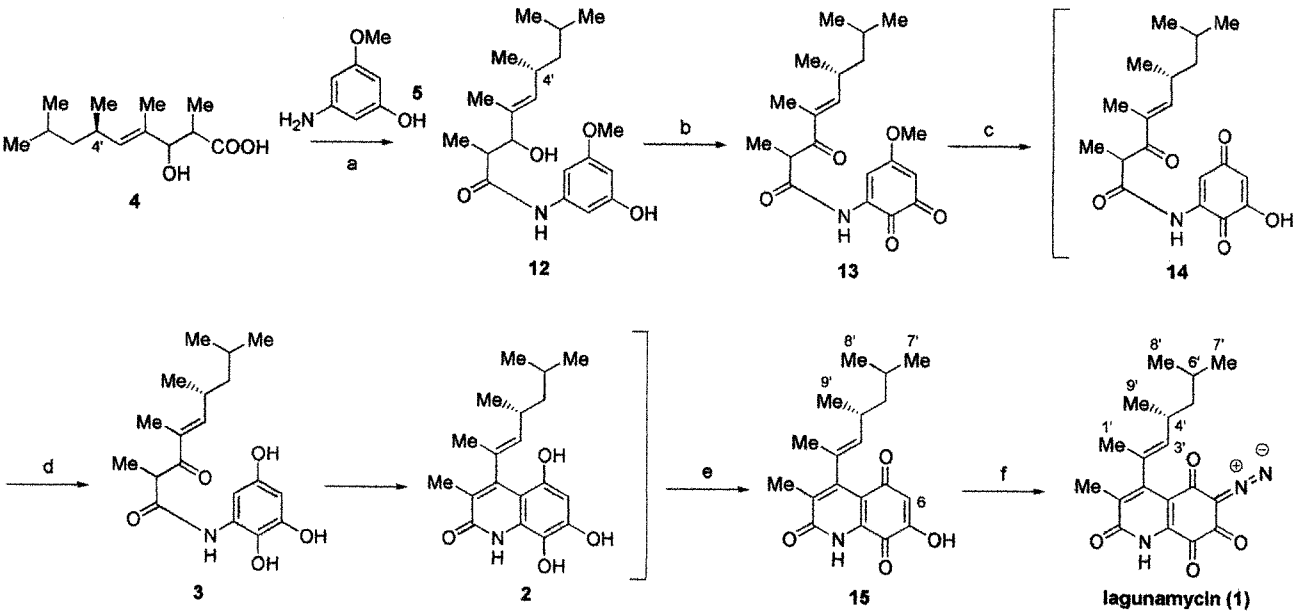
2. To avoid the difficulty from steric interaction between the side chain and the quinolone moiety, we planned to construct the quinolone **2** by Knorr condensation with the β-ketoamide **3**,[2] which would be obtained by coupling of the β-hydroxycarboxyacid **4** and the aniline **5**. The β-hydroxycarboxyacid **4** might be derived from the α,β-unsaturated imide **6**,[3c] which had already been obtained by our developed remote stereoinduction reaction with the *N*,*O*-ketene acetal **8**.[3]

The actual synthesis of lagunamycin (**1**) was started from construction of the side chain moiety **4** (Scheme 2). Our remote stereoinduction reaction with the ketene *N*,*O*-acetal **8** and isobutyraldehyde (**7**) gave the adduct **6** in excellent yield and stereoselectivity in multi-gram scale as expected from our previous report.[3c] De-oxygenation at C5′ position was realized by hydride reduction with the sulfonate **9**. Treatment of phenylsulfonate **9** with super hydride ($LiBEt_3H$) made rapid progress of the reductive removal of oxazolidine ring at −78 °C and promoted de-sulfonation at room temperature to give the primary alcohol **10**. The allylic alcohol **10** was oxidized to the aldehyde **11**,[4] which was submitted to aldol reaction with the dianion derived from propionic acid. The resulting β-hydroxycarboxylic acid **4** was used for the further transformation as a diastereomeric mixture.

Construction of the quinolone moiety and completion of total synthesis of lagunamycin is described in Scheme 3. Condensation of the β-hydroxycarboxylic acid **4** and the aniline **5**[5] with WSCI afforded the anilide **12** in excellent yield. Treatment of anilide **12** with *o*-iodoxybenzoic acid (IBX) to promote Nicolaou oxidation[6] smoothly (30 min) at room temperature gave the quinone moiety and oxidation of allylic alcohol slowly (overnight) at 40 °C gave the β-ketoamide **13**. The structure of **13**[4] was determined as *o*-quinone as shown in Figure 1. The NOE between the methoxy proton and both protons on the quinone ring was observed. Additionally, the HMBC spectrum shows the cross peaks between the methoxy proton and both C3 and C5 carbons. These results support the *o*-quinone structure of **13**. The



Scheme 2. Reagents and conditions: (a) Ref. 3c; (b) LHMDS, $PhSO_2Cl$, THF, −78 to −40°C, 94%; (c) $LiBEt_3H$, THF, −78 °C to rt, 12 h, 65%; (d) MnO_2, hexane, 40°C, 12 h, 92%; (e) LDA, $CH_3CH_2CO_2H$, THF, −78 °C, 30 min, 70%.



Scheme 3. Reagents and conditions: (a) WSCI·HCl, CH_2Cl_2, rt, 2 h, 96%; (b) IBX, PhMe–DMSO, rt, 30 min, then 40 °C, 12 h, 83%; (c) 10% H_2SO_4 aq, CH_3CN, rt, 15 min; (d) $Na_2S_2O_4$, 40 °C, 12 h; (e) OXONE®, rt, 15 min, 87% from **13**; (f) *p*-acetamidobenzenesulfonyl azide, DBU, THF, rt, 4 h, 52%.

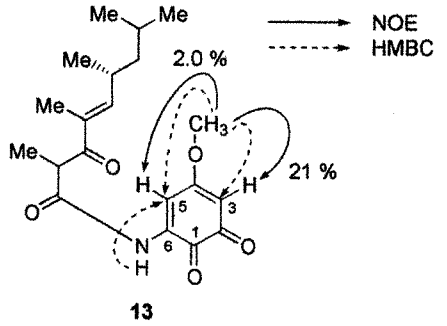


Figure 1. Structure of *o*-quinone **13**.

o-quinone **13** was transformed to the quinolone **15** by the one-pot procedure. Subsequent manipulation of quinone **13** (red solution) including (i) hydrolysis of methyl ether to convert to the unstable quinone **14** (yellow solution), (ii) selective reduction of the quinone moiety with $Na_2S_2O_4$ to provide the very labile trihydroxyanilide **3** (colorless solution), (iii) Knorr condensation under the acidic conditions[2] to give quinolone **2** (pale yellow solution), and (iv) oxidation of hydroquinone with Oxone, delivered the quinone **15**[4] (orange solution) in high yield.[7] Finally, treatment of **15** with *p*-acetamidobenzenesulfonyl azide[8] in the presence of DBU gave lagunamycin (**1**),[9] whose analytical data were consistent with those reported previously.[1] Thus, total synthesis of lagunamycin was accomplished and the absolute structure of **1** was determined as 4′*R* configuration.

To prove the existence of rotational isomers, the following NMR experiments were carried out. ^{1}H NMR spectra of lagunamycin (**1**) in dimethyl sulfoxide-d_6 were observed at different temperatures including 24 °C, 40 °C, 60 °C, 80 °C, and 110 °C (Fig. 2). The ^{1}H NMR spectrum of **1** at 24 °C showed two kinds of compounds. At 80 °C, the peaks assigned as H3′ and H4′ got simple, and a broad peak of H1′ became doublet showing allylic coupling with H3′ ($J_{1',3'} = 1.2$ Hz). The peaks around 0.9 ppm became simpler, however, nine peaks were observed yet. After cooling from 80 °C to room temperature, the resulting sample gave the same spectrum as the original one obtained at 24 °C. At 90 °C (not included in Fig. 2), eight peaks were observed around 0.9 ppm and the sample began to decompose slowly. At 110 °C, three methyl groups of lagunamycin including H7′, H8′, and H9′ appeared as three doublets, which imposed on the peaks of the unidentified degradation products (three doublets at 0.89, 0.92, and 1.00 ppm). Therefore, additional NMR experiments on rotation of the side chain were practiced with the more stable quinone **15** (Fig. 3). The ^{1}H NMR spectrum of **15** showed two isomers at 26 °C and its behavior at different temperatures was the same as that of lagunamycin (**1**) without remarkable decomposition. The peaks around 0.9 ppm became simpler at 100 °C, and finally, they fixed to three doublets at 110 °C. The spectrum at 110 °C became the simple one as expected from the planar structure of **15**. After cooling to room temperature, the resulting sample gave the same spectrum as the original one obtained at 26 °C. The feature of temperature-dependence of the quinone **15** was as same as that of lagunamycin (**1**). Thus, the origin of complexity of NMR spectra was confirmed due to the existence of a rotational isomer.

Additionally, the NOE experiments made clear the ratio of rotational isomers at room temperature (Fig. 4). The relations between H9 and H9′, H1′ and H4′, and between H9 and H6′ were observed. The 600 Hz ^{1}H NMR spectrum made it possible to distinguish the three methyl groups of rotational isomers (the major isomer:the minor isomer = 1.2:1).[9] The NOESY spectrum of **1** (in $CDCl_3$, 27 °C) determined the stereochemistry of these isomers. The relations between H9 and H6′ of the major isomer, H9 and H7′ of the major isomer,

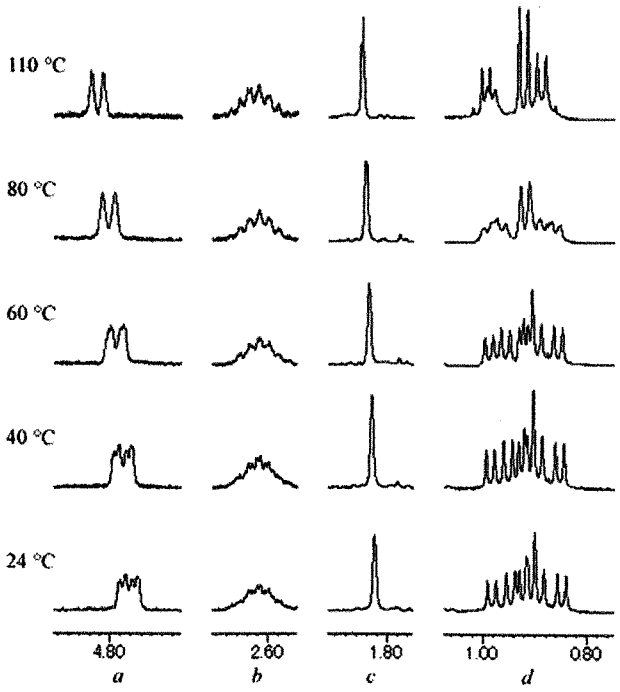


Figure 2. ^{1}H NMR spectrum of lagunamycin (**1**) in DMSO-d_6 at the various temperatures: (a) H3′; (b) H4′; (c) H1′; (d) H7′, 8′, and 9′.

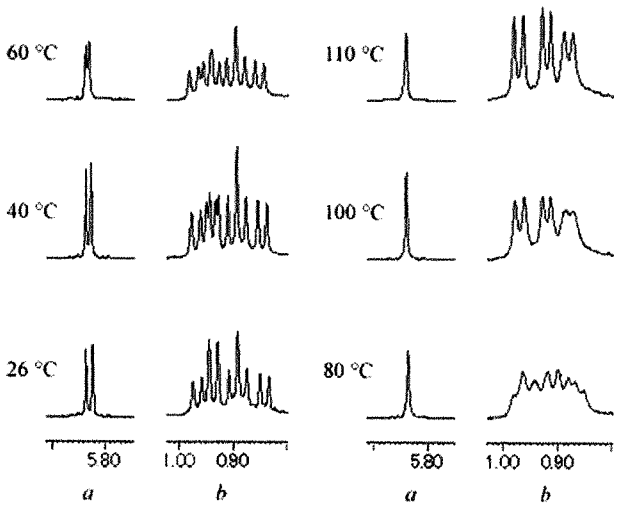


Figure 3. ^{1}H NMR spectrum of the quinone (**15**) in DMSO-d_6 at various temperatures: (a) H6; (b) H7′, 8′, and 9′.

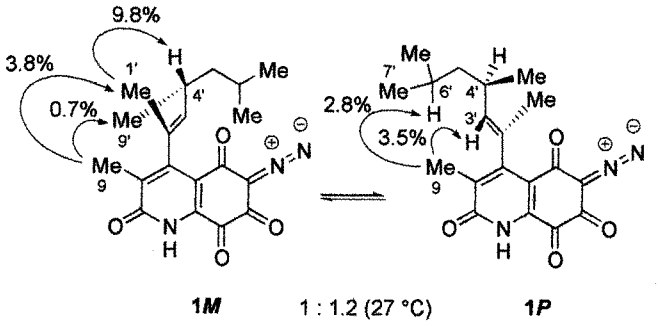


Figure 4. The NOE relation of rotational isomers in $CDCl_3$.

and between H9 and H9′ of the minor isomer were observed. These results revealed the ratio of two isomers at room temperature to be ***1M*:*1P*** = 1:1.2.

In conclusion, we achieved the first total synthesis of lagunamycin to determine the absolute structure and confirmed the existence of rotational isomers.

Acknowledgments

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Supplementary data

The spectrum data of compounds **11**, **13**, and **15**, ^1H NMR spectra of synthetic lagunamycin (400 MHz and 600 MHz in $CDCl_3$), ^{13}C NMR spectrum of synthetic lagunamycin (100 MHz in $CDCl_3$) and NMR spectra of natural lagunamycin reprinted from Ref. 1a are provided as supplementary data, which can be found in the online version, at doi:10.1016/j.tetlet.2006.06.158.

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7. One-pot transformation of *o*-quinone **13** to *p*-quinone **15**: Quinone **13** (13.4 mg, 37.0 μmol) was dissolved into a mixture of acetonitril and 10% H_2SO_4 aq and the mixture was stirred at room temperature for 15 min. $Na_2S_2O_4$ (25.8 mg, 148 μmol) was then added and the resulting mixture was heated to 40 °C for 12 h. After cooling to room temperature, Oxone (182 mg, 297 μmol) was added to the mixture, which was stirred at room temperature for 15 min. The reaction mixture was extracted with ethyl acetate. Evaporation and purification by silica gel column chromatography (hexane:ethyl acetate = 2:1, containing 1% trifluoroacetic acid) gave orange solid **15** (10.6 mg, 87%).
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9. Lagunamycin (**1**) (the value in bracket is data of the isomer): (synthetic): $[\alpha]_D^{26}$ −33.0 (*c* 0.20, MeOH) {natural $[\alpha]_D^{26}$ −33 (*c* 0.20, MeOH)}; ^1H NMR (600 MHz, $CDCl_3$, 27 °C) δ 0.92 [0.89] (3H, d, J = 6.7 Hz), 0.93 [0.96] (3H, d, J = 6.7 Hz), 1.01 [1.02] (3H, d, J = 6.8 Hz), 1.11–1.27 (2H, m), 1.56–1.67 (1H, m), 1.903 [1.898] (1H, d, J = 1.3 Hz), 2.190 [2.186] (3H, s), 2.63–2.73 (1H, m), 4.87 [4.85] (1H, dd, J = 9.4, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$, 27 °C) δ 14.1 [14.0], 16.83 [16.80], 20.1 [20.6], 22.2 [22.5], 23.3 [23.2], 26.0 [25.6], 30.4 [30.3], 46.7 [46.5], 87.6 [87.7], 116.4 [116.3], 129.9 [129.8], 134.8 [135.3], 137.2 [137.1], 138.5 [138.7], 151.6 [151.5], 161.30 [161.35], 168.6 [168.7], 172.53 [172.4], 172.54 [172.6]; MS (FAB$^+$) *m/z* 356 $[M+H]^+$, 328 $[M+H-N_2]^+$; HRMS (FAB$^+$) calcd for $C_{19}H_{21}N_3O_4$ $[M+H]^+$ 356.1610, found 356.1589; IR (KBr) 3437 (br), 2954, 2926, 2870, 2146, 1716, 1682, 1651, 1632, 1387, 1369, 1321, 1286, 1178.

The First Total Synthesis of Vinaxanthone, a Fungus Metabolite Possessing Multiple Bioactivities

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Vinaxanthone (**1**) has been biomimetically synthesized from vanillin (**2**) through an intermolecular Diels–Alder cycloaddition between two molecules of the precursor **11**.

Vinaxanthone (**1**) was first isolated by the Yokose and Seto group in 1991 from the culture broth of a fungus *Penicillium vinaceum* to show selective inhibitory activity against phospholipase C, and its structure was also determined by NMR studies.[1]

Subsequently, the two groups of Wrigley and Kumagai have isolated vinaxanthone (**1**) in 1994 and 2003 as fungus metabolites having potent CD4-binding activity and semaphorin inhibitory activity, respectively.[2,3]

Especially, semaphorin 3A has been reported to cause collapse of neurite growth cones, resulting in inhibition of neuronal outgrowth in vitro and in vivo. Therefore, semaphorin inhibitors are expected to be potential drugs for the treatment of traumatic neuronal injury.[4]

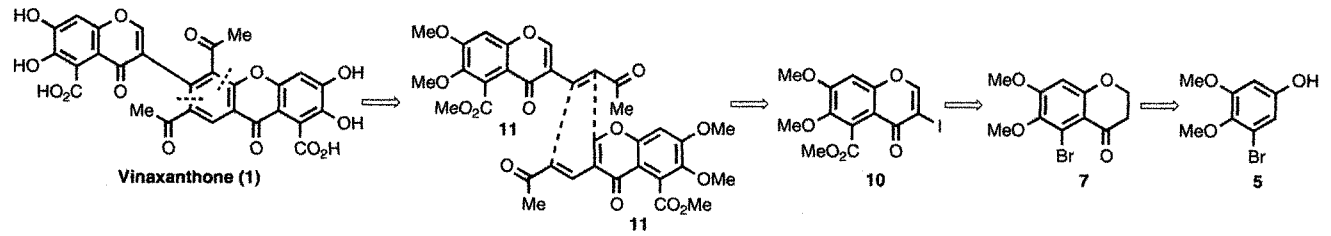
Structurally, the unprecedented molecular architecture is characterized by its polycyclic xanthone core with polyacidic functions.

From the outset of our synthetic studies, we were motivated, among other things, by the question of how the fascinating structure **1** is biogenetically produced. It seems likely that an intermolecular Diels–Alder (IMDA) cycloaddition between two molecules of the precursor such as **11** is operative.

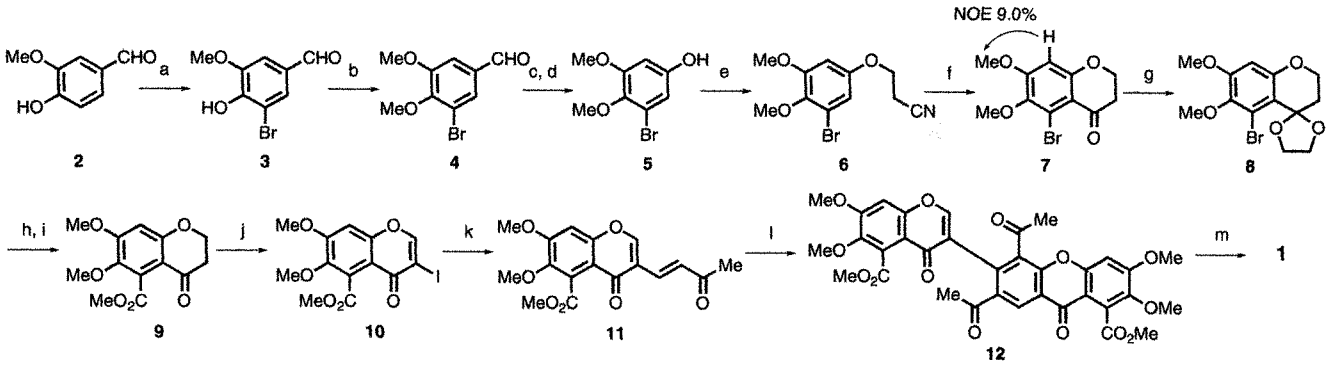
Herein, we report the implementation of a biomimetic strategy for the first total synthesis of vinaxanthone (**1**).

From a retrosynthetic perspective for maximum convergency (Scheme 1), we initially envisioned the IMDA reaction of the precursor **11** to be a means potentially well suited to the assembly of the natural product **1**. Access to this advanced intermediate was to be gained by a cross-coupling of **10** with methyl vinyl ketone. The key compound **10** would be prepared through **7** from **5**, which could be derived from vanillin (**2**) by Baeyer–Villiger reaction.[5]

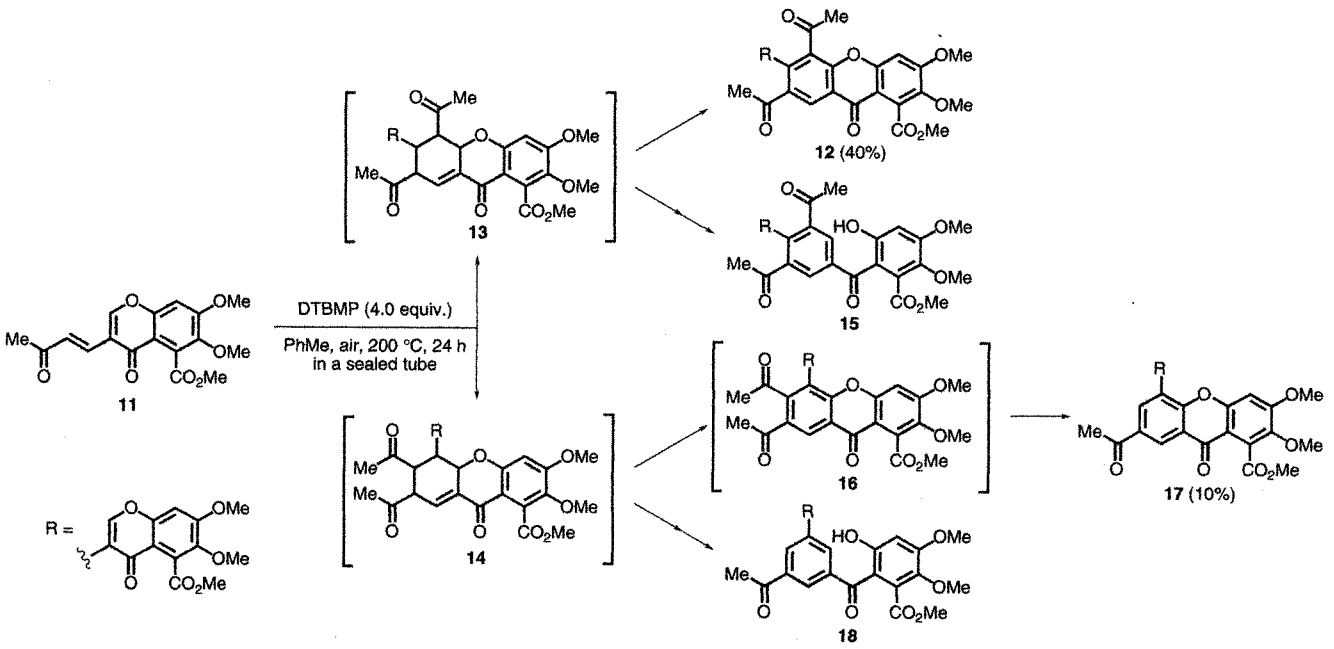
The present synthesis began with the regioselective bromination of vanillin (**2**),[6] followed by O-methylation to give the 3-bromobenzaldehyde **4** in almost quantitative yield (Scheme 2). The aldehyde was submitted to the Baeyer–Villiger reaction with *m*CPBA to give, after de-O-formylation, the phenol **5**. The Michael addition of **5** to acrylonitrile with DBU afforded the adduct **6**.[7,8] The hydrolysis of the nitrile group to the carboxylic acid was followed by the Friedel–Crafts type reaction with $AlCl_3$ to give the dihydrobenzopyranone **7** in 80% yield. The structure **7** was supported by ^1H NMR studies includ-



Scheme 1.



Scheme 2. (a) Br_2/AcOH, rt, 6 h, 95%, (b) Me_2SO_4, K_2CO_3/acetone, 50 °C, 9.5 h, 94%, (c) *m*CPBA/CH_2Cl_2, reflux, 11 h, (d) 0.1 M Et_3N–MeOH, rt, 2 h, 81% in 2 steps, (e) acrylonitrile, DBU, 75 °C, 72 h, 74%, (f) $AlCl_3$/aq. $MeNO_2$, 60 °C, 0.5 h, 80%, (g) ethylene glycol, TsOH, $CH(OMe)_3$/PhMe, 80 °C, 11 h, 84%, (h) *n*-BuLi, $ClCO_2Me$/THF, −78 °C, 1 h, (i) 5% HCl–MeOH, rt, 2 h, 44% in 2 steps, (j) I_2/DMSO, 110 °C, 5 h, 65%, (k) methyl vinyl ketone, $Pd(OAc)_2$, Et_3N/MeCN, 50 °C, 7.5 h, 88%, (l) DTBMP/PhMe, air, 200 °C (sealed tube), 24 h, 40% (see Scheme 3), (m) $AlCl_3$/PhMe, 110 °C, 2 h, 74%.



Scheme 3.

ing NOE observation. As a direct conversion of **7** to **9** proved to be problematic, the carbonyl group of **7** was protected by ethylene acetal to give **8**.

The lithiated **8** reacted with methyl chloroformate to give the carbomethoxy derivative, followed by deprotection to the ketone **9**. This was treated with iodine in DMSO to give the vinyl iodide **10**, which was subjected to a cross-coupling with methyl vinyl ketone in the presence of $Pd(OAc)_2$ to provide the key intermediate **11**.[9]

In the IMDA cycloaddition studies, a large number of variables including acid catalysts, solvents, reaction time, and temperature were tested. The best results were realized by heating a solution of **11** in PhMe with 4.0 equiv. of 2,6-di-*t*-butyl-4-methylphenol (DTBMP) in a sealed tube at 200 °C for 24 h with air.[7] These conditions led to the aromatized product **12** as crystals in 40% yield, after silica-gel column chromatography with 1,2-dichloroethane–2-butanone and recrystallization from acetone–$CHCl_3$, with recovery (30%) of the starting **11**. The intact adduct **13** was not observed without aromatization (Scheme 3). The formation of the regio-isomers **14** and **16** was anticipated, but, in the event, only the deacetylated isomer **17** was obtained in 10% yield. Also, the ring-opened products **15** and **18** were isolated as minor products in less than 5% yields. The structures of all these products were determined by NMR studies, and the structure **12** was unambiguously confirmed by X-ray crystallographic analysis.[10]

Without DTBMP, the IMDA reaction gave **15** and **18** as the major products (22 and 30%) with the desired **12** (17%). These ring-opened compounds result from a sequence including elimination of the phenol portion in the intermediary adducts **13** and **14**, and concomitant oxidative aromatization. For the formation of **18**, the deacetylation is further required. These findings suggested that the additive DTBMP seemed to be first oxidized to the corresponding quinone,[11] which in turn oxidized the intact adduct **13** to give the aromatized product **12**. However, the addition of oxidants (MnO_2, PbO_2, and TEMPO) gave no desired product.

Deprotection of **12** proceeded nicely with $AlCl_3$ in PhMe at 110 °C to give the hydroxy-carboxylic acid **1** (Scheme 2).[12] This was identical in all respects with natural vinaxanthone (**1**),[13] completing the first total synthesis.

This work was financially supported by the 21COE "Center for Practical Nano-Chemistry," the Consolidated Research Institute for Advanced Science and Medical Care, and Scientific Research on Priority Area "Creation of Biologically Functional Molecules" from the Ministry of Education, Culture, Sports, Science and Technology.

This paper is dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

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13 An authentic sample of natural vinaxanthone was kindly provided by Drs. M. Nakatsuka, T. Kimura, and K. Kumagai, Dainippon Sumitomo Pharma Co., Ltd.

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TETRAHEDRON LETTERS

The first total synthesis and structural determination of TMC-66

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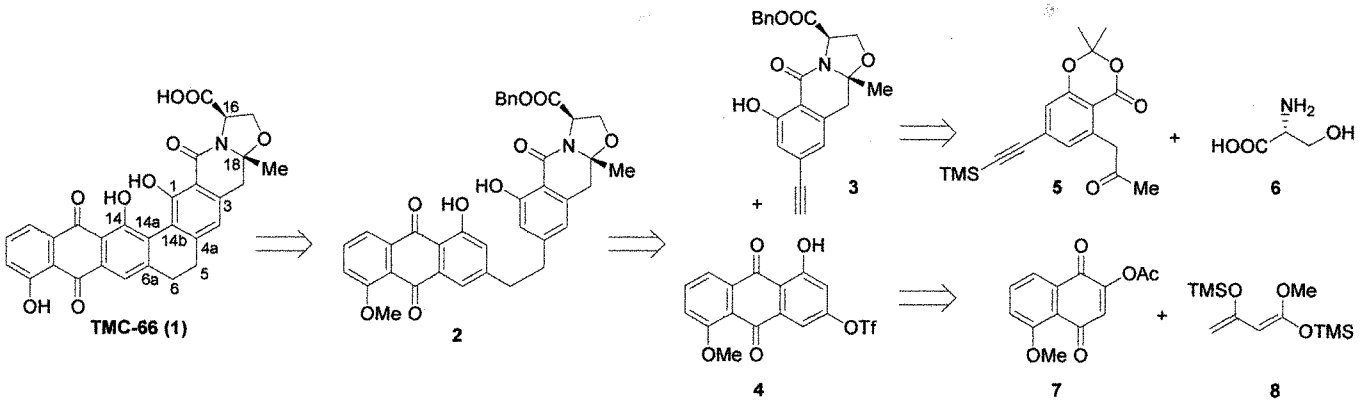
Abstract—The first total synthesis and structural determination of TMC-66 was achieved. The oxidative coupling with electron-withdrawing group-attached phenols was realized with a novel copper (II) reagent. The total synthesis was accomplished in short steps by efficient construction and coupling of segments.



Scheme 1. Retrosynthetic analysis of TMC-66.

TMC-66 was isolated as an endothelin converting enzyme (ECE) inhibitor by Tanabe Seiyaku group.[1] ECE inhibitors have been expected to be therapeutically useful chemicals for treatment of the diseases such as hypertension. TMC-66 has the benzo[*a*]naphthacenequinone[2,3] skeleton fused with an amino acid component. Interested in the structure and bioactivities, we embarked the synthetic studies on TMC-66 (**1**). Herein, we present the first total synthesis and structural determination of TMC-66 (**1**).

Our retrosynthetic analysis is shown in Scheme 1. The key step to construct the benzo[*a*]naphthacenequinone skeleton was intramolecular oxidative coupling between C14a and C14b of **2**, which included phenols attaching different electro-withdrawing groups. Oxidative coupling with phenols possessing strongly electro-withdrawing groups is challenging problem as well as control of regioselectivity. The precursor **2** should be constructed by Sonogashira coupling with same size segments **3** and **4**. Tricyclic **3** would be afforded by condensation of ketoester **5** and D-serine (**6**). Anthraquinone **4** might be derived by Diels-Alder reaction of naphthoquinone **7** and diene **8**. Both segments, **3** and **4**, should be synthesized in short steps to establish efficiency and convergency.

The anthraquinone segment **4** was constructed in three steps from a commercially available 5-methoxy-1-tetralone (**9**) (Scheme 2). The subsequent air oxidation[4] and acetylation

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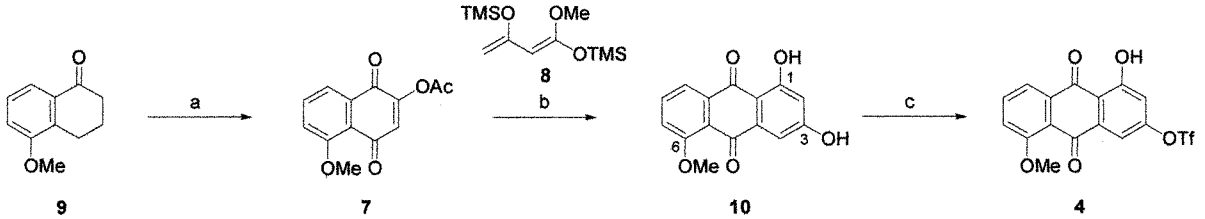
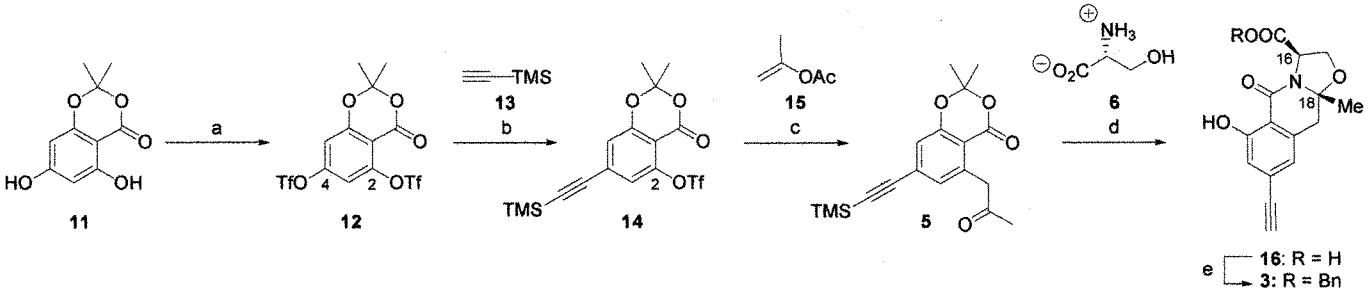
gave naphthoquinone **7**. Diels-Alder reaction with **7** and **8** followed by aromatization afforded 1,3-dihydroxy-6-methoxyanthraquinone (**10**). Selective sulfonylation at O3 produced mono-triflate **4**, the anthraquinone segment.

Another segment **3** was synthesized from acetonide **11** (Scheme 3). Commercially available **11** was converted to bistriflate **12**, which was submitted to the regioselective Sonogashira coupling[5] with trimethylsilylacetylene (**13**) to afford monotriflate **14** in quantitative yield. The C2 position of the triflate **14** was substituted smoothly with the acetonyl group by Migita's procedure[6] in the presence of LiCl[7] and Buchwald ligand[8] to give ketoester **5**. Treatment of **5** with a mixture of D-serine (**6**, 1.2 eq.) and NaOMe (1.0 eq.) in MeOH at 60 °C provided tricyclic **16** as single isomer. Trimethylsilyl group of **5** was removed quickly under these conditions to give *exo*-acetylene moiety. The resulting carboxylic acid **16** was benzylated to obtain ester **3**, the counter part of anthraquinone **4**. Methyl group of **3** was found *cis* to the carboxyl group by nOe experiment (Figure 1). Thus, the stereochemistry of the C18 position was determined as (*R*)-configuration.



Scheme 2. Synthesis of anthraquinone **4**. Reagents and conditions: (a) O_2, *t*-BuOK, *t*-BuOH, rt, 45 min, then Ac_2O, rt, 2 h, 47%; (b) **8**, toluene, 110 °C, 23 h, then pyridine, DMAP, 110 °C, 1.5 h, 70%; (c) TfCl, NaHMDS, HMPA, THF, 0 °C, 5 min, 74%.



Scheme 3. Synthesis of oxazolidine **3**. Reagents and conditions: (a) Tf_2O, pyridine, 0 °C, 5 min, 91%; (b) $PdCl_2(PPh_3)_2$, CuI, *i*-Pr_2NH, toluene, rt, 5 min, quant.; (c) *n*-Bu_3SnOMe, $Pd_2(dba)_3{\cdot}CHCl_3$, 2-diphenylphosphino-2'-(*N*,*N*-dimethylamino)-biphenyl, LiCl, toluene, 110 °C, 5 min, 83 %; (d) NaOMe, MeOH, 60 °C, 1 d; (e) BnBr, $CsCO_3$, HMPA, rt, 12 h, 72% in 2 steps.

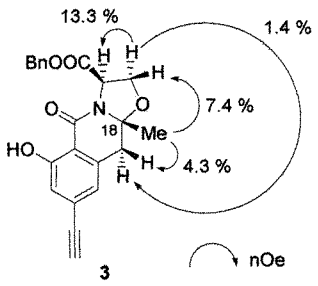
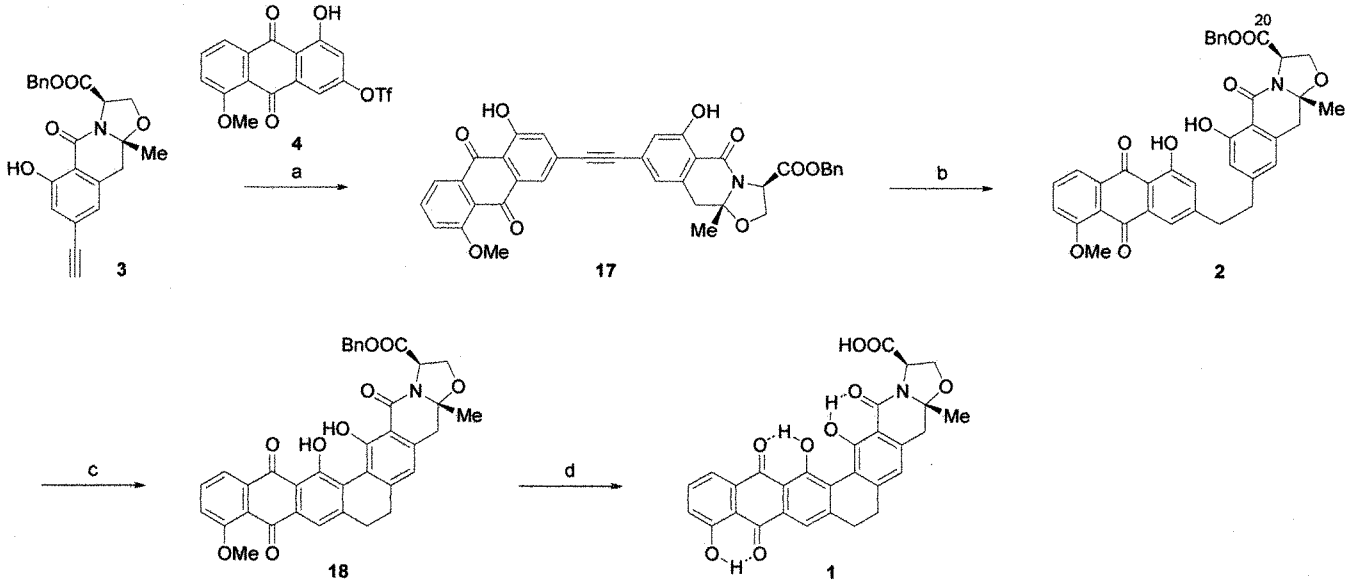


Figure 1. The structural determination of tricyclic **3**.

Connection of fragments **3** and **4** and completion of total synthesis of TMC-66 was shown in Scheme 4. Sonogashira coupling with **3** and **4** proceeded to give hexacyclic **17**, which was reduced selectively at acetylene moiety without cleavage of benzyl group to afford **2**. The next intramolecular oxidative coupling was problematic. Among a variety of known oxidants,[9] only Koga's reagent $[CuCl(OH){\cdot}(TMEDA)_2]$[10] gave the desired heptacyclic **18**, but in low yield (~20%). After a number of experiments, we found that the conditions including $CuCl(OH){\cdot}(NMI)_2$ in refluxing DMF were effective to give the desired **18**. The reaction proceeded regioselectively to afford **18** in 89% yield. The ester group at C20 position on the substrate **2** was essential to the intramolecular oxidative coupling. The carboxylic acid derivative of **2** decomposed under various conditions of oxidative coupling and did not provide the corresponding heptacyclic product. The structure of **18** was confirmed by nOe and HMBC as shown in Figure 2. Correlation between H7 and C8, H12 and C13, and H4 and C19 were observed. Additionally, nOe was observed between H4 and H19. Thus, oxidative coupling product **18** should possess the TMC-66 skeleton. Finally, de-O-methylation accompanied with de-O-benzylation was realized by treatment of **18** with BBr_3 to obtain TMC-66 (**1**). The spectral data of the synthetic **1** was identical with that of the natural TMC-66. The brown solution of the synthetic TMC-66 showed the optical rotation $[\alpha]_D^{27}$ −180° (*c* 0.01, $CHCl_3$), levorotatory as the natural product ($[\alpha]_D^{24}$ −327° (*c* 0.01, $CHCl_3$)).[1] Thus, the total synthesis of TMC-66 was accomplished to determine its absolute configuration as (16*R*,18*R*)-configuration.

The optical purity of the synthetic **1** was confirmed with a chiral 1,2-diphenylethane-1,2-diamine[11] by ^{1}H NMR (Figure 3). The spectrum A is that of a mixture of racemic TMC-66[12] and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine, while the spectrum B is that of a mixture of synthetic (-)-TMC-66 and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine. The peaks around δ 7.75 ppm were corresponding to H7, H11, and H12, and those of δ 4.50 ppm were corresponding to H16, H17 (two protons), and CH-N of the chiral diamine. The spectrum A shows that (+)- and (-)-TMC-66 are distinguishable in the presence of a chiral 1,2-diphenylethane-1,2-diamine. Obviously, the spectrum B is that of highly optical pure TMC-66.



Scheme 4. Total synthesis of TMC-66 (**1**). Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, CuCl, *i*-Pr_2NH – DMF (1 : 5), rt, 5 min, 78%; (b) H_2, $RhCl(PPh_3)_3$, xylene, 120 °C, 1 h, 74%; (c) $CuCl(OH)\cdot(NMI)_2$, DMF, reflux, 1.75 h, 89%; (d) BBr_3, CH_2Cl_2, -78 °C, 30 min, 70%. NMI = *N*-methylimidazole

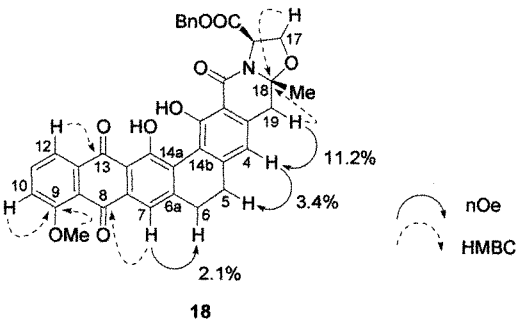


Figure 2. The structural determination of heptacyclic **18**.

In conclusion, the first total synthesis and structural determination of TMC-66 (**1**) have been achieved. The regioselective intramolecular oxidative coupling of **2** was realized in high yield using $CuCl(OH)\cdot(NMI)_2$ as an oxidant. The efficient and stereoselective route to the benzo[*a*]naphthacenequinone fused with a chiral oxazoline ring has been established.

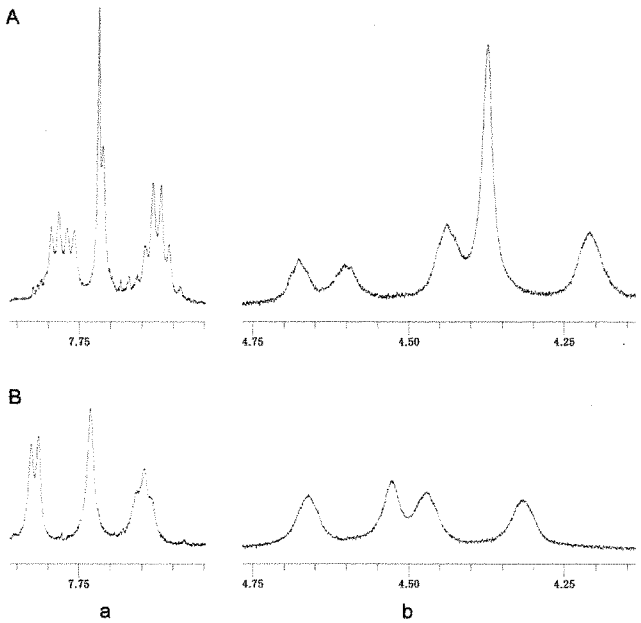


Figure 3. ^{1}H NMR spectra of (**A**): 2:1 mixture of racemic TMC-66 + (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine and (**B**): 2:1 mixture of synthetic (-)-TMC-66 + (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine. (From left side) a: H12, H7, H11, b: H16, H17a, H17b, C<u>H</u>-NH_2 of diamine.

Acknowledgments

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12. Racemic TMC-66 was synthesized from racemic serine by disclosed procedure.

Supplementary Material

The spectrum data of compounds **2**, **3**, **4**, **5**, **17**, **18**, and synthetic **1**, and ^{1}H NMR spectra (600 MHz in $CDCl_3$) of synthetic **1**, a 2:1 mixture of racemic **1** and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine, and a 2:1 mixture of synthetic **1** and (1*R*, 2*R*)-1,2-diphenylethane-1,2-diamine, are presented as supplementary data, which can be found in the online version.

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Total Synthesis of Khafrefungin Using Highly Stereoselective Vinylogous Mukaiyama Aldol Reaction

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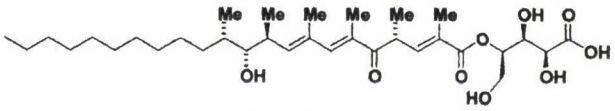
ABSTRACT

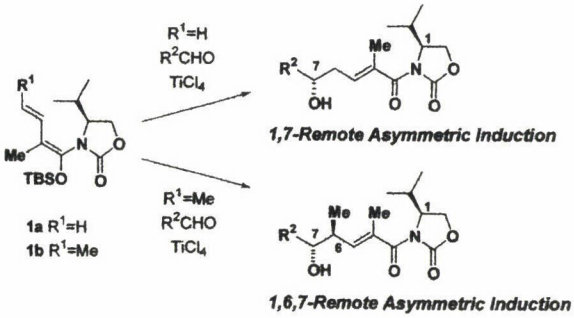


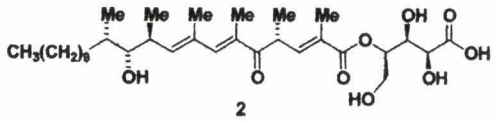
Khafrefungin

A convergent total synthesis of khafrefungin was accomplished on the basis of (1) the highly stereoselective $TiCl_4$-mediated vinylogous Mukaiyama aldol reaction using vinylketene silyl *N,O*-acetal and (2) *syn*-selective aldol reaction of enal 5a and ethyl ketone 6 followed by *anti*-dehydration under Mitsunobu conditions.

We recently reported a highly stereoselective vinylogous Mukaiyama aldol reaction of vinylketene silyl *N,O*-acetal **1**, which also provides a unique and remarkable entry to a remote asymmetric induction (Scheme 1).[1,2] From a synthetic point of view, this method can directly afford the δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl unit that is seen in polyketide natural products.[3] In order to demonstrate the usefulness of our methodology, we investigated the total synthesis of khafrefungin (**2**) (Figure 1). In the polyketide moiety of khafrefungin, we can recognize two sets of the vinylogous Mukaiyama aldol adducts.

Scheme 1. Remote Asymmetric Induction





2

Figure 1. Structure of khafrefungin (**2**).

Khafrefungin (**2**) is an antifungal agent isolated from the fermentation culture MF6020 by a Merck group in 1997.[4] It has been shown to inhibit inositol phosphorylceramide (IPC)

(1) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604.

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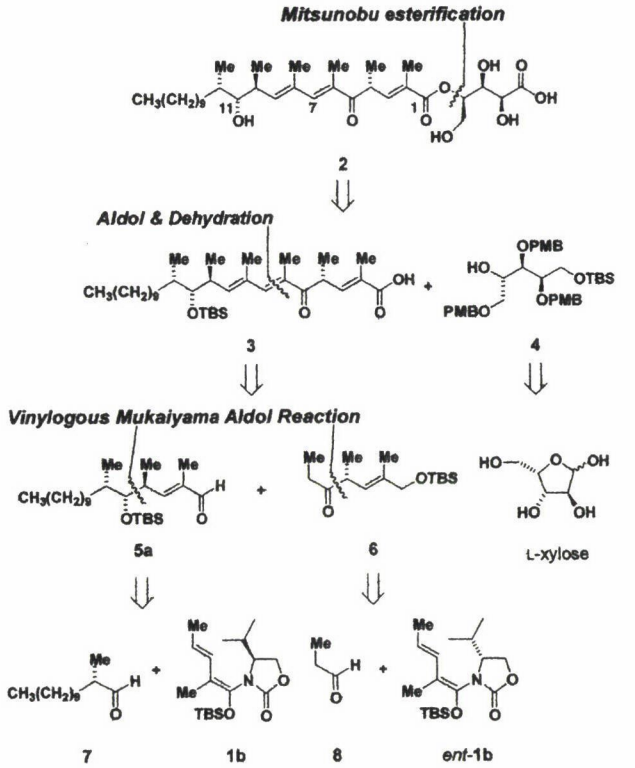
synthase, which catalyzes the fungal specific step in *Saccharomyces cerevisiae* and pathogenic fungi such as *Cryptococcus neoformans* and *Candida albicans* in picomolar and nanomolar concentrations and causes ceramide accumulation.[5] Distinct from other sphingolipid inhibitors such as viridiofungin A, myriocin, and australifungin, khafrefungin does not impair sphingolipid synthesis in mammals. A convergent total synthesis of khafrefungin and its derivatives has been achieved by Kobayashi and co-workers on the basis of their excellent catalytic and enantioselective aldol reaction.[6]

Our retrosynthetic analysis of khafrefungin (**2**) is outlined in Scheme 2. Khafrefungin was divided into two fragments,

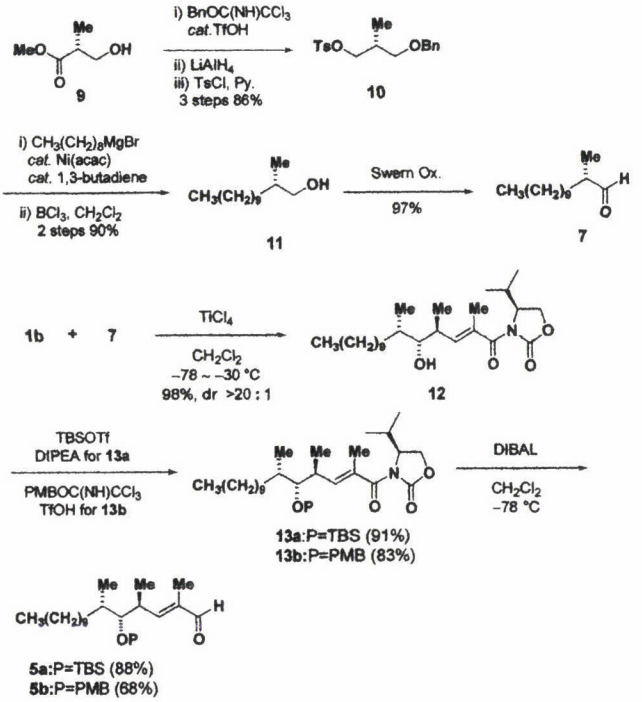
Scheme 2. Retrosynthetic Analysis



the polyketide acid part **3** and the aldonic acid part **4**. We planned to couple these parts by Mitsunobu esterification. Alcohol **4** (aldonic acid part) could be prepared from L-xylose. Polyketide acid **3** could be assembled via the aldol condensation of enal **5a** and ethyl ketone **6** and dehydration. We envisioned that both enal **5a** and ethyl ketone **6** could be stereoselectively prepared by the vinylogous Mukaiyama aldol reaction. According to the above retrosynthetic analysis, enal **5a** could be accessed from chiral aldehyde **7** and the vinylketene silyl *N,O*-acetal **1b** and ethyl ketone **6** from propionaldehyde (**8**) and *ent*-**1b**, respectively.

The synthesis of enal **5a** (Scheme 3) commenced with the

Scheme 3. Synthesis of C7−C22 Fragment



protection of commercially available methyl (*R*)-β-hydroxyisobutyrate (**9**) as a benzyl ether. The benzyl ether was then subjected to a reduction using lithium aluminum hydride and tosylation of the resulting alcohol. The Ni-catalyzed cross-coupling reaction of tosylate **10** with a Grignard reagent using Kambe's protocol[7] provided the benzyl ether in excellent yield, and the benzyl group was cleanly removed by exposure to boron trichloride to obtain chiral alcohol **11**. The primary alcohol **11** was oxidized to give aldehyde **7** using the standard Swern conditions.[8] According to the established protocol, the vinylogous Mukaiyama aldol reaction of chiral aldehyde **7** with the vinylketene silyl *N,O*-acetal **1b** using $TiCl_4$, which proceeded in the matched manifold, afforded the correspond-

(3) For synthetic application of this methodology, see: (a) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333. (b) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 5415. (c) Nakamura, T.; Shirokawa, S.; Hosokawa, S.; Nakazaki, A.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 677. (d) Hosokawa, S.; Kuroda, S.; Imamura, K.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 6183.

(4) Mandala, S. M.; Thornton, R. A.; Rosenbach, M.; Milligan, J.; Garcia-Calvo, M.; Bull, H. G.; Kurtz, M. B. *J. Biol. Chem.* **1997**, *272*, 32709.

(5) Reviews: (a) Kolter, T.; Sandhoff, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1532. See also: (b) Mandala, S. M.; Harris, G. H. *Methods Enzymol.* **2000**, *311*, 335−348. (c) Dickson, R. C. *Annu. Rev. Biochem.* **1998**, *67*, 27. (d) Other IPC inhibitors: Nagiec, M. M.; Nagiec, E. E.; Baltisberger, J. A.; Wells, G. B.; Lester, R. L.; Dickson, R. C. *J. Biol. Chem.* **1997**, *272*, 9809. (e) Mandala, R. A.; Thornton, R. A.; Milligan, J.; Rosenbach, M.; Garcia-Calvo, M.; Bull, H. G.; Harris, G.; Abruzzo, G. K.; Flattery, A. M.; Gill, C. J.; Bartizal, K.; Dreikorn, S.; Kurtz, M. B. *J. Biol. Chem.* **1998**, *273*, 14942.

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(7) (a) Terao, J.; Watanabe, H.; Ikumi, A.; Kuniyasu, H.; Kambe, N. *J. Am. Chem. Soc.* **2002**, *124*, 4222. (b) Terao, J.; Kambe, N. *Bull. Chem. Soc. Jpn.* **2006**, *5*, 663.

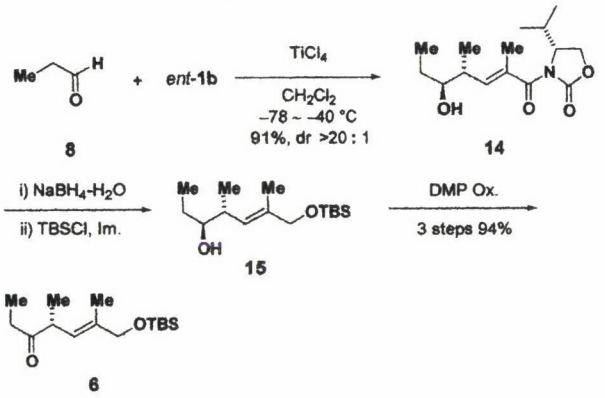
(8) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

ing C(10)−C(11) *anti*-aldol adduct **12** in 98% yield with >20:1 diastereoselectivity.

The secondary hydroxyl group of the aldol adduct **12** was protected as the *tert*-butyldimethylsilyl (TBS) ether by the reaction with *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and diisopropylethylamine (DIPEA). The *p*-methoxybenzyl (PMB) ether **13b** was provided by reaction with PMB trichloroacetimidate and a catalytic amount of trifluoromethanesulfonic acid.[9] Reductive removal of the chiral auxiliary in **13a** and **13b** using DIBAL produced the aldehyde **5a** and **5b**, respectively. The stereochemistry of **5b** (thus **12**) was confirmed by comparison of the spectral data with those reported by Kobayashi.[6a]

The C(1)−C(6) ethyl ketone **6** was synthesized starting from propionaldehyde (**8**) as summarized in Scheme 4. The

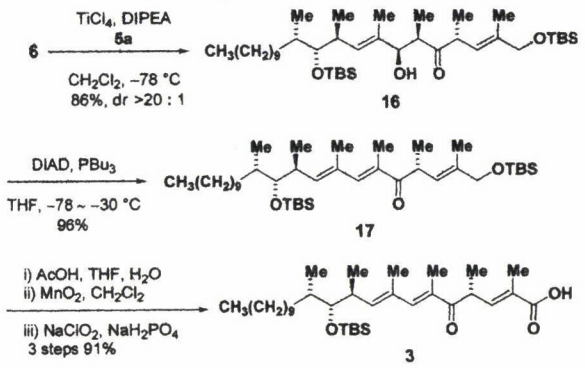
Scheme 4. Synthesis of C1−C6 Fragment



vinylogous Mukaiyama aldol reaction of propionaldehyde with the vinylketene silyl *N,O*-acetal ***ent*-1b** using $TiCl_4$ afforded the corresponding *anti*-aldol adduct **14** in 91% yield with high diastereomeric ratio (>20:1 dr). Reductive removal of the chiral auxiliary, followed by the protection of the resulting primary alcohol as a TBS ether, and Dess-Martin oxidation of the secondary alcohol provided ethyl ketone **6**.[10]

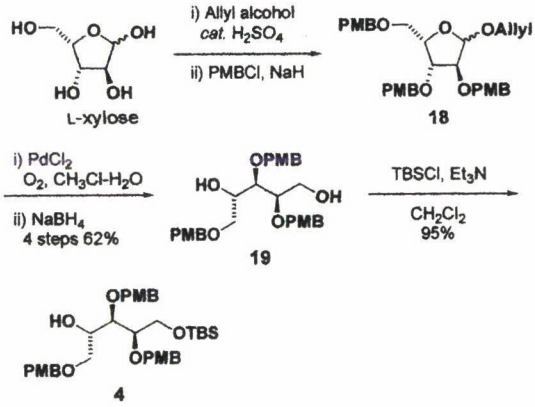
Aldol condensation of ethyl ketone **6** and enal **5a** was accomplished by using $TiCl_4$ and DIPEA in CH_2Cl_2 at −78 °C to afford *syn*-aldol adduct **16** in 86% yield (Scheme 5).[11] We then attempted an *anti*-dehydration of **16**. However, most of the typical *anti*-dehydration methods (MsCl/DMAP/Py, MsCl/Et_3N/CH_2Cl_2, TFAA/2,6-lutidine/CH_2Cl_2 followed by HCl/acetone, and $SOCl_2$/Py/CH_2Cl_2) were unsuccessful. In contrast, the desired dienone **17** was obtained in 96% yield under Mitsunobu conditions (DIAD and tributylphosphine in THF at −30 °C).[12] Dienone **17** was converted to acid **3** in 91% yield for the three steps by selective cleavage of the primary TBS ether followed by MnO_2 oxidation and $NaClO_2$ oxidation.[13]

Scheme 5. Fragment Assembly Aldol Reaction



The aldonic acid part **4** was prepared from L-xylose (Scheme 6). Thus, the allyl glycosidation of L-xylose was

Scheme 6. Synthesis of Aldonic Acid Part



carried out by treatment with allyl alcohol, and the remaining hydroxyl groups were protected with the PMB group. Deprotection of the allyl group was successfully performed with $PdCl_2$ in $CHCl_3/H_2O$ under an O_2 atmosphere to give the hemiacetal, which on subsequent reduction with sodium borohydride in MeOH provided the diol in 62% yield for the four steps.[14] The resulting diol was protected selectively as its TBS ether to give secondary alcohol **4**.

With both segments in hand, we next carried out an esterification of the secondary alcohol **4** with the unsaturated acid **3** under Mitsunobu conditions to afford the desired ester **20** in 86% yield (Scheme 7). The primary TBS ether was selectively deprotected with AcOH/THF/H_2O, and the resultant primary alcohol was oxidized to a carboxylic acid **21** by a two-step sequence [(i) Dess−Martin oxidation; (ii) $NaClO_2$ oxidation]. Finally, deprotection of the secondary TBS ether and three PMB ethers with 25% TFA/CH_2Cl_2 completed the total synthesis of khafrefungin (**2**). The spectroscopic data

(9) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139.
(10) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
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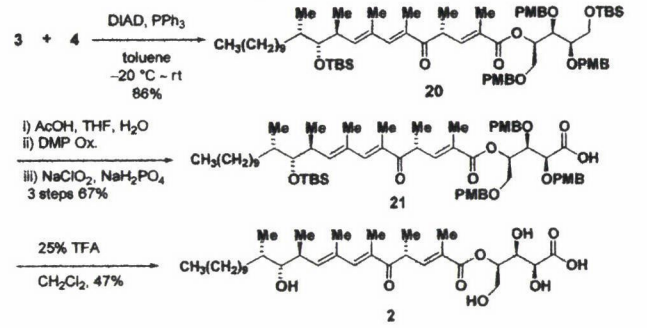
(12) Mitsunobu, O. *Synthesis* **1981**, 1.
(13) Bal, B. S.; Chiders, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
(14) (a) Mereyala, H. B.; Guntha, S. *Tetrahedron Lett.* **1993**, *34*, 6929. (b) Mereyala, H. B.; Lingannagura, S. R. *Tetrahedron* **1997**, *53*, 17501.

Scheme 7. Completion of the Total Synthesis



(^{1}H NMR, ^{13}C NMR, IR, HRMS, optical rotaiton) were in all respects identical to the data reported by Kobayashi and co-workers.[6a]

In summary, we were able to achieve a convergent synthesis of khafrefungin. Key transformations in the sequence included (i) construction of the C(1)−C(5) and C(7)−C(11) δ-hydroxy-α,γ-dimethyl-α,β-unsaturated carbonyl unit using the vinylogous Mukaiyama aldol reaction and (ii) *syn*-selective aldol condensation and *anti*-dehydration under Mitsunobu conditions.

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Supporting Information Available: Experimental details and spectroscopic data for compounds **2**−**4**, **5a**, **6**, **12**, **14**, **17**, and **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Enantioselective Total Synthesis of Convolutamydines B and E

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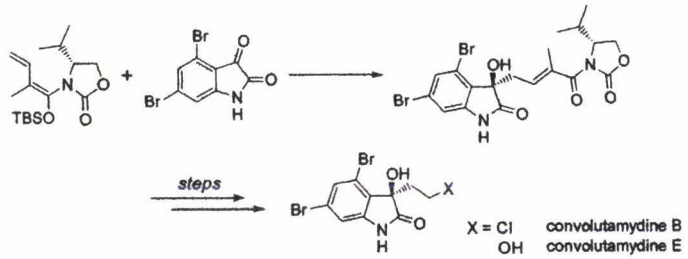
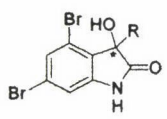
ABSTRACT



The first enantioselective total synthesis of convolutamydines B and E has been achieved using our vinylogous Mukaiyama aldol reaction. The synthesis features highly diastereoselective vinylogous Mukaiyama aldol reaction with isatin instead of aldehydes to construct a chiral center of convolutamydines. Additionally, the absolute configuration of natural convolutamydine B has been determined as *R* by its CD spectrum.

Convolutamydines A−E (**1**−**5**) isolated from the Floridian marine bryozoan *Amathia convoluta* by Kamano et al. are members of a family of oxindole alkaloids having a 4,6-dibromo-3-hydroxyoxindole as a common skeleton (Figure 1).[1] Each convolutamydine differs in a side chain moiety at C-3. Convolutamydines A and B (**1**, **2**) induce the appearance of characteristic features, associated with normally differentiated cells, in the tumor cell line HL-60. The possible biological effects of the other convolutamydines (C−E, **3**−**5**) have not been evaluated due to the scarcity of these derivatives. Furthermore, the stereochemistry of the chiral center at C-3 has not yet been established. The 3*R* configuration was assumed on the basis of the empirical rule for the correlation of CD spectra and absolute configuration proposed by Aimi et al.[2] Although syntheses of convolutamydines (A, C, and E) have already been reported by several groups, these have all been of racemic compounds.[3]



Convolutamydine A ; R= -CH_2COCH_3 (**1**)
B ; R= -CH_2CH_2Cl (**2**)
C ; R= -CH_3 (**3**)
D ; R= -$CH{=}CH_2$ (**4**)
E ; R= -CH_2CH_2OH (**5**)

Figure 1. Structures of convolutamydines A−E (**1**−**5**).

These facts prompted us to attempt an enantioselective synthesis of convolutamydines in order to determine the absolute stereochemistry as well as to provide these compounds for biological study. The most straightforward approach to this class of compounds is apparently a nucleo-

(1) (a) Kamano, Y.; Zhang, H.-P.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Pettit, G. R. *Tetrahedron Lett.* **1995**, *36*, 2783−2784. (b) Zhang, H.-P.; Kamano, Y.; Ichihara, Y.; Kizu, H.; Komiyama, K.; Itokawa, H.; Pettit, G. R. *Tetrahedron* **1995**, *51*, 5523−5528. (c) Kamano, Y.; Kotake, A.; Hashima, H.; Hayakawa, I.; Hiraide, H.; Zhang, H.-P.; Kizu, H.; Komiyama, K.; Hayashi, M.; Pettit, G. R. *Collect. Czech. Chem. Commun.* **1999**, *64*, 1147−1153.

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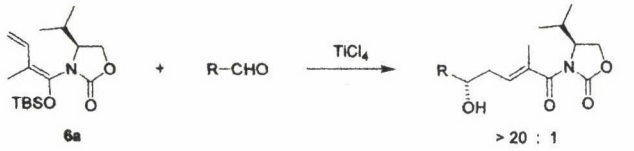
philic addition of an appropriate nucleophile to 4,6-dibromoisatin; however, such a strategy was employed only for the synthesis of convolutamydine A by base-mediated aldol reaction racemic with acetone. To the best of our knowledge, the first example of enantioselective addition (up to 77% ee) to isatin was very recently reported by Tomasini et al. using organocatalysis.[4] We recently developed a highly stereoselective vinylogous Mukaiyama aldol reaction using vinylketene silyl *N,O*-acetal **6a** (Scheme 1).[5] Substrates for

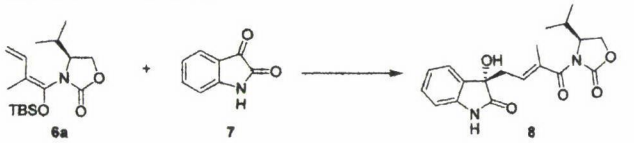
Scheme 1. Vinylogous Mukaiyama Aldol Reaction



vinylogous Mukaiyama aldol reaction were limited to aldehydes, and we were also interested in the reaction with isatin derivatives.

Prior to the reaction with 4,6-dibromoisatin, we used isatin **7** as a model substrate in order to establish the optimal conditions (Table 1). As per the previous protocol, titanium

Table 1. Optimization of Vinylogous Mukaiyama Aldol Reaction with Isatin (**7**)



entry	method	isatin (equiv)	$TiCl_4$ (equiv)	concn (mM)	T (°C)	yield (%)	dr[a]
1	A	2.0	2.0	10	−78 to −20	32	9:1
2	A	4.0	2.0	5	−78 to −20	60	30:1
3	A	6.0	2.0	5	−78 to −20	90	31:1
4	A	6.0	3.0	5	−78 to −20	50	23:1
5	B	6.0	2.0	5	−78	69	60:1

[a] Determined by ^1H NMR analysis.

tetrachloride (2 equiv) was added to the dichloromethane solution of isatin **7** at −78 °C, followed by the dropwise addition of **6a** (method A). Then the reaction mixture was stirred at −20 °C to obtain **8** in 32% yield. It was quite interesting to find that the reaction proceeded in a stereoselective manner (9:1 ratio).[6]

High yield with excellent selectivity was observed by using an excess of isatin **7** (6 equiv) in 5 mM concentration (entry 3). A large excess of $TiCl_4$ decreased both chemical yield and selectivity (entry 4). However, method A did not afford **8** in a reproducible manner. During these experiments, we observed that the reaction mixture becomes homogeneous when $TiCl_4$ was added. Therefore, we attempted to change the order of addition. Thus, the mixture of isatin **7** and $TiCl_4$ in dichloromethane was stirred at 0 °C for 30 min before addition of **6a** at −78 °C (Method B). This procedure afforded **8** in good yield with excellent selectivity and reproducibility (entry 5). The observed stereoselectivity is noteworthy considering (1) the high degree of remote asymmetric induction and (2) the electrophile is a ketone, albeit it is a part of ketoamide.

$TiCl_4$-mediated reaction of *Z*-vinylketene *N,O*-acetal **6b** and isatin **7** was also attempted, producing the corresponding adduct in relatively low yield with a 1.7:1 diastereomeric ratio. These differences in chemical yield and selectivity are in good agreement with the previous results using aldehydes.[5] For the introduction of a C2 unit as the side chain of a convolutamydine, it may be more suitable to introduce an acetate unit rather than crotonate unit. Consequently, isatin **7** was also subjected to an aldol reaction with **6c** and **6d** under typical Evans and Mukaiyama conditions, respectively. In both cases, the corresponding aldol adduct was isolated in relatively low yield with low selectivity as shown in Figure 2. Therefore, only the vinylogous Mukaiyama aldol reaction

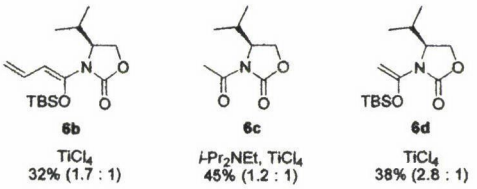


Figure 2. Typical nucleophiles for aldol reaction.

using **6a** proceeded in a stereoselective manner.

We reported that vinylketene *N,O*-acetal **6a** had a conformation such that the dienolate was orthogonal to the oxazolidin-2-one.[5] Approach of isatin **7** from the upper face of the dienolate plane should be hindered by steric interaction with the isopropyl group of the chiral auxiliary (Figure 3,

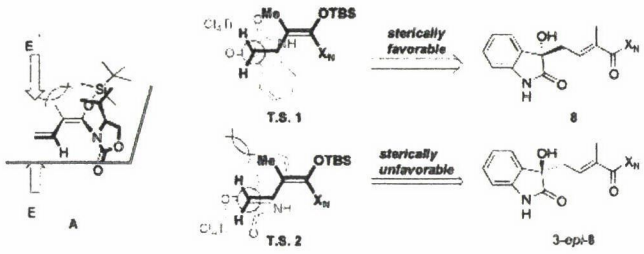


Figure 3. Transition states of vinylogous Mukaiyama aldol reaction (X_N = oxazolidinone.)

(4) Luppi, G.; Cozzi, P. G.; Monari, M.; Kaptein, B.; Broxterman, Q. B.; Tomasini, C. *J. Org. Chem.* **2005**, *70*, 7418−7421.

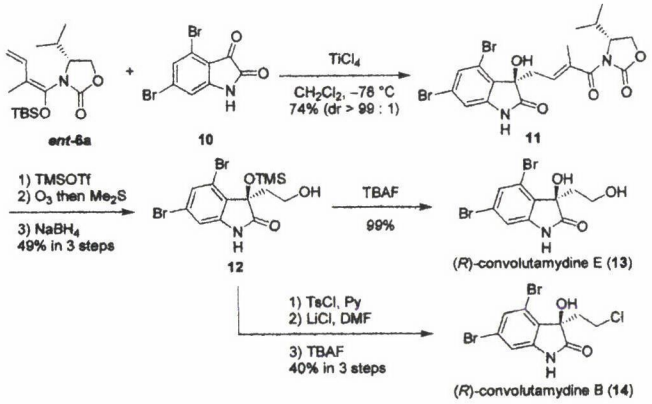
(5) Shirokawa, S.-i.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604−13605.

(6) See the Supporting Information for determination of the stereochemistry.

A). In addition, transition state 1 (**T.S.1**) is sterically more favorable than transition state 2 (**T.S.2**) because in **T.S.2** the methyl group at the α-position of vinylketene *N,O*-acetal **6a** can sterically interact with the aromatic ring of isatin **7** (Figure 3).

With optimal conditions established, we next applied the present protocol to the total syntheses of both enantiomers of convolutamydines E and B and to the determination of their absolute configurations. According to Aimi's estimation,[2] we first attempted the synthesis of (*R*)-convolutamydines which would be synthesized from 4,6-dibromoisatin **9**[7] and vinylketene *N,O*-acetal *ent*-**6a** derived from D-valine (Scheme 2).

Scheme 2. Total Synthesis of Convolutamydines B and E



The vinylogous Mukaiyama aldol reaction of 4,6-dibromoisatin **9** and *ent*-**6a** proceeded smoothly to afford aldol adduct **10** quantitatively almost as a single isomer. Aldol adduct **10** was then converted into a common intermediate **11** in three steps. (*R*)-Convolutamydine E (**12**) was obtained from **11** by removal (99%) of the TMS group in **11**.[6] The synthesis of (*R*)-convolutamydine B (**13**) was also achieved by the simple transformations from **11** [tosylation, chlorination, followed by desilylation (40% yield in three steps)]. In the same manner, (*S*)-convolutamydines B (*ent*-**13**) and E (*ent*-**12**) were also synthesized from vinylketene *N,O*-acetal **6a** derived from L-valine. In all cases, the synthetic convolutamydines were in high enantiomeric excess (>97% ee) as determined by chiral HPLC analyses, and spectral data (^{1}H and ^{13}C NMR) and HRMS data were identical with those of natural products.

(7) (a) Shepherd, R. G. *J. Org. Chem.* **1947**, *12*, 275−283. (b) Carlin, R. B.; Forshey, W. O., Jr. *J. Am. Chem. Soc.* **1950**, *72*, 793−801. (c) Sandmeyer, T. *Helv. Chim. Acta* **1919**, *2*, 234−242.

With both enantiomers in hand, we next attempted to determine the absolute configurations of convolutamydines B and E by the comparison of the optical rotations.[1b,c] However, the $[\alpha]_D$ value of **13** and *ent*-**13** ($[\alpha]^{28}_D$ <1 for both **13** and *ent*-**13**) were much lower than the reported data ($[\alpha]^{25}_D$ +18) for natural convolutamydine B.[1b] Despite the disagreement of these optical rotations, the CD spectrum of *R*-isomer **13** was perfectly matched with that of the natural product; **13** exhibits a negative Cotton effect in the long-wave region (285−245 nm) and a positive effect in the short-wave region (245−210 nm), while *ent*-**13** exhibits exactly the opposite behavior (Figure 4). Accordingly, convolutamydine B was unambiguously established as *3R*. Unfortunately, neither the $[\alpha]_D$ value nor the CD spectrum of convolutamydine E have been reported, so we have been unable to determine the absolute configuration of convolutamydine E.

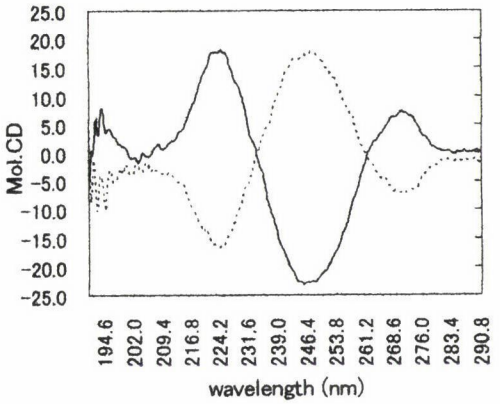


Figure 4. CD spectra of **13** (*R*-isomer, solid curve) and *ent*-**13** (*S*-isomer, dashed curve).

In summary, we have developed a highly stereoselective addition to a isatin derivative for the first time by vinylogous Mukaiyama aldol reaction. We also achieved the enantioselective synthesis of convolutamydines B and E and determined the absolute configuration of convolutamydine B.

Acknowledgment. We thank Prof. Kenso Soai and Dr. Itaru Sato (Tokyo University of Science) for the measurement of circular dichroism spectra.

Supporting Information Available: Detail experimental procedure and characterization data for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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THE CHEMICAL RECORD

Total Syntheses of Polyketide-Derived Bioactive Natural Products

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ABSTRACT: Recent progress of total syntheses in our laboratory has been described along with our background and methodologies. The target bioactive polyketides are classified into three categories according to their structures: (i) lactone-fused polycyclic compounds [(+)-cochleamycin A, (+)-tubelactomicin A, and (−)-tetrodecamycin], (ii) aromatic compounds [(−)-tetracycline, (−)-BE-54238B, lymphostin, and (−)-lagunamycin], and (iii) acyclic polyketides [xanthocillin X dimethylether, (+)-trichostatin D, and (+)-actinopyrone A]. Features of the total syntheses are described. Original methodologies have been developed and applied to construct the inherent structures of the target molecules. Most syntheses cited herein are the first total syntheses, and the absolute structures of the target molecules have been determined. © 2006 The Japan Chemical Journal Forum and Wiley Periodicals, Inc. Chem Rec 6: 217–233; 2006: Published online in Wiley InterScience (www.interscience.wiley.com) DOI 10.1002/tcr.20084

Key words: polyketides; total synthesis; natural products; synthetic design; synthetic methods

Introduction

When a stone is thrown into a pond, several waves are produced in succession, gradually spreading until they finally cover the whole pond. The first total synthesis of bioactive natural products is a stone thrown into the pond of the chemistry of natural products. In particular, the first total syntheses require the creation of original concepts and synthetic methodologies, and include the assignment of the absolute structure of bioactive natural products as well as verification of their biological activities.

This review concentrates on the new waves in our total syntheses of polyketide-derived natural products to emphasize our synthesis philosophy and concept as well as our strategies and methodologies.[1]

Total syntheses of the following bioactive polyketides are addressed: cochleamycin A, tubelactomicin A, tetrodecamycin, tetracycline, BE-54238B, lymphostin, lagunamycin, xanthocillin X dimethylether, trichostatin D, and actinopyrone A. These molecules are classified into three categories: (i) lactone-fused polycyclic compounds (cochleamycin A and tubelactomicin A), (ii) aromatic compounds (tetrodecamycin, tetracycline, BE-54238B, lymphostin, and lagunamycin), (iii) and acyclic polyketides (xanthocillin X dimethylether, trichostatin D, and actinopyrone A). Although each category contains numerous natural products, every molecule cited herein has an inherent structure, for which we have elaborated the skeleton, oxidation stage, and arrangement of functional groups with stereogenic centers.

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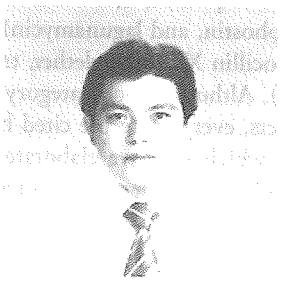
Total Syntheses of Lactone-Fused Natural Products

Macrolides have attracted chemists with their elegant figures and remarkable bioactivities, and have contributed to the growth of synthetic organic chemistry including the methodologies of stereoselective construction of a carbon chain, organometallic chemistry, macrocyclization, and stereoselective glycosylation as well as protection of functional groups. Many chemists stepped into the unknown forest to reach the top of the mountain. In the 1980s, endeavors in our laboratory were rewarded with the achievement of total syntheses of some bioactive macrolides including tylosin (**1**),[2] oleandomycin (**2**),[3] and rifamycin W (**3**).[4] In developing screening methods and analytical technology, chemists discovered macrolides bearing various bioactivities and disclosed their complex structures. Recently, complicated lactone compounds fused to carbocyclic systems such as cochleamycin A (**4**),[5] tubelactomicin A (**5**),[6] and tetrodecamycin (**6**)[7] were found. In this chapter, we present our recent results of synthetic studies on these compounds.

Total Synthesis of (+)-Cochleamycin A

Cochleamycin A (**4**) was isolated by the Kirin Brewery group from a cultured broth of *Streptomyces* sp. to show cytotoxicity against P388 leukemia cells and antimicrobial activities.[8] The structure, including the relative stereochemistry, was revealed by exhaustive nuclear magnetic resonance (NMR) studies to be endowed with a 5-6-10-6-membered tetracyclic core (Fig. 1).[9] Not surprisingly, the combination of architectural complexities and bioactivities produced considerable interest, resulting in impressive synthetic studies from two other groups.[10,11] Both groups used "transannular" Diels–Alder reactions to construct a cochleamycin skeleton, because the formation of a 10-membered ring was well known to be difficult.

Kuniaki Tatsuta received his Ph.D. from Keio University, Japan, in 1969 working under the direction of Professor S. Umezawa and joined the faculty as Assistant Professor. Immediately after he was appointed as Assistant Professor in 1973, he joined Professor R. B. Woodward's group at Harvard University as Postdoctoral Fellow (1973–1975) and, in 1985, was promoted to Professor of Organic Chemistry, Keio University. In 1993, Dr. Tatsuta moved to Waseda University as Professor of Bioactive Substances Science and, in 2004, was appointed as Dean of the Graduate School of Science and Engineering. He has been a Visiting Professor at Cambridge University and at Paris VI University in 1988 and 1994, respectively. Professor Tatsuta is the recipient of the Divisional Award of the Chemical Society of Japan (1986), Award of the Synthetic Organic Chemistry Japan (1998), Distinguished Award of the Chemical Society of Japan (2001), and the Imperial Medal with Purple Ribbon of Japan (2002). His research focuses on the total syntheses of bioactive natural products to develop new medicines as well as strategies, and he has already accomplished the total syntheses of 91 kinds of natural products including representative compounds of the so-called big four antibiotics: aminoglycoside, β-lactam, macrolide, and tetracycline. In 1988, his anticancer agent, THP-adriamycin, was marketed as pirarubicin. ■



Seijiro Hosokawa was born in Kurashiki, Japan, in 1968. He received his B.S. and M.S. degrees from Hokkaido University under the supervision of Professor Haruhisa Shirahama, and his Ph.D. from Nagoya University under the supervision of Professor Minoru Isobe in 1996. After a year of postdoctoral research at Nagoya University and one additional year at the Scripps Research Institute under the supervision of Professor K. C. Nicolaou, he was appointed an Assistant Professor in Susumu Kobayashi's group at the Tokyo University of Science. In 2003, he moved to Dr. Tatsuta's group at Waseda University. His research interests include the development of new synthetic methods and the synthesis of bioactive compounds. ■

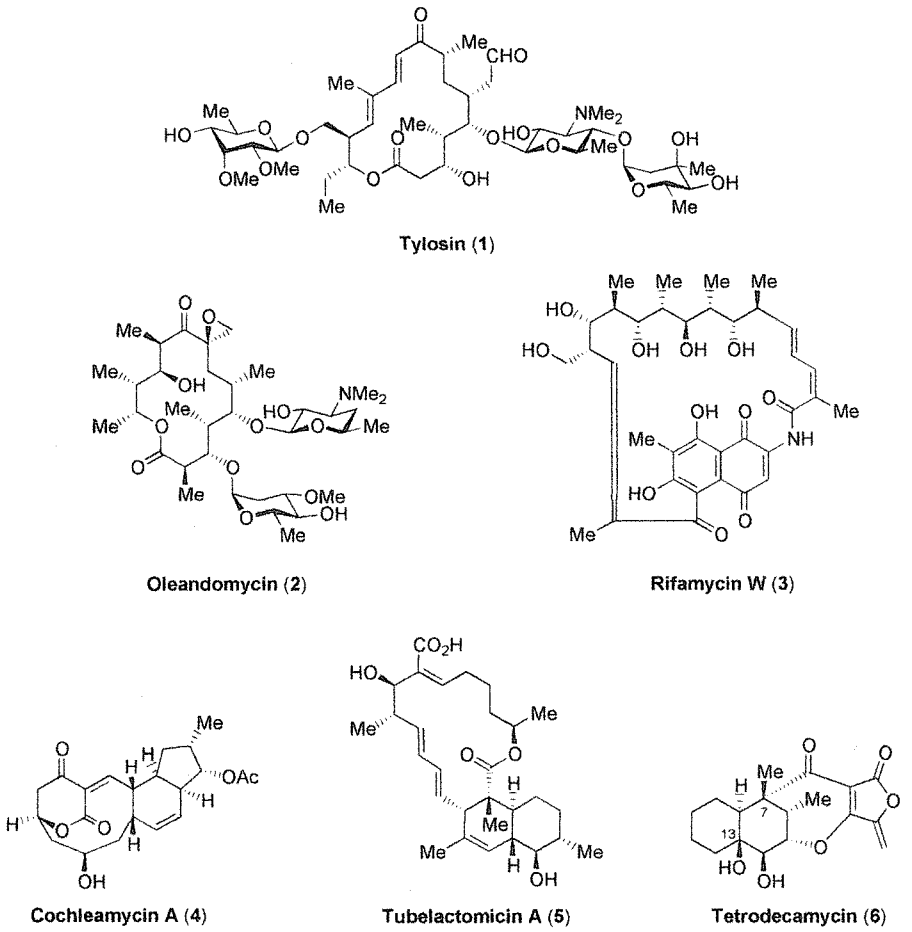


Fig. 1. Macrolides and lactone-fused natural products.

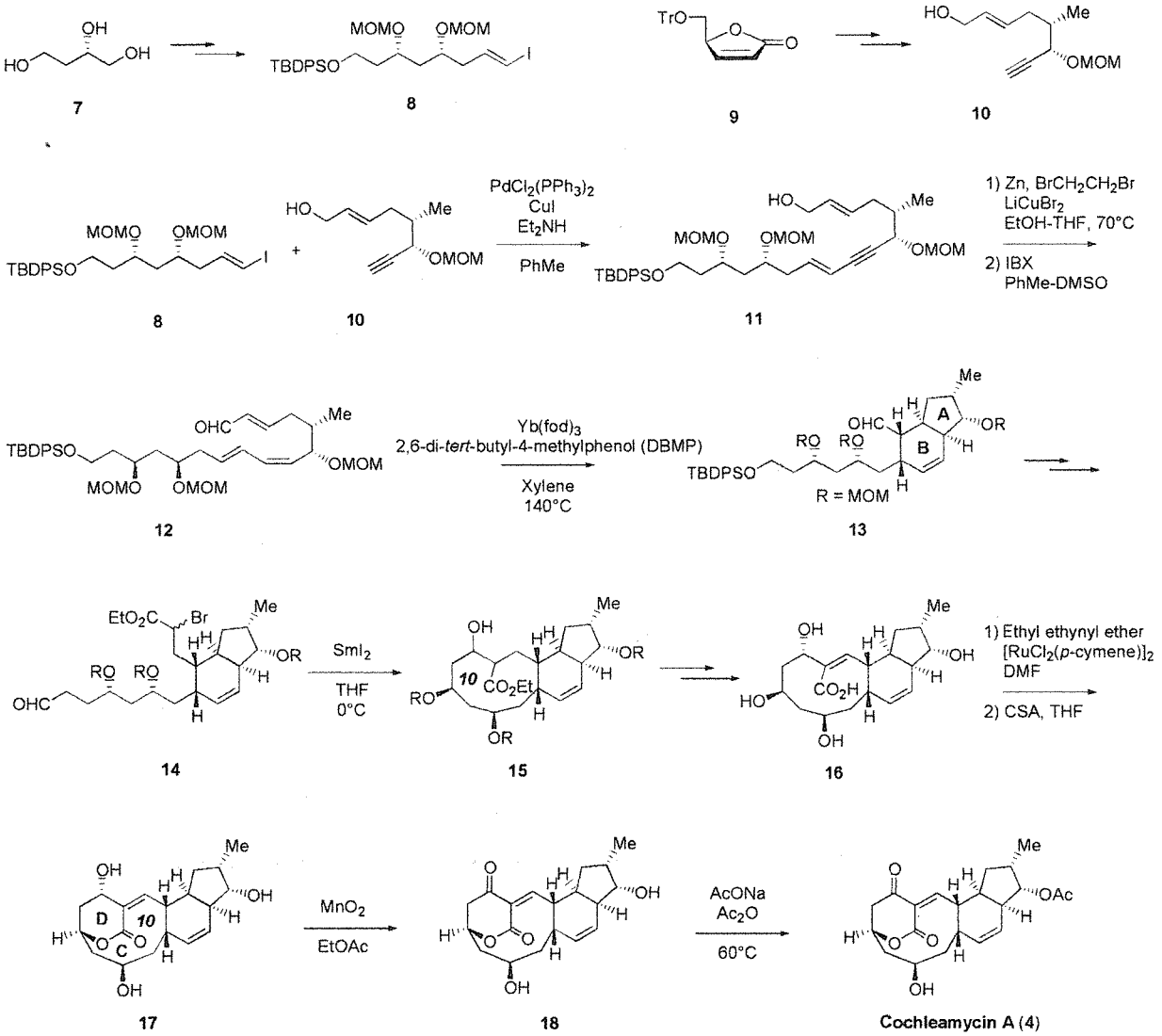
We used an "intramolecular" Diels-Alder reaction followed by direct construction of the 10-membered rings. Here, we describe the first total synthesis of cochleamycin A (**4**) accomplished in our laboratory.[5]

The first total synthesis of cochleamycin A to determine the absolute structure was achieved as shown in Scheme 1.

Coupling of **8** and **10**, derived from **7** and **9**, respectively, proceeded smoothly to give an alcohol **11** in quantitative yield. This was selectively reduced to the *cis,trans*-diene structure, which was crucial to the construction of the desired A–B ring by intramolecular Diels–Alder reaction. Oxidation of allylic alcohol gave the α,β-unsaturated aldehyde **12**, which was submitted to intramolecular Diels–Alder reaction in the presence of $Yb(fod)_3$ at 140°C.[12] The desired adduct **13** was obtained as a single product from **11** in 70% yield. This intramolecular Diels–Alder reaction produced four critical stereocenters as expected. After conversion of **13** to the α-bromoester **14**, the precursor of a 10-membered ring, the desired cyclization of **14** was accomplished with SmI_2 to give 10-6-5-membered tricyclic product **15** as a single product,[13] including the fully elaborated structure ready for conversion to the requisite seco acid **16**. Each of the four hydroxyl groups of **16** was discriminated from the others. Lactonization of **16** was tested under various conditions to construct the C—D ring and the best result was realized by using Kita's conditions[14] to afford the other 10-membered lactone **17**, which possessed a δ-lactone ring. The allylic alcohol of the lactone **17** was oxidized to an α,β-unsaturated ketone **18** by exposure to MnO_2. Finally, selective acetylation was accomplished with NaOAc and Ac_2O at 60°C to afford cochleamycin A (**4**). The synthetic **4** was identical in all respects with natural cochleamycin A including optical rotation, completing the first total synthesis that established the absolute structure.

Total Synthesis of (+)-Tubelactomicin A

Tubelactomicin A (**5**) (Fig. 1) was isolated from a culture broth of *Nocardia* sp. MK703-102F1 to show strong, specific antimi-

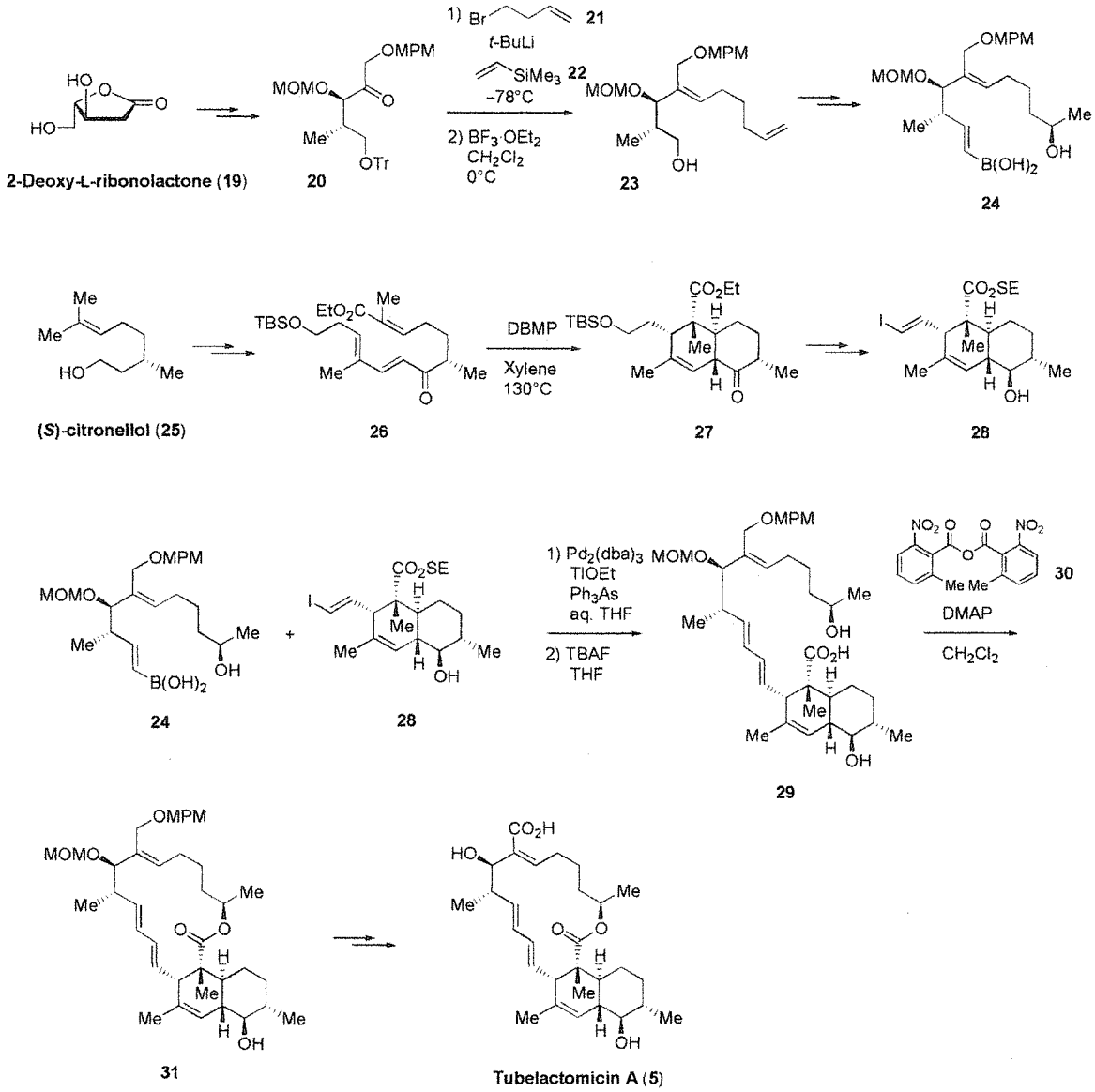


Scheme 1. Total synthesis of cochleamycin A. IBX, *o*-iodoxybenzoic acid; DMF, dimethylformamide; TBDPSO, oxygen attached with *tert*-butyldiphenylsilyl; DMSO, dimethyl sulfoxide; CSA, 10-camphorsulfonic acid; THF, tetrahydrofuran.

crobial activities against drug-resistant mycobacterium.[15] The structure was determined by X-ray crystallographic analysis to be the 16-membered lactone fused with a *trans*-decalin skeleton. As the morbidity of tuberculosis with drug-resistant strains increases worldwide, new, effective drugs are needed for treatment of *Microbacterium tuberculosis*.[16] Its interesting chemical structure, combined with its antitubercular activities, has made (+)-tubelactomicin A (**5**) an attractive target for synthesis, although total synthesis has already been accomplished by the Tadano group using an intramolecular Diels–Alder reaction.[17] Independently, we accomplished the total synthesis of (+)-tubelactomicin A (**5**), which is presented in (Scheme 2).[6]

The stereochemical array of the northern part (**24**) was derived from 2-deoxy-L-ribonolactone (**19**). 2-Deoxy-L-ribonolactone (**19**) was converted to ketone **20**, which was submitted to the three-component connection with bromide **21**, *t*-BuLi, and vinylsilane **22** followed by elimination under acidic conditions to obtain the tri-substituted olefin **23** as a single isomer. Further transformation of the olefin **23** gave the northern part **24**. In contrast, the decalin moiety (**28**), the southern part of tubelactomicin A, was constructed by an intramolecular Diels–Alder reaction.[5,18] (*S*)-Citronellol (**25**) was converted to the triene **26**. The stereoselective Diels–Alder reaction to construct four additional chiral centers was realized by heating **26** in xylene, which gave **27** as a single product. The decalin **27** was converted to alcohol **28** to couple with the northern part **24**.

Treatment of the mixture of **24** and **28** under the conditions of Suzuki coupling and the following deprotection gave



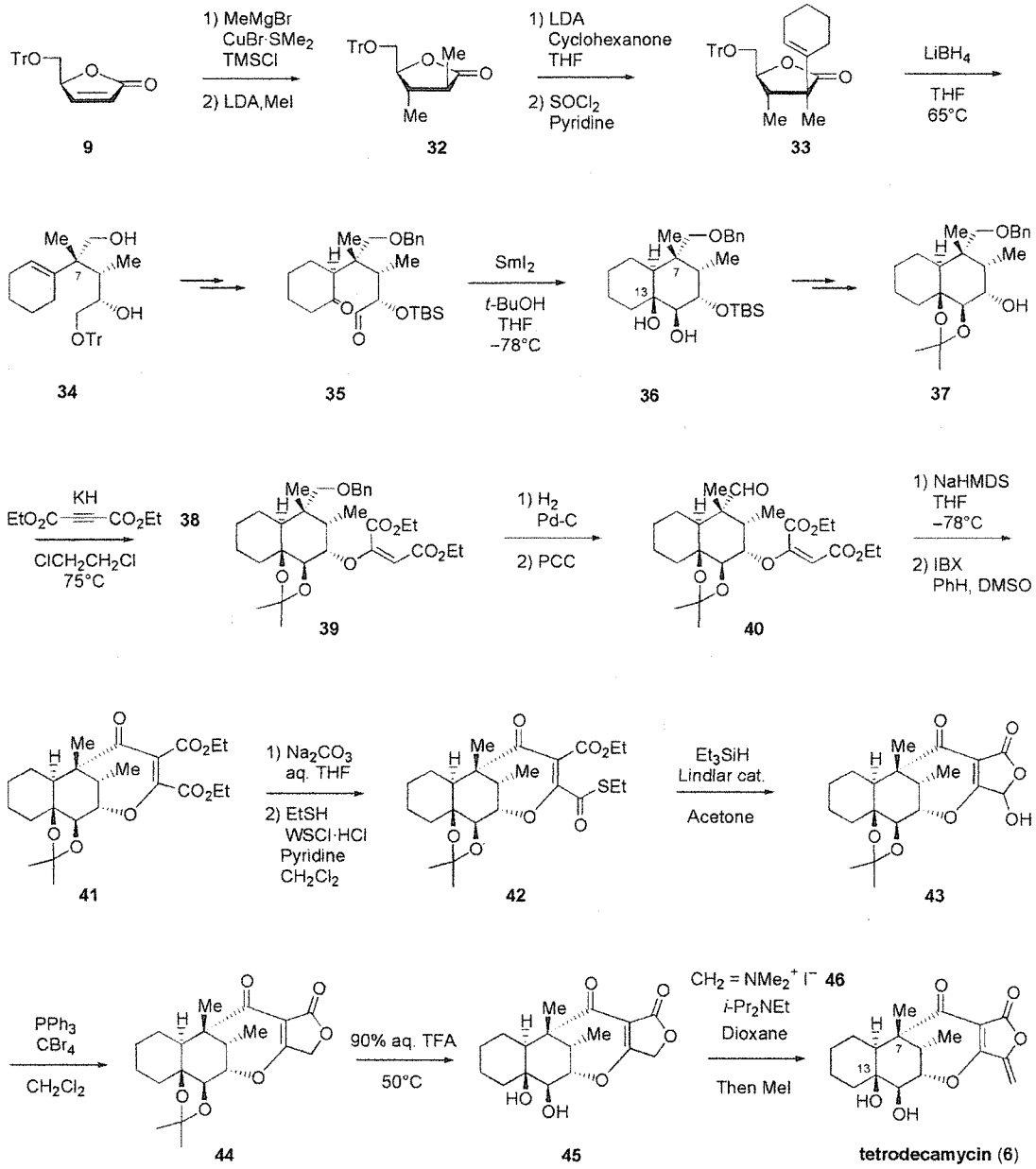
Scheme 2. Total synthesis of tubelactomicin A. TBAF, tetrabutylammonium fluoride; DMAP, 4-dimethylaminopyridine; TBSO, oxygen attached with *tert*-butyldimethylsilyl.

the tetraene product **29**.[19] The seco-acid derivative **29** was submitted to the macrolactonization by the Shiina method[20] to construct the lactone **31**. Deprotection and selective oxidation afforded (+)-tubelactomicin A (**5**).

Total Synthesis of (−)-Tetrodecamycin

(−)-Tetrodecamycin (**6**) (Fig. 1) was isolated from a culture broth of *Streptomyces* sp. MJ885mF8 to show antimicrobial activities especially against *Pasteurella piscicida*.[21] The structure is distinguished by X-ray crystallography as a tetronic acid-containing tetracyclic skeleton, one cyclohexane ring of which is fully and diversely substituted.[22] Moreover, the quaternary carbons are located at C7 and C13.[23] The imposing structure and optical medicinal importance of this molecule attracted a great amount of attention from other researchers since the disclosure of the structure,[24] although total synthesis was not reported until our synthesis.[7]

The total synthesis of (−)-tetrodecamycin was initiated with the stereoselective conversion of the carbohydrate derivative **9** (Scheme 3).[5,25] Michael addition and a subsequent methylation gave a 2,3-dimethyl derivative **32**.[25] Reaction of the lithiated **32** with cyclohexanone was followed by dehydra-



Scheme 3. Total synthesis of tetrodecamycin. IBX, *o*-iodoxybenzoic acid; LDA, lithium diisopropylamide; TMSCl, trimethylsilyl chloride; TFA, trifluoroacetic acid; WSCl, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide; PCC, pyridinium chlorochromate; OTBS, oxygen attached with *tert*-butyldimethylsilyl.

tion to stereoselectively give the quaternary product **33**, which was submitted to hydride reduction to give the diol **34**. After transformation to ketoaldehyde **35**, SmI_2-mediated pinacol coupling proceeded to afford the *cis*-diol **36** as a single product.[26] Michael addition of the alcohol **37** to diethyl acetylenedicarboxylate (**38**) gave the adduct **39**, which was converted to the aldehyde **40**. Treatment of **40** with sodium hexamethyldisilazide (NaHMDS) constructed the seven-member ring[27] smoothly, and the resulting alcohol was oxidized to the ketone **41**. The diester **41** was submitted to regioselective saponification to give monocarboxylic acid, which was transformed to the thioester **42**. Reduction of **42** with Et_3SiH to the corresponding aldehyde[28] accompanied the cyclization to the acetal **43**. Further reduction of the lactone **43** was realized by our newly developed method using CBr_4 and PPh_3.[29] Deacetonation of **44** afforded the diol **45**, which, upon treatment with Eschenmoser's reagent (**46**),[30] underwent introduction of an *exo*-methylene group to give (−)-tetrodecamycin (**6**).

Total Syntheses of Bioactive Aromatics

Aromatic antibiotics are one of the major groups in polyketide compounds. The planarity and functionality of aromatics are important factors of their bioactivity. A variety of aromatic rings has given chemists imagination, and many striking transformations have been produced. Figure 2 shows some of the aromatics produced by total synthesis in our laboratory.[31–35] In this chapter, we present our recent results including tetracycline (**53**),[36] BE-54238B (**54**),[37] lymphostin (**55**),[38] and lagunamycin (**56**).[39]

Total Synthesis of (–)-Tetracycline

For almost half a century, tetracycline (**53**) has been well known as a major antibiotic from the standpoint of its unique structural features as well as its antibacterial activities (Fig. 2).[40] The total synthesis of the tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962,[41] followed by Muxfeldt's terramycin synthesis in 1968,[42] and culminated by Stork's 12a-deoxytetracycline synthesis in 1996.[43] However, all those syntheses were accomplished only in racemic forms. The total synthesis of natural (–)-tetracycline (**53**) remained an unanswered challenge until achievements in our laboratory in 2000.[36] Recently, another success regarding the total synthesis of (–)-tetracycline was presented by the Myers group.[44] Here, we focus on the first total synthesis of (–)-tetracycline (**53**) accomplished in our laboratory.[36]

The starting **57** derived from D-glucosamine[45] was converted to olefin alcohol **58**, which was submitted to selenylation[46] to give **60** (Scheme 4). Treatment of **60** with borane followed by H_2O_2 oxidation gave the alcohol stereoselectively by simultaneous formation of a new olefin group, which was followed by benzylation to afford **61**. The enol ether **61** was subjected to a Ferrier reaction to give β-hydroxyketone **62**.[47] Epimerization at the C2 position of **62**, possessing two benzyloxy groups and one hydroxyl group at the β-positions, was realized by treatment with 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) at −30°C, and following elimination of the hydroxyl group, performed in a one-pot mesylation-β-elimination procedure to give the enone **63**. The Diels–Alder reaction of **63** and **64** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (DBMP) proceeded from the β-face of **63** regio- and stereoselectively as expected.[48] This highly stereoselective reaction gave a labile adduct which, upon acidic oxidation, was transformed to the α,β-unsaturated ketone **65**. The tandem

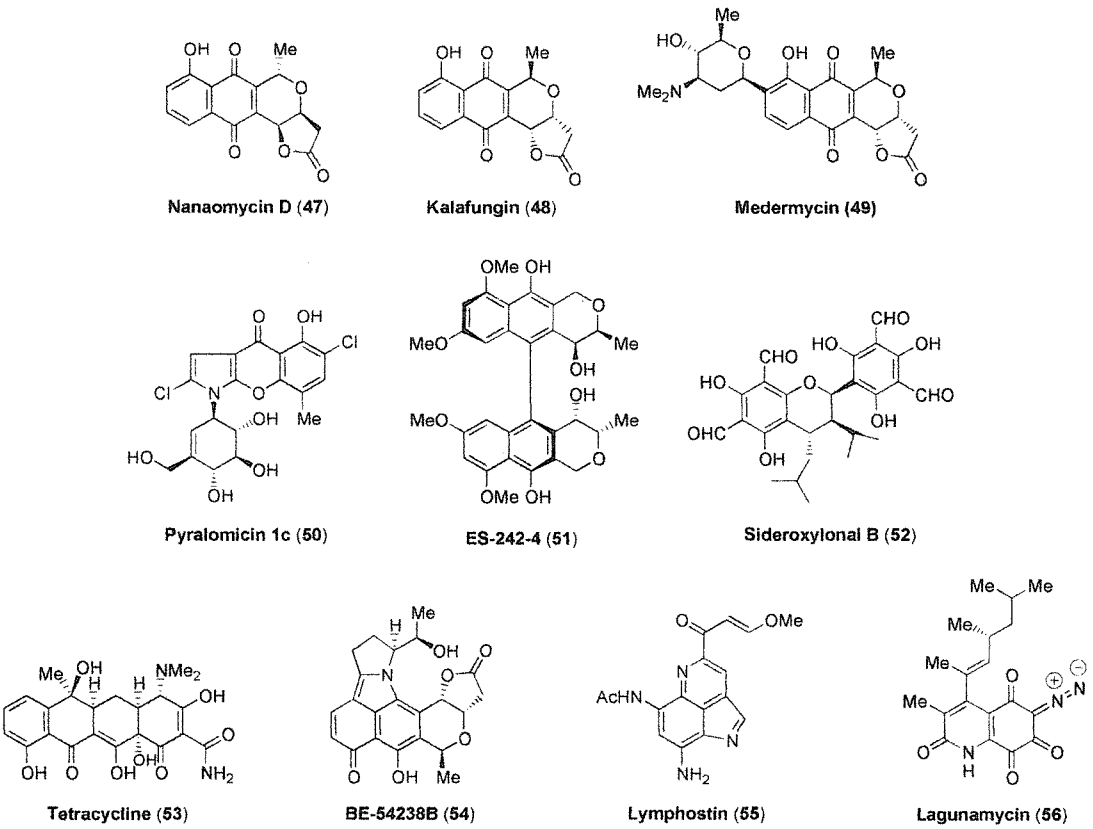
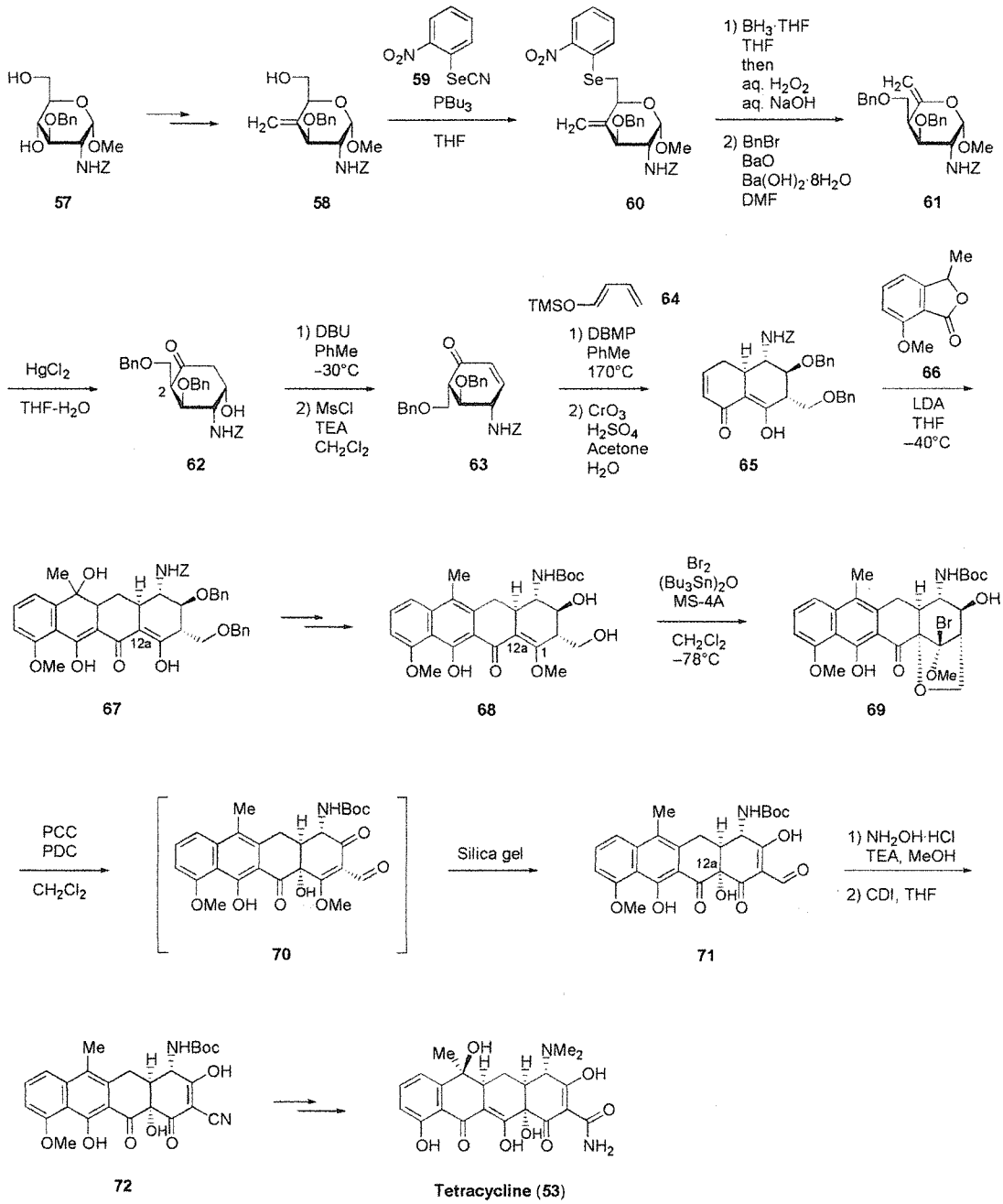


Fig. 2. Bioactive aromatics.



Scheme 4. Total synthesis of tetracycline. DMF, dimethylformamide; DBMP, 2,6-di-*tert*-butyl-4-methylphenol; TEA, triethylamine; NHZ, (nitrogen-hydrogen) attached with benzyloxycarbonyl; PDC, pyridinium dichromate; CDI, 1,1′-carbonyldiimidazole.

Michael–Dieckmann-type reaction of **65** with the isobenzofuranone **66**[49] gave the tetracyclic compound **67**.

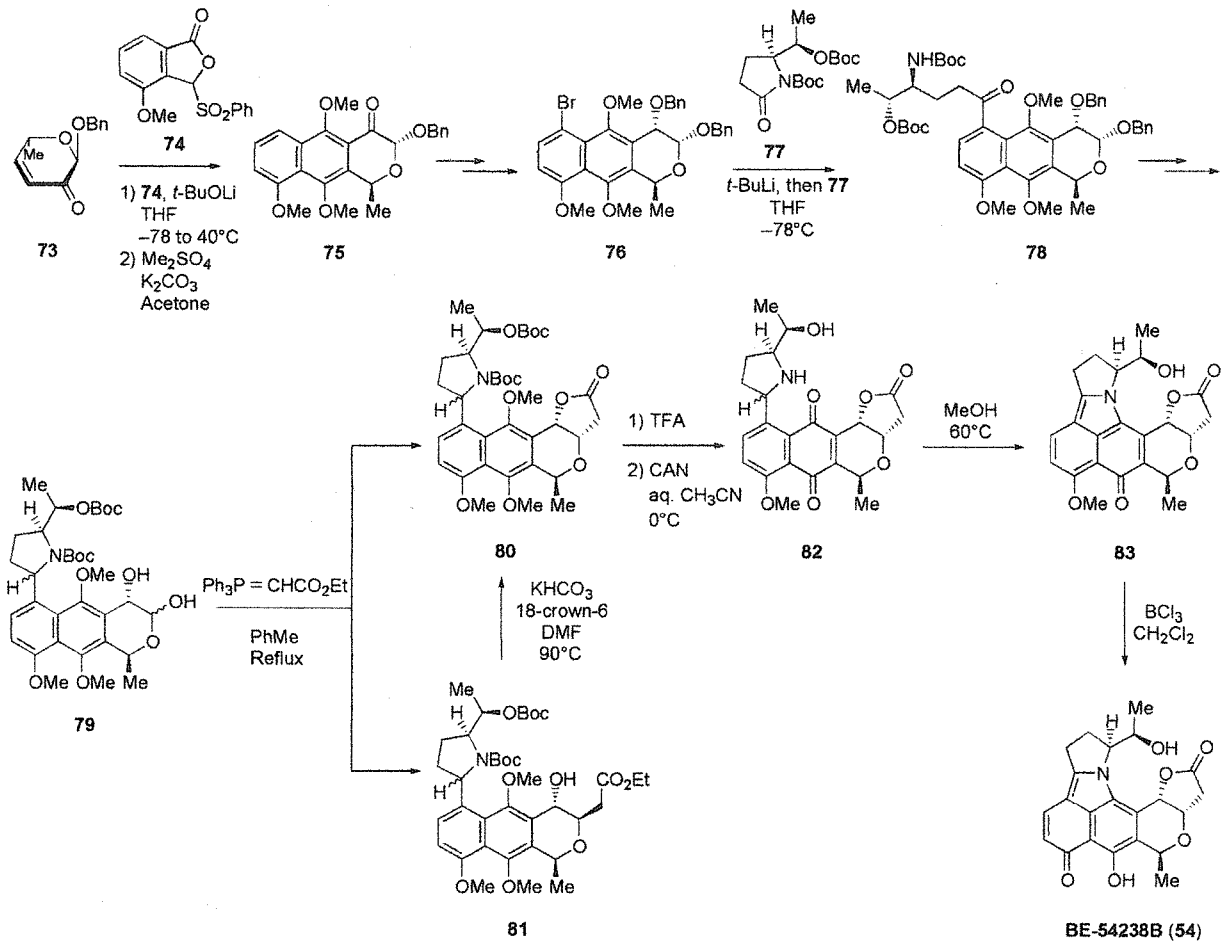
With the tetracyclic **67** available, we turned to oxidation of the right ring. In particular, stereoselective introduction of the hydroxyl group at C12a was one of the crucial problems of this synthesis. Aromatization and manipulation of protective groups gave the diol **68**, which was adequate for oxidation of the right wing. The primary alcohol of **68** participated in the bromination of C1–12a olefin to give a secondary alcohol **69**. Treatment of **69** with a mixture of pyridinium chlorochromate (PCC) and pyridinium dichromate (PDC) in dichloromethane followed by purification with silica gel

afforded **71** in 61% yield. This transformation, probably through intermediate **70**, realized concurrent oxidation of primary and secondary alcohols accompanying introduction of C12a hydroxyl group in one pot. The resulting **71** was transformed to the nitrile **72** by our newly developed method, treatment of aldehyde **71** with hydroxylamine followed by dehydration with 1,1′-carbonyldiimidazole (CDI). The cyanide **72** was transformed to (−)-tetracycline (**53**) in a few steps, which was neutralized with HCl in MeOH to afford a hydrochloride salt. This salt was identical in all respects with the hydrochloride of natural (−)-tetracycline (**53**), completing the first total synthesis.

Total Synthesis of (−)-BE-54238B

Pyranonaphthoquinone antibiotic BE-54238B (**54**) was isolated by the Banyu group from a culture broth of *Streptomyces* sp. A54238 to show antitumor activities.[50] The absolute structure of **54** was determined by NMR studies and X-ray analysis to be a nanaomycin analog fused with a pyrrolidine ring and, therefore, to belong to the family of pyranonaphthoquinone antibiotics (Fig. 2).

We achieved the enantioselective total synthesis of **54** to confirm its absolute structure (Scheme 5).[37] The tricyclic precursor **75** was prepared according to our reported procedures from the lactone **74** and the enone **73** derived from L-rhamnose.[31] Pyranohydronaphthoquinone **75** was converted to the bromide **76**, which was lithiated to couple with the L-pyrogultamic acid derivative **77** to obtain the ketone **78**. After construction of the pyrrolidine **79**, a Wittig reaction gave the lactone **80** and hydroxyl ester **81**, in 67 and 22% yields, respectively. The lactone **80** was suitable for the synthesis of the natural product **54**, while the hydroxyl ester **81** was transformed to **80** in high yield by heating with $KHCO_3$ and 18-crown-6 in dimethylformamide (DMF). Acidic removal of two Boc groups in **80** was followed by oxidative de-*O*-methylation to give the quinone **82**. This was effectively cyclized to **83** as



Scheme 5. Total synthesis of BE-54238B. DMF, dimethylformamide; CAN, cerium(IV) ammonium nitrate.

expected; **83** was de-*O*-methylated by BCl_3 to give the tautomerized compound **54** as the hydrochloride salt, which was identical in all respects with the salt of the natural BE-54238B (**54**).

Total Synthesis of Lymphostin

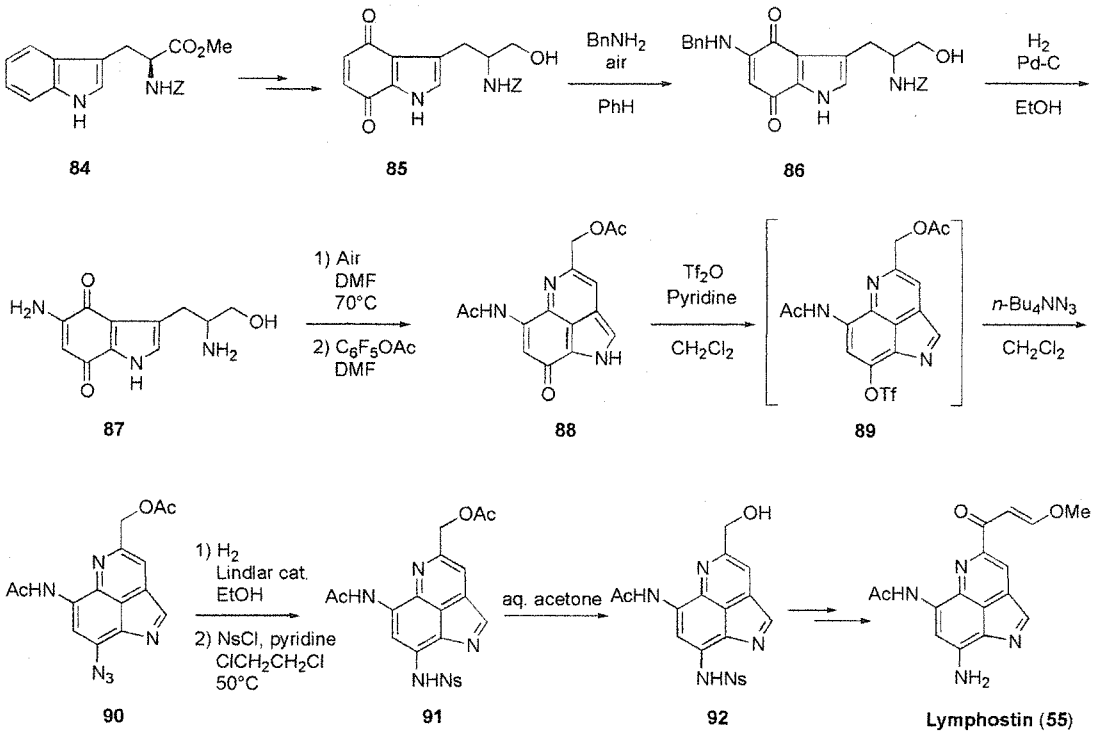
Polycyclic heteroaromatic compounds were studied as both synthetic targets to develop new methodologies and biological activities to discover new drugs. Recently, lymphostin (**55**)[51] was isolated as significant bioactive compounds, possessing interesting structures with multi-heteroaromatic rings containing a tetranitrogen-substituted benzene ring (Fig. 2). Until our first total synthesis of lymphostin (**55**),[38] there had been no examples of synthesizing such structures.

Lymphostin (**55**) was isolated by the Kyowa Hakko group from a culture broth of *Streptomyces* sp. as an immunosuppressant to show potent inhibitory activity against lymphocyte kinase. In addition to its novel action mechanism, impinging on a crucial biological cascade, the structure of **55** interested us as a focused target for total synthesis. We achieved total synthesis of lymphostin (**55**) using our proposed biosynthetic sequence to construct the core structure of **55** through cyclization and oxidation of the indolequinone **86** derived from tryptophan (Scheme 6).

The starting *N*-carbobenzyloxy-L-tryptophan methyl ester (**84**) was converted to the racemic indolequinone **85**.[52] A regioselective reaction of the quinone **85** with benzylamine[53] followed by oxidation to obtain aminoindolequinone **86** was achieved in one pot by exposure of **85** to benzylamine under air at room temperature. Hydrogenolysis of **86** afforded the diamino derivative **87**. This was cyclized concomitant with aromatization by heating in DMF with air followed by acetylation to give the desired iminoquinone **88**.[54] Transformation of the iminoquinone **88** to diaminopyrroloquinoline **91** was realized by the introduction of an azido group and subsequent reduction. Treatment of **88** with Tf_2O followed by *n*-Bu_4NN_3 afforded the tautomerized azide **90**. **90** was reduced on the Lindlar catalyst and protected by an *o*-nitrobenzenesulfonyl (Ns) group[55] to afford **91**. Selective deacetylation to obtain the primary alcohol **92** was quantitatively carried out by simple exposure to aqueous acetone. Manipulation of **92** to construct the side chain and removal of the Ns group gave lymphostin (**55**).

Total Synthesis of (−)-Lagunamycin

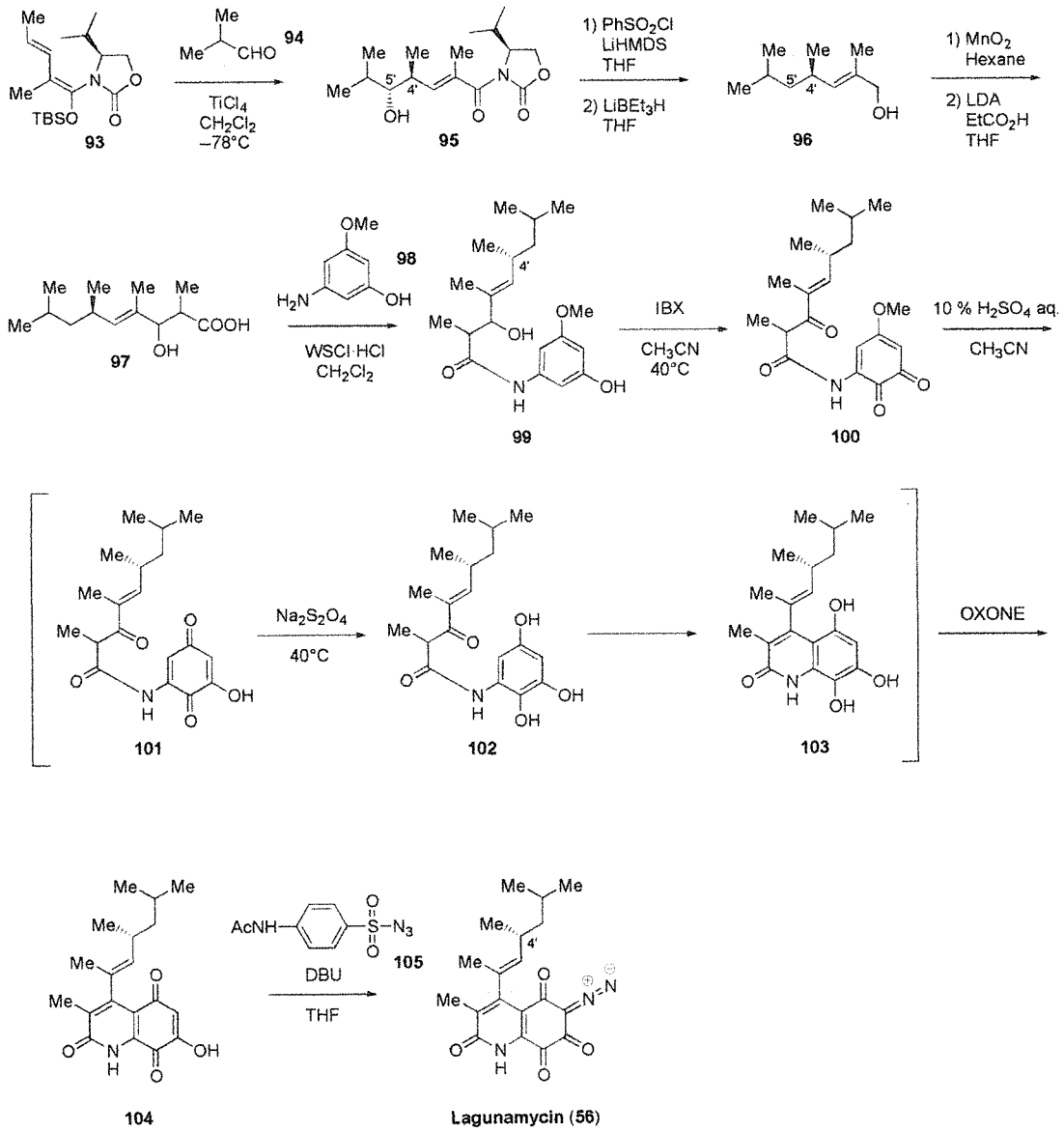
Lagunamycin (**56**), a metabolite isolated from the culture filtrate of *Streptomyces* sp., AA0310 showed inhibitory activity against 5-lipoxygenases and antibacterial activity against



Scheme 6. Total synthesis of lymphostin.
DMF, dimethylformamide.

Gram-positive bacteria.[56a] The structure of lagunamycin (**56**) was elucidated to possess the diazotetraoxoquinoline skeleton with the branched alkyl chain attached, as shown in Fig. 2, by a combination of NMR studies and chemical degradations.[56b] Existence of the rotational isomers caused by the bulky side chain against the 9-methyl group attached to the quinoline plane was believed because of the complexity of the NMR spectra of lagunamycin (**56**).[56b] Interested in the structure and bioactivities, we embarked on synthetic studies of lagunamycin (**56**).

The actual synthesis of lagunamycin (**56**) was started from construction of the side chain moiety **97** (Scheme 7). Recently, we developed remote stereoinduction with the chiral *N,O*-ketene acetal **93**,[57] which has applied to construct the acyclic polyketide unit in high stereoselectivity. This reaction, using the ketene *N,O*-acetal **93** and isobutyraldehyde (**94**), gave the adduct **95** in excellent yield (99%) and stereoselectivity (>50 : 1) on a multigram scale as in our previous report.[57] Deoxygenation at the C5′ position was carried out by *O*-sulfonation of **95** followed by reduction with super hydride ($LiBrEt_3H$). The resulting allylic alcohol **96** was oxidized to aldehyde, which was submitted to aldol reaction with the dianion derived from propionic acid to give β-hydroxycarboxylic acid **97**.



Scheme 7. Total synthesis of lagunamycin. IBX, *o*-iodoxybenzoic acid; DBU, 1,8-diazabicyclo[5,4,0]undec-7-ene.

Coupling of the carboxylic acid **97** and aniline **98**[58] with *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (WSCI) afforded anilide **99** in 91% yield. The anilide **99** was treated with *o*-iodoxybenzoic acid to promote Nicolaou oxidation[59] quickly to give the quinone moiety and oxidation of allylic alcohol slowly (overnight) at room temperature to give β-ketoamide **100**. The *o*-quinone **100** was transformed to quinolone **104** in a one-pot procedure. Subsequent manipulation of quinone **100** including: (i) hydrolysis of methyl ether to convert to quinone **101**, (ii) selective reduction of the quinone moiety with $Na_2S_2O_4$ to provide the labile trihydroxyanilide **102**, (iii) Knorr condensation under acidic conditions[60] to give quinolone **103**, and (iv) oxidation of hydroquinone with Oxone delivered *p*-quinone **104** in 87% yield. Finally, treatment of **104** with *p*-acetoaminophenylsulfonyl azide (**105**)[61] in the presence of DBU gave lagunamycin (**56**), of which the analytical data were consistent with those reported previously.[56] Thus, total synthesis of lagunamycin was accomplished, and the absolute structure of **56** was determined as 4'*R* configuration.

Total Syntheses of Acyclic Polyketides

Acyclic polyketides are also a major group and their polypropionate and/or polyacetate chains possess a variety of chiral center arrangements and oxidation states. The acyclic asymmetric chemistry for macrolide is applicable to these systems, and the success of short-step synthesis depends on the choice and delivery of chiral sources. Convergence is also indispensable in establishing an efficient route. We already achieved total synthesis of the natural products belonging to this group such as maniwamycin B (**106**),[62] calbistrin A (**107**),[18] and deacetylcaloporoside (**108**).[63] Recently, we developed new methodologies to realize an efficient route to the acyclic polyketides. Here, we present the total synthesis of xanthocillin X dimethylether (**109**),[64] trichostatin D (**110**),[65] and actinopyrone A (**111**).[66]

Total Synthesis of Xanthocillin X Dimethylether

Xanthocillin X dimethylether (**109**), which showed antiviral activity against Newcastle disease, vaccinia, and herpes simplex viruses, were produced by *Aspergillus* sp. and determined spectrometrically to be the derivatives of 1,4-bis-(4-hydroxyphenyl)-2,3-diisonitrilo-1,3-butadiene.[67] Further investigation was hampered by the scarcity and instability of such natural products, although the synthesis of **109** was reported in 1962 before isolation of the natural product without any detailed experimental data and references to the stereochemistry.[68] Obviously, the challenge of creating the vinyl isonitrile structure in the laboratory added to the appeal of the project.[69] Here, we describe the first stereoselective total synthesis of xanthocillin X dimethylether (**109**) to demonstrate the utility and versatility of our method.[64] The short and prac-

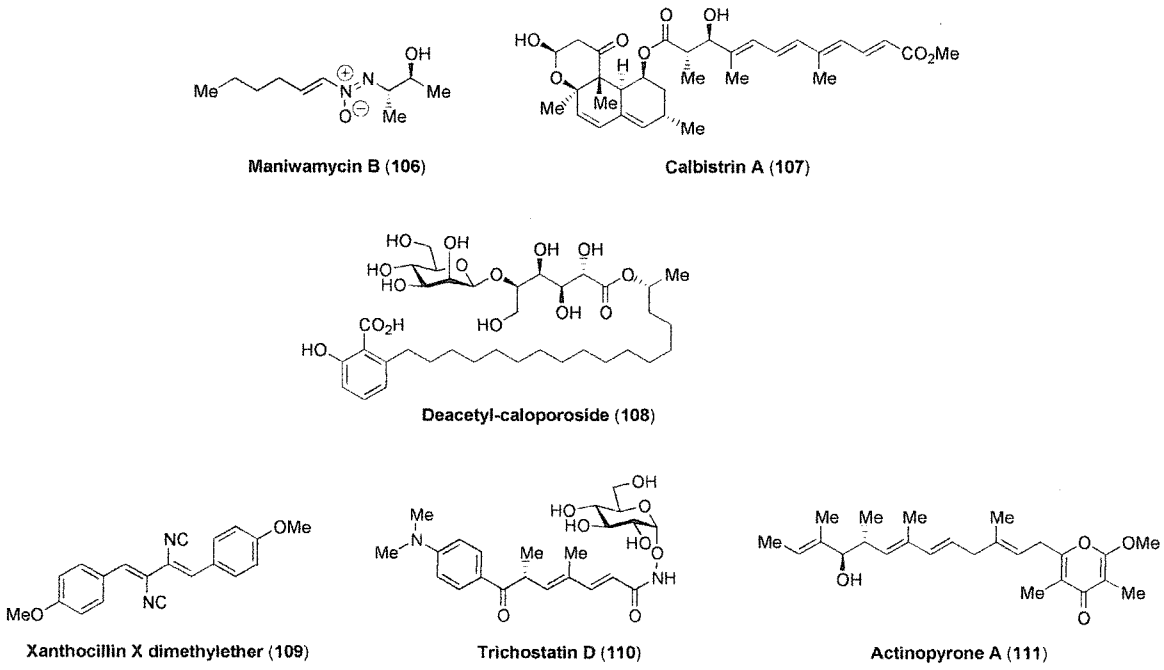
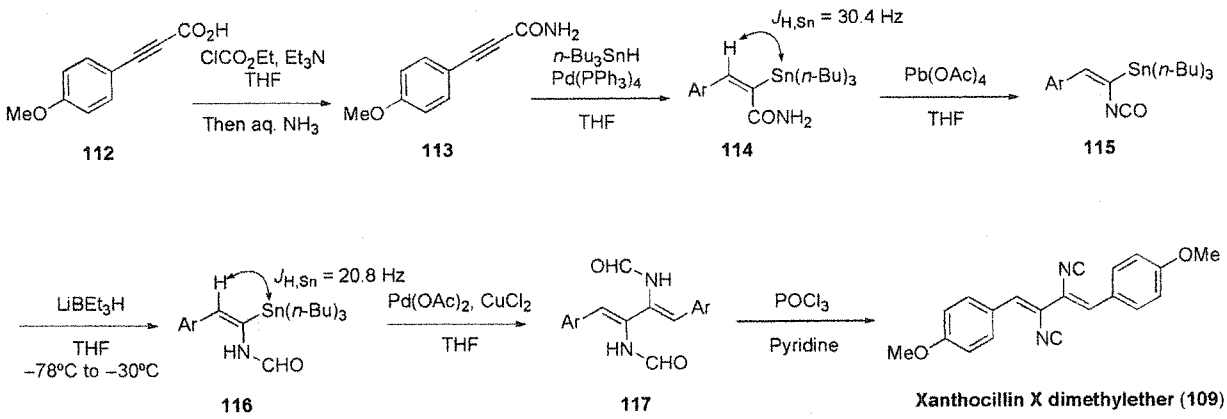


Fig. 3. Acyclic polyketides.



Scheme 8. Total synthesis of xanthocillin X dimethylether.

tical synthesis of xanthocillin X dimethylether (**109**) is presented in Scheme 8.

The mixed anhydride of **112** was treated with ammonia to give the amide **113**, which was converted to the (*E*)-vinylstannane **114**. After some experimentation, a remarkable procedure for converting **114** into **115** was discovered. The Baumgarten oxidative rearrangement[70] of **114** with $Pb(OAc)_4$ gave the isocyanate **115**, which was isolated to be reduced by $LiBEt_3H$ to the *N*-formamide **116**. The configurations of **114** and **116** were supported by their coupling constants ($J_{H,Sn}$ = 30.4 and 20.8 Hz, respectively). Compound **116** was submitted to Pd-catalyzed homocoupling[71] to give the symmetrical (*Z,Z*)-diene **117**. In the final stage, dehydration of **117** with $POCl_3$ in pyridine proceeded smoothly to afford (*Z,Z*)-diisonitrile **109**, which was fairly stable even in a solid state. The infrared and ^{1}H-NMR spectra of the synthetic isonitrile **109** were identical with the reported data[72] of the natural xanthocillin X dimethylether, completing the stereoselective total synthesis of the natural product **109** to confirm its absolute structure.

Total Synthesis of (+)-Trichostatin D

Trichostatin D (**110**) was isolated as an inducer of phenotypic reversion in oncogene-transformed cells from the broth of an actinomycete *Streptomyces violaceusniger* (Fig. 3).[73] Because various oncogenes correlate with tumor phenotypes, the inducers of phenotypic reversion in oncogene-transformed cells are expected to be selective antitumor agents. Trichostatin D has a chiral center at the middle position of the chain structure. This structure was suitable for application in our remote stereoinduction reaction.[57] Here, we describe the first synthesis of trichostatin D (**110**) (Scheme 9).[65]

The remote stereoinduction method with the chiral silyl ketene-*N,O*-acetal **118** and *p*-bromobenzaldehyde (**119**) proceeded to give the adduct **120** in excellent yield (97%) with high stereoselectivity (96:4, both isolated isomers possessed the desired 6*R* configuration). After protection as the *tert*-butyldimethylsilyl (TBS) ether **121**, the imide **121** was directly converted to the α,β-unsaturated aldehyde **122** in high yield (91%) by treatment with diisobutylaluminum hydride (DIBAL) at −78°C. After transformation to the dienoic acid **123**, oxidation at the benzyl position gave (+)-trichostatic acid (**124**), the common polyketide chain of the trichostatin family.

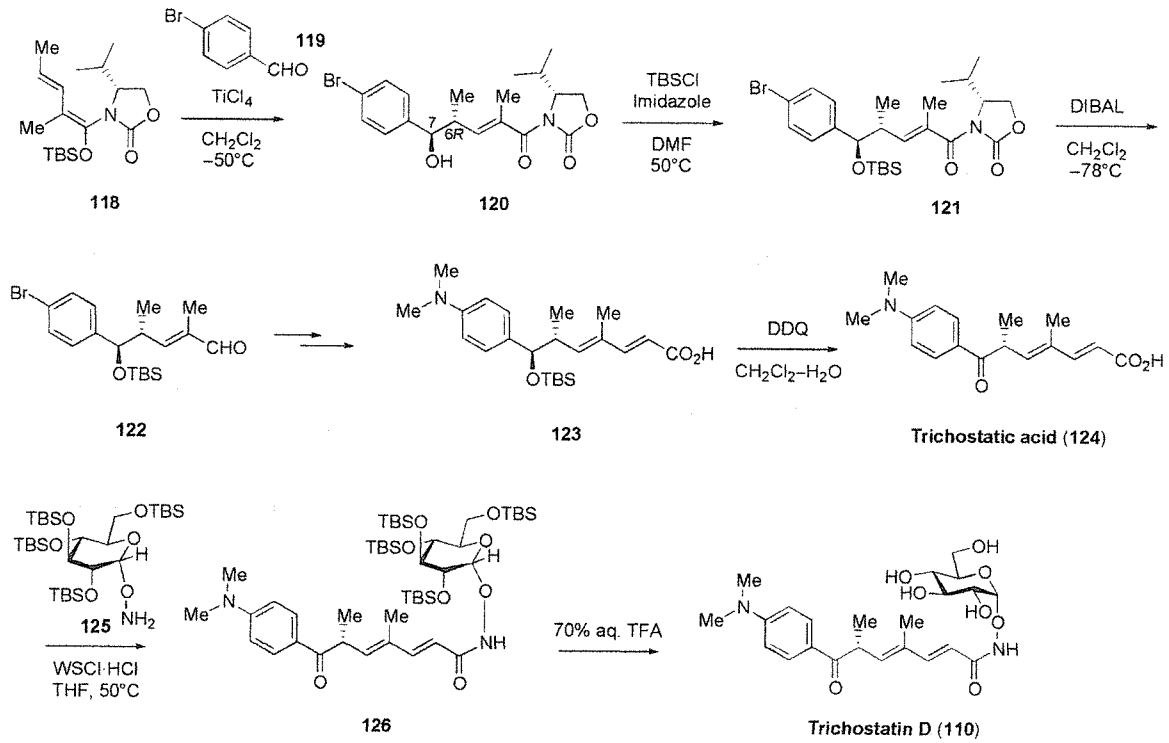
Finally, condensation of **124** with **125** prepared by our glycosylation method[74] and following de-*O*-protection afforded (+)-trichostatin D (**110**).

Total Synthesis of (+)-Actinopyrone A

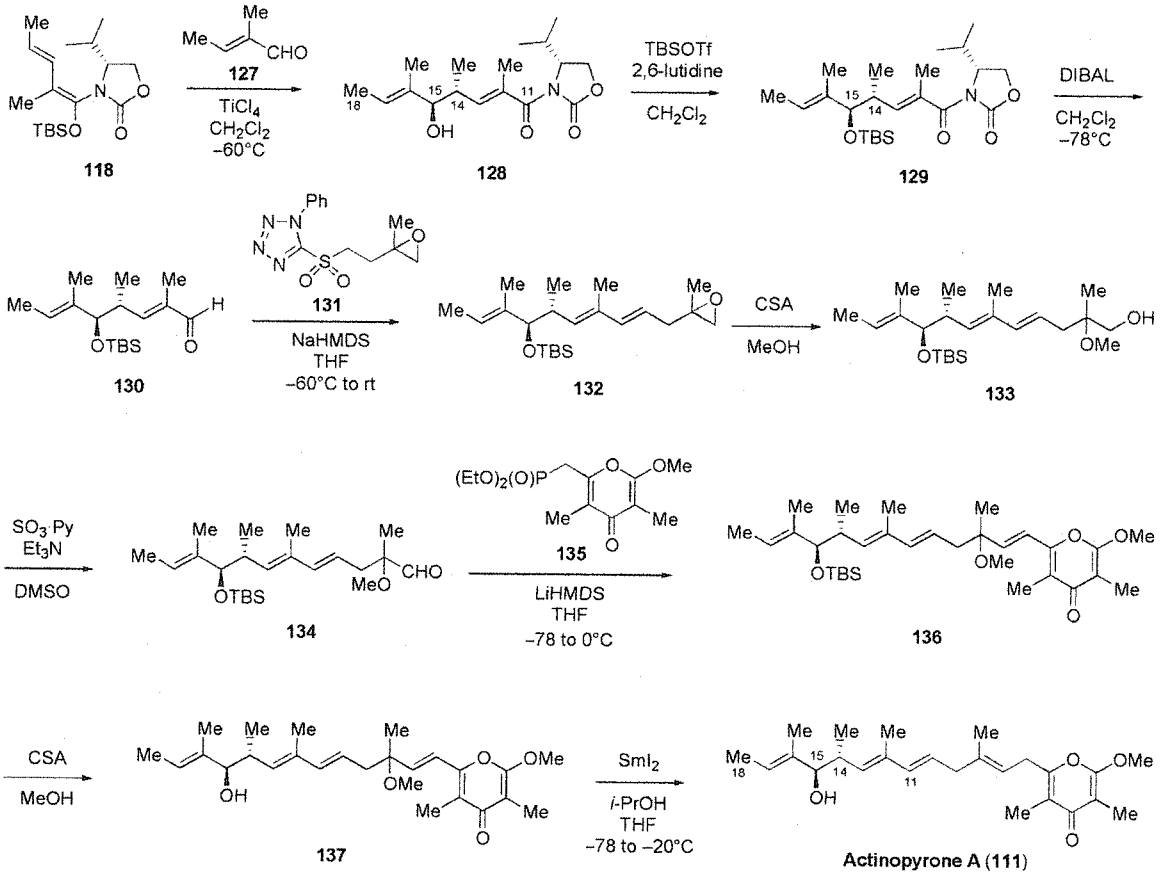
Actinopyrone A (**111**) was isolated from *Streptomyces pactum* S12538 as a relatively unstable compound possessing coronary vasodilating and antimicrobial activities.[75] Later, it was also found to exhibit potent anti-*Helicobacter pylori* activity.[76]

In addition to multi-bioactivity, little toxicity makes actinopyrone A (**111**) an attractive candidate for chemotherapy. However, the instability of **111** makes further research difficult; even the absolute structure had not been disclosed until our total synthesis. Here, we present the first total synthesis of actinopyrone A (**111**) (Scheme 10).[66]

Stereoselective construction of the C11–18 unit **128** was achieved by our remote stereocontrol method.[57] The coupling of silyl dienolate **118**[65] and tiglic aldehyde (**127**) in the presence of $TiCl_4$ gave the C14–C15 *anti*-adduct **128** as a single isomer. Protection of **128** as TBS ether afforded a crystalline **129**, which stereochemistry determined to be the (14*R*,15*R*)-isomer by X-ray crystallography, as expected from our previous work.[57] The chiral auxiliary of **129** was removed to give the aldehyde



Scheme 9. Total synthesis of trichostatin D. DIBAL, diisobutylaluminum hydride; TBSCl, *tert*-butyldimethylsilyl chloride.



Scheme 10. Total synthesis of actinopyrone A. TBSOTf, *tert*-butyldimethylsilyl trifluoromethanesulfonate; NaHMDS, sodium hexamethyldisilazide; rt, room temperature; CSA, 10-camphorsulfonic acid.

130 by treatment with DIBAL at −78°C.[65] The aldehyde **130** was converted to the triene **132** by Kocienski's method[77] using the sulfone **131**. The epoxide **132** was transformed under acidic conditions to the primary alcohol **133**, which was oxidized to afford the aldehyde **134**. The pyrone moiety was introduced by the Horner–Wadsworth–Emmons reaction of **134** with the phosphonate **135** to afford the stable vinylpyrone **136**. De-*O*-silylation of **136** under acidic conditions proceeded to provide **137**. The final and key step was ready. Treatment of the vinylpyrone **137** with SmI_2 in the presence of *i*-PrOH promoted reductive deconjugation to give actinopyrone A (**111**) in 70% yield. The synthetic **111** was identical in all respects with the natural product including optical rotation. Thus, the absolute structure of actinopyrone A (**111**) was determined to be the (14*R*,15*R*)-configuration.

Conclusion

In total synthesis, the most noteworthy aspect is the philosophy of the approach. An important point is also the completion of the synthesis, just as artists never exhibit their unfinished work and since a synthesis cannot be an "Unfinished Symphony." Considering the many kinds of useful reactions that were developed to serve as key steps in chemical synthesis, such as asymmetric epoxidation, asymmetric reduction, enantiospecific aldol reaction, and olefin metathesis, and considering the many kinds of enantiomerically pure materials such as carbohydrates and amino acids, any complex natural product could be synthesized. Consequently, a philosophy of synthesis is more urgently required than ever before.

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Review

Total syntheses of bioactive natural products from carbohydrates

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Abstract

Total syntheses of bioactive natural products recently accomplished in our laboratories are described. They are classified by structures of target molecules and are focused on our original approach to their own structures. The target molecules include nanaomycin, kalafungin, BE-54238B, tetracycline, rosmarinecine, thienamycin, luminacines C_1 and C_2, tetrodecamycin, cochleamycin A, and tubelactomicin A, which have been synthesized as optically pure form from carbohydrates.

Keywords: Total synthesis; Natural product; Carbohydrate; Structural determination; Enantiodivergent synthesis; Michael–Dieckmann cyclization; Intramolecular Diels–Alder reaction

Contents

1. Introduction

Anybody can draw a picture, but pictures painted by famous painters such as van Gogh, Monet and Picasso are praised as "art". At the present time, anyone may be able to synthesize natural products, even those having

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complicated structure by advanced organic chemistry. Hence, "art" is much more essential to be introduced into the organic synthesis. That is the significance of the synthesis and development of bioactive compounds. The authors are of the opinion that "art" is a sublimate of originality, and, in the 21st century, it should be accompanied with some additional features.

All the structures of natural products are very beautiful and attractive. Then, we would like only to relate them to our favorite compounds, carbohydrates. In our opinion, carbohydrates are the language of chiral natural products; therefore, we have focused on the use of carbohydrates as chiral precursors in organic synthesis.

Herein, we would like to present our recent work in the total synthesis and development of medicinally useful natural products, which use carbohydrates as chiral sources to determine the absolute structure of the natural products and to clarify their structure - activity relationships.

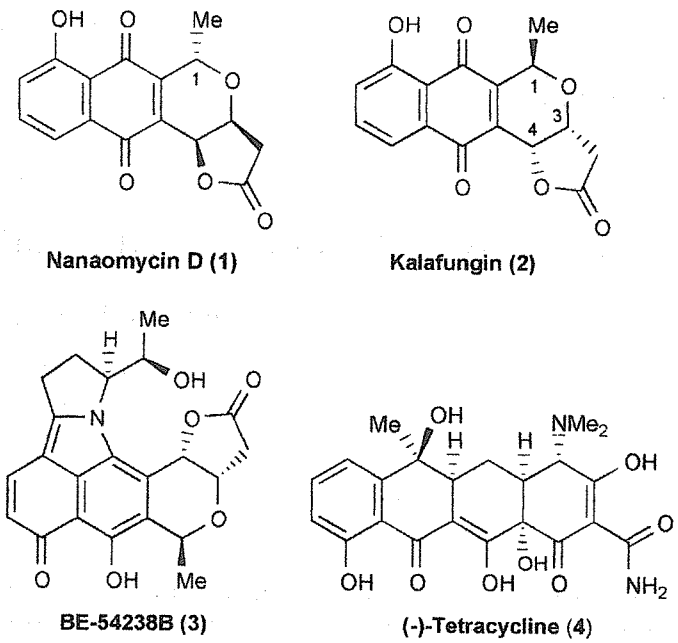


Fig. 1.

2. The total syntheses of pyranonaphthoquinone antibiotics using tandem Michael–Dieckmann cyclization

Pyranonaphthoquinone antibiotics (**1**~**3**) and tetracycline (**4**) are well-known antibiotics possessing significant antimicrobial activities and unique structures. These compounds have densely functionalized and aromatic ring-fusing polycyclic system. These unique structures have drawn attention both for syntheses with developing new methodologies and for creation of novel biologically active compounds. During total syntheses of natural products possessing aromatic rings and oxygenated cyclohexanes, we developed a novel methodology to synthesize those structures in short steps with convergency, meaning tandem Michael–Dieckmann cyclization [1–3]. Herein, we describe the total syntheses of **1**~**4** using Micheal–Dieckmann cyclization combined with carbohydrate chemistry [1–4].

2.1. The total syntheses of nanaomycin D and kalafungin

Pyranonaphthoquinone antibiotics (**1**~**3**) have been shown to possess significant antimicrobial activities and potential antitumor activities [5–7]. We have already reported the first total syntheses of related antibiotics such as nanaomycin D (**1**) [8], kalafungin (**2**) [9,10], and BE-52534B (**3**) [11] (Fig. 1), and developed synthetic strategy for the stereoselective construction of densely-functionalized pyranonaphthoquinones from carbohydrates [12–24]. During synthetic studies on nanaomycin D (**1**) and kalafungin (**2**), a new methodology to enable to synthesize both enantiomers from one enantiomeric carbohydrate had been developed in our laboratory, meaning "enantiodivergent synthesis" [12,13,25–30].

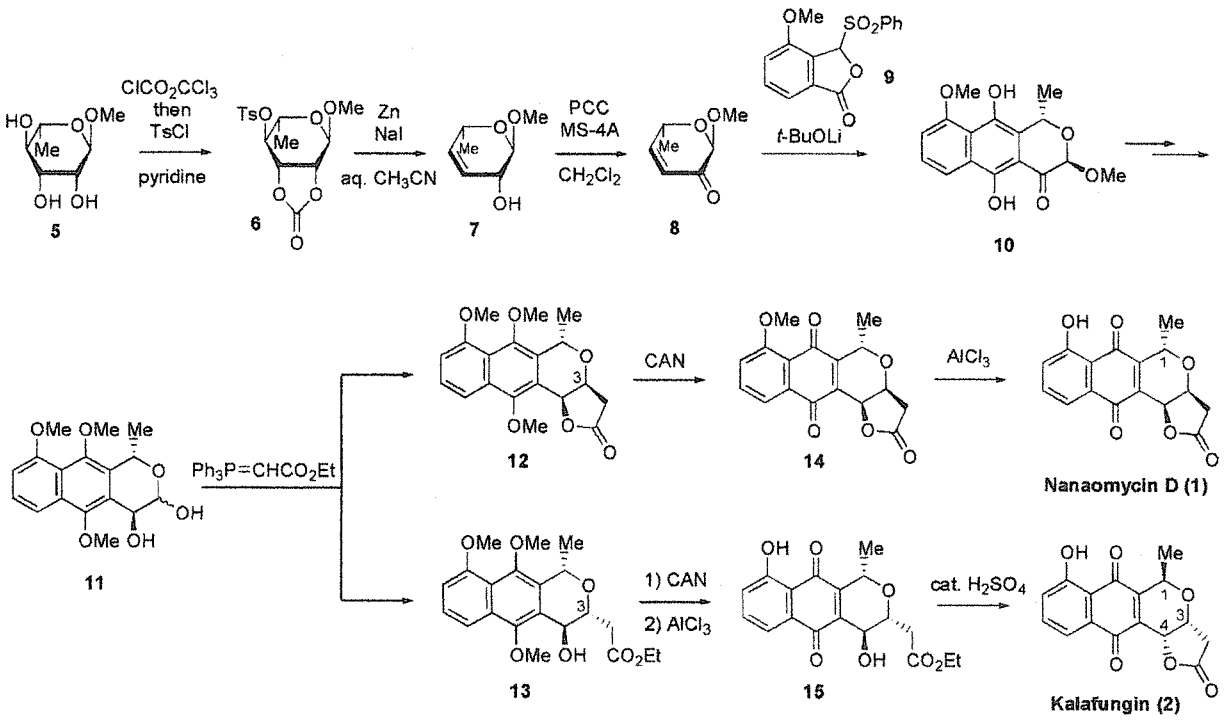
Carbohydrates have been used widespread as chiral sources in asymmetric syntheses of natural products [31–37]. Although various carbohydrates are available, in most of them one enantiomer is natural abundant but another isomer is difficult to get in much quantity. Thus, it is hopeful that both enantiomeric chiral synthons in total synthesis are derived from one enantiomer of a carbohydrate. This concept was realized as shown in Scheme 1.

Methyl L-rhamnoside **5** was converted into the carbonate **6** in 80% over all yield in one pot reaction with trichloromethyl chloroformate and then tosyl chloride in pyridine. Treatment of **6** with zinc powder and sodium iodide in refluxing aqueous acetonitrile gave the unsaturated alcohol **7** [38–40]. Oxidation of **7** with pyridinium chlorocromate afforded the stable α,β-unsaturated ketone **8**. Michael–Dieckmann condensation of **8** with isobenzofuranone **9** [41,42] gave naphthopyranone **10**, which was transformed to lactol **11** in three steps. The lactol **11** was submitted to Wittig reaction, which afforded the lactone **12** and the hydroxyl ester **13** [43,44]. The lactone **12** was oxidized to the quinone **14**, which was de-*O*-methylated to give nanaomycin D (**1**). On the other hand, the hydroxyl ester **13** was converted to the quinone **15**, which was subjected to acidic isomerization to produce kalafungin (**2**), the enantiomer of nanaomycin D (**1**).

These syntheses of pyranonaphthoquinone antibiotics show the power of the enantiodivergent synthesis to construct any arrangement of stereocenters from an abundant carbohydrate.

2.2. The total synthesis of BE-54238B

Pyranonaphthoquinone antibiotics, BE-54238 B (**3**), were isolated by the Banyu group from the culture broth of *Streptomyces* sp. A54238 to show antitumor activities [11]. The absolute structure of **3** was determined by NMR studies and X-ray analysis to be a nanaomycin analog



Scheme 1. Total syntheses of nanaomycin D and kalafungin.

fused with a pyrrolidine ring, and therefore, to belong to a family of pyranonaphthoquinone antibiotics (Fig. 1).

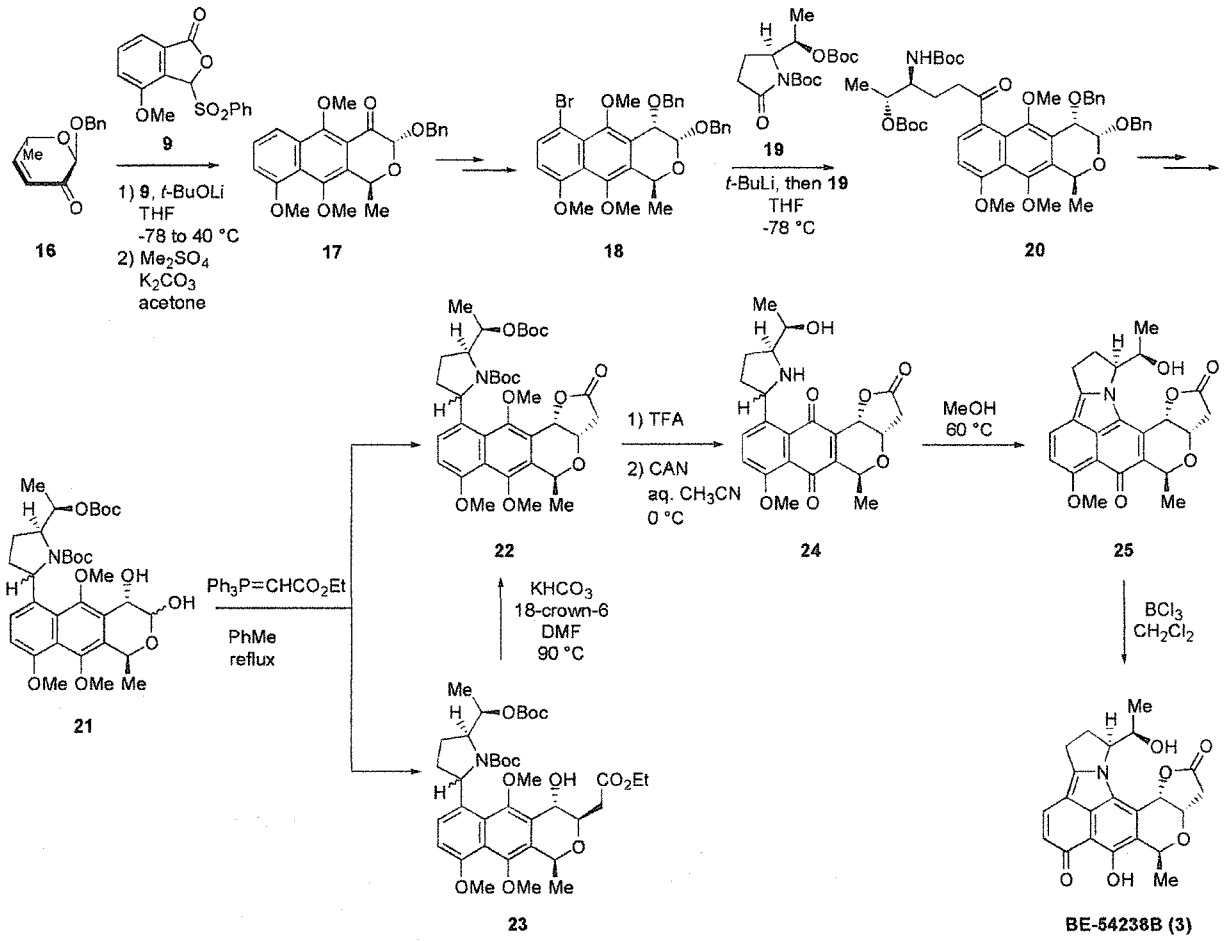
We achieved the enantioselective total synthesis of **3** to confirm its absolute structure (Scheme 2) [45]. The *O*-benzyl precursor **17** was prepared according to our reported procedures from the lactone **9** [12,13] and the enone **16** derived from L-rhamnose. Pyranohydronaphthoquinone **17** was converted to the bromide **18** which was lithiated to couple with L-pyrogultamic acid derivative **19** to obtain the ketone **20**. After construction of pyrrolidine **21**, Wittig reaction gave the lactone **22** and hydroxyl ester **23**, in 67% and 22% yields, respectively. The lactone **22** was suitable for the synthesis of the natural product **3**, while the hydroxyl ester **23** was transformed to **22** in high yield by heating with $KHCO_3$ and 18-crown-6 in DMF. Acidic removal of two Boc groups in **22** was followed by oxidative de-*O*-methylation to give the quinone **24**. This was effectively cyclized to **25** as expected. **25** was de-*O*-methylated by BCl_3 to give the tautomerized compound **3** as the hydrochloride salt, which was identical in all respects with the salt of the natural BE-54238B (**3**).

2.3. *The first total synthesis of (−)-tetracycline*

For almost half a century, tetracycline (**4**) has been well known as a major antibiotic from the viewpoint of its unique structural features as well as antibacterial activities [46] (Fig. 1). The total synthesis of tetracycline families was initiated by Woodward's 6-demethyl-6-deoxytetracycline synthesis in 1962 [47], followed by Muxfeldt's terramycin synthesis in 1968 [48], and culminated by Stork's 12a-deoxytetracycline synthesis in 1996 [49]. However, all those syntheses have been accomplished only in racemic forms. The total synthesis of natural (−)-tetracycline (**4**) had remained an unanswered challenge, until achievements in our laboratory in 2000 [50]. Recently, another success to the total synthesis of (−)-tetracycline was presented by Meyers group [51,52]. Herein, we focus on the first total synthesis of (−)-tetracycline (**4**) accomplished in our laboratory [50].

The starting **26** derived from D-glucosamine [53] was converted to olefin alcohol **27**, which was submitted to selenylation [54] to give **29** (Scheme 3). Treatment of **29** with borane followed by H_2O_2 oxidation gave stereoselectively the alcohol by simultaneous formation of a new olefin group, which was followed by benzylation to afford **30**. Enol ether **30** was subjected to Ferrier reaction to give β-hydroxyketone **31** [55]. Epimerization at C_2 position of **31**, possessing two benzyloxy groups and one hydroxyl group at β-positions, was realized by treatment with DBU at −30 °C, and following elimination of hydroxyl group was proceeded in one pot mesylation-β-elimination sequence to give enone **32**. Diels–Alder reaction of **32** and **33** in the presence of 2,6-di-*tert*-butyl-4-methylphenol (DBMP) proceeded from the β-face of **32** regio- and stereo-selectively as expected [56]. This highly stereoselective reaction gave a labile adduct, which upon acidic oxidation was transformed to the α,β-unsaturated ketone **34**. The tandem Michael-Dieckmann type reaction of **34** with the isobenzofuranone **35** [57] gave tetracyclic compound **36**.

The tetracyclic **36** in hand, we turned to the oxidation of the right ring. Especially, stereoselective introduction of hydroxyl group at C_{12a} was one of the key problems of this



Scheme 2. Total synthesis of BE-54238B.

synthesis. Aromatization and manipulation of protective groups gave diol **37**, which was adequate to oxidation of the right wing. The primary alcohol of **37** participated to the bromination of C_{1-12a} olefin to give the secondary alcohol **38**. Treatment of **38** with a mixture of PCC and PDC in dichloromethane followed by purification with silica gel afforded **40** in 61% yield. This transformation, probably via intermediate **39**, realized concurrent oxidation of primary and secondary alcohols accompanying with introduction of C_{12a} hydroxyl group in one pot. The resulting **40** was transformed to the nitrile **41** by our newly developed method, treatment of aldehyde **40** with hydroxylamine followed by dehydration with 1,1′-carbonyldiimidazole (CDI). Cyanide **41** was transformed to (−)-tetracycline (**4**) in a few steps, which was neutralized with HCl in MeOH to afford the hydrochloride. This was identical with the hydrochloride of natural (−)-tetracycline (**4**) in all respects, completing the first total synthesis.

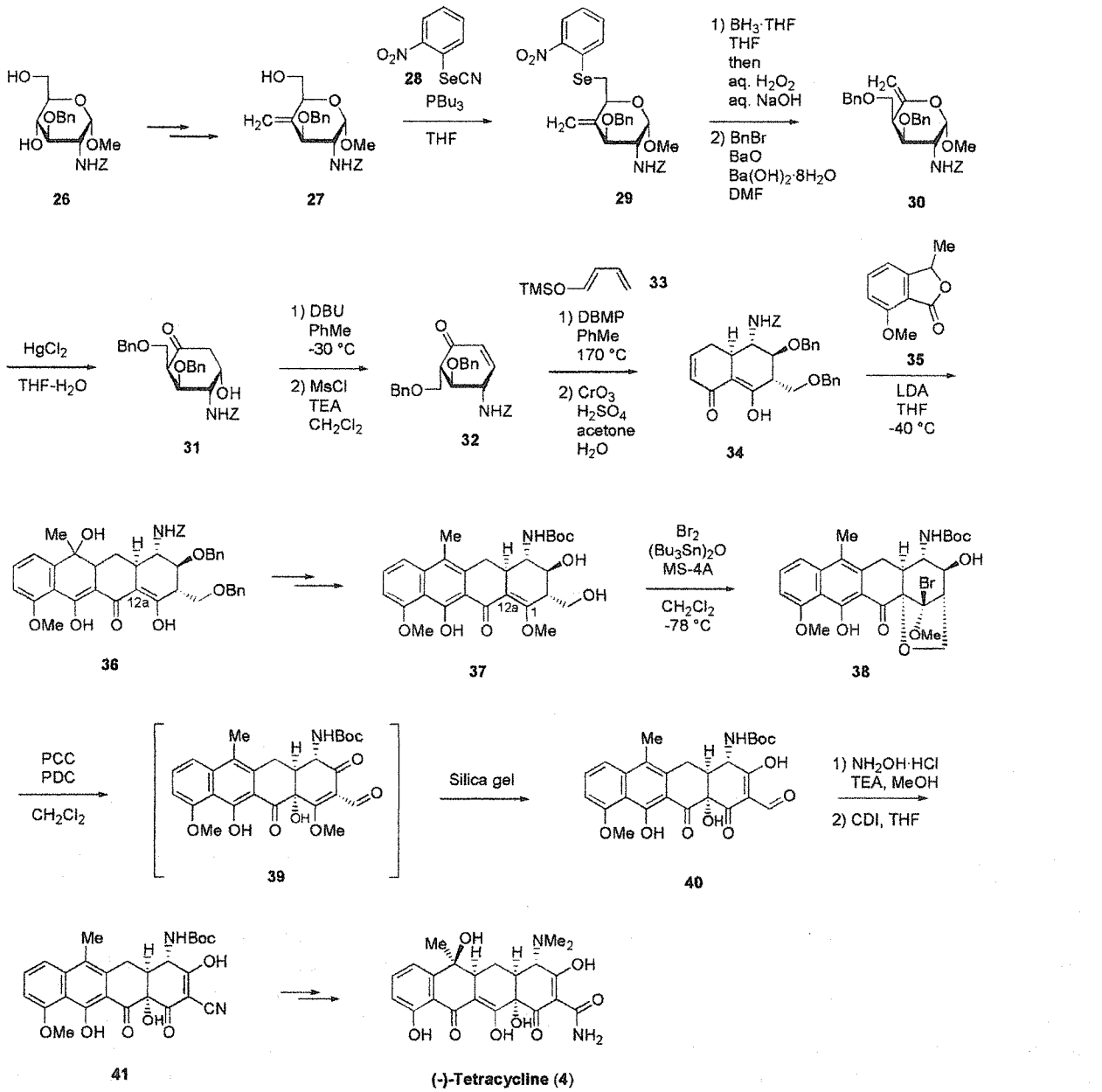
3. The total syntheses of nitrogen-containing polyhydroxy compounds using the skeletal rearrangement of glucosamines

A variety of carbohydrates have been used for stereospecific syntheses of natural products as chiral sources [1–3,25,26,58]. However, little has been reported using amino sugars [59], because of their scanty derivatives. The methodology to use glycosamine would enable to construct nitrogen-containing polyhydroxy compounds frequently seen in natural products. The utility of glycosamines in syntheses of optically active compounds has been developed in our laboratory [60,61]. Herein, we describe the novel methodology to use amino sugars, which includes the specific reaction of glucosamines.

3.1. The stereoselective total synthesis of (−)-rosmarinecine

The pyrrolizidine alkaloids, which occur naturally in various plant species, have drawn attention for syntheses because of their structure and biological properties. Until total syntheses of (−)-rosmarinecine (**42**) (Fig. 2) in our laboratory [61], there had not been reported on completely stereoselective syntheses of optically active pyrrolizidine alkaloids [62–65]. The stereoselective synthesis of (−)-rosmarinecine (**42**) is summarized in Scheme 4.

The key reaction of our methodology includes a rearrangement of cyclic disulfonate derivative of a glycosamine. The starting methyl α-D-glucosaminide **45** reacted with **46** to give exclusively cyclic sulfonate **47**. **47** was subjected to rearrangement to produce [3,0,3]-bicylic compound **50** via 5 membered ring **49**. The sulfonate **50**



Scheme 3. Total synthesis of (−)-tetracycline.

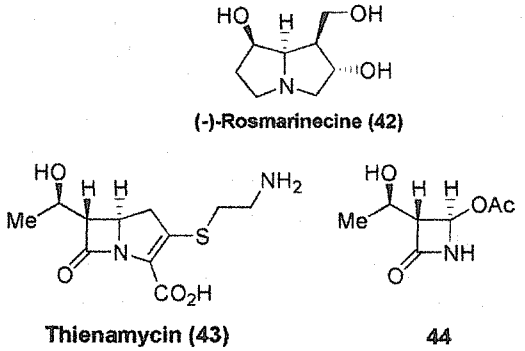
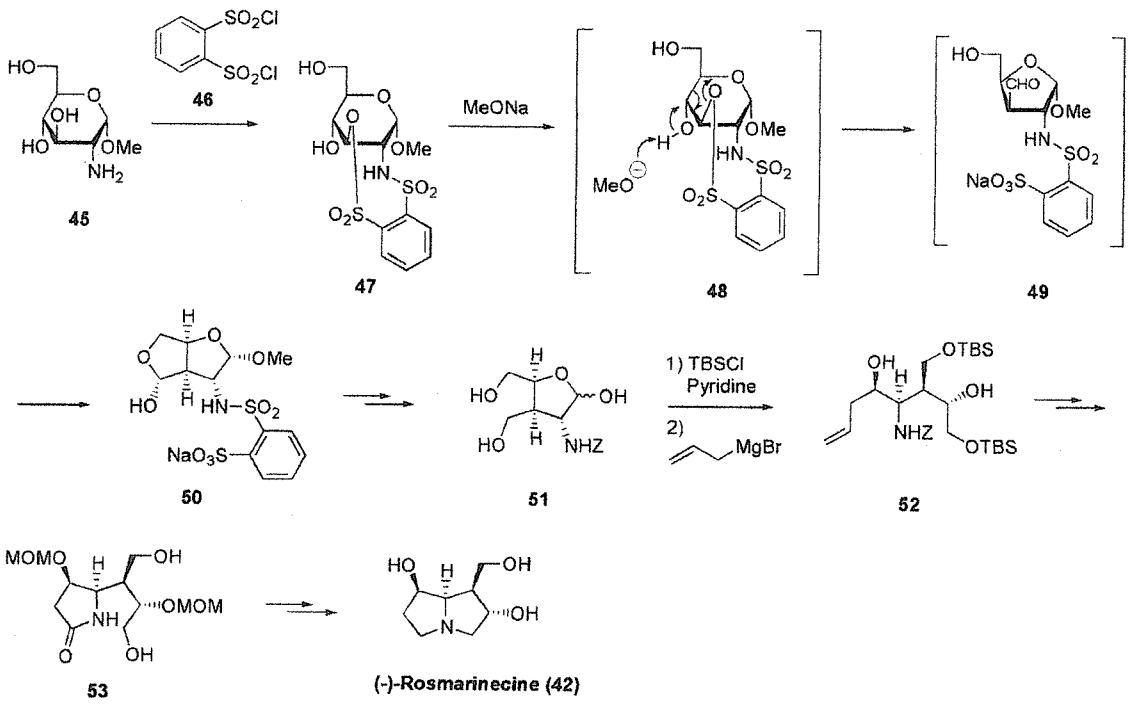


Fig. 2.

was converted to the triol **51**, which contained already felicitously placed functional groups and an anomeric carbon of potential value for the stereoselective introduction of hydroxyl groups and carbon chain. Silylation to protect primary alcohols of **51** gave the corresponding disilyl furanoside, which was submitted to Grignard reaction with allylmagnesium bromide in ether to afford the single *threo* amimo alcohol **52** by chelation control approach [66,67]. Further manipulation of **52** gave (−)-rosmarinecine (**42**) through the lactam **53**.

3.2. The formal total synthesis of (+)-thienamycin

The molecular architecture associated with the β-lactam antibiotics has posed some of the greatest challenges in synthetic chemistry, and this family has provided the stimulus for the development of methodology for the construction of their skeletons and side chains.



Scheme 4. Total synthesis of (−)-rosmarinecine.

(+)-Thienamycin (**43**) (Fig. 2) was discovered in fermentation broth of *Streptomyces cattleya* to show exceptional antibacterial potency and spectrum [68]. The first stereocontrolled synthesis of **43** has been reported by Merck group [69], and the transformation of (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**44**) to (+)-thienamycin (**43**) was also made more attractive by another Merck group [70]. Consequently, the synthesis of **44** constitutes a formal total synthesis of (+)-thienamycin (**43**).

(+)-4-Acetoxy-3-hydroxyethyl-2-azetidinone (**44**) (Fig. 2) and its derivatives have been well known as the highly versatile intermediates [71] for the synthesis of carbapenem antibiotics such as thienamycin (**43**) [68], imipenem, meropenem [72] and so on.

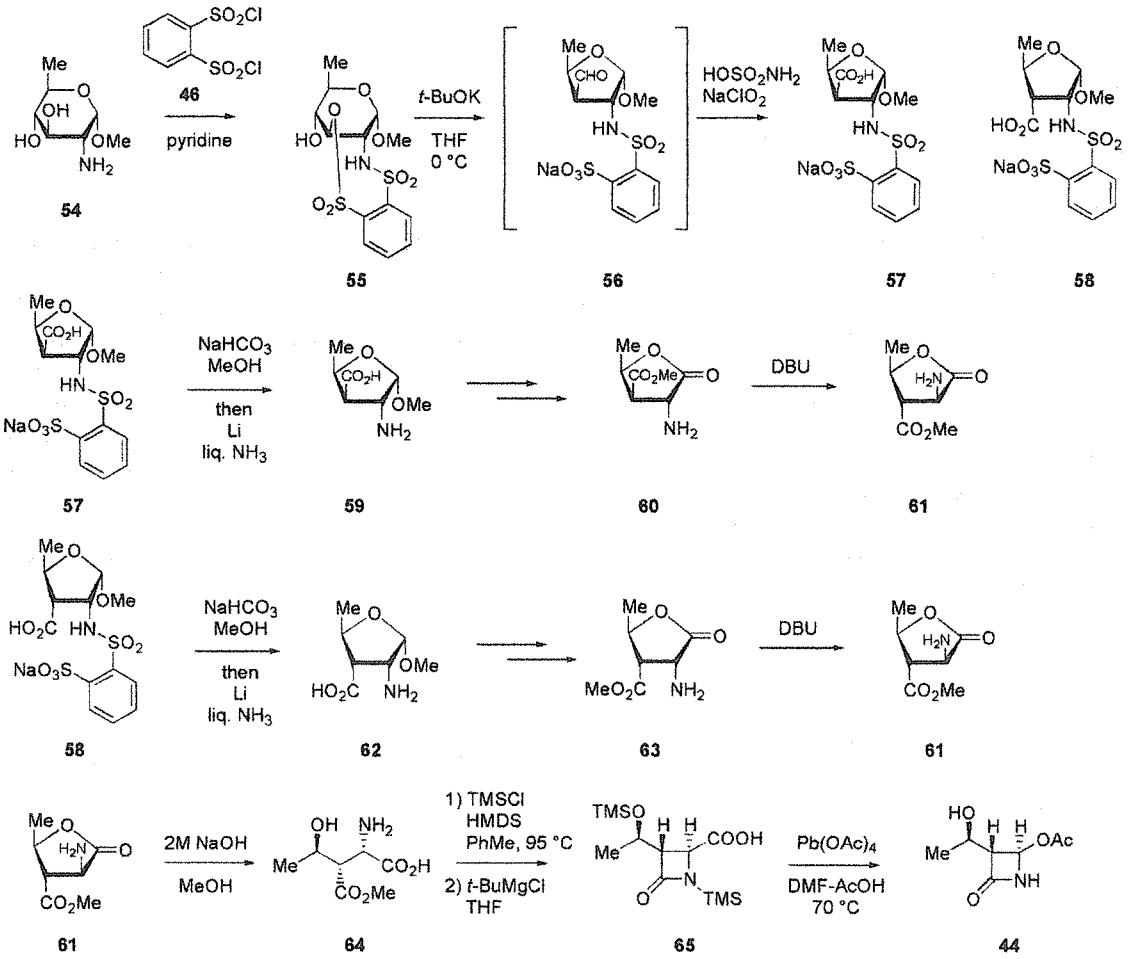
The synthesis of **44** was initiated by Sankyo group [73], followed by Merck group [74], and culminated in the practical preparation by two Japanese companies [75,76] using Noyori-Murahashi's asymmetric procedures and chem-enzymatic procedures, respectively.

Herein is described our enantiospecific synthesis of **44** from a carbohydrate through a skeletal rearrangement and stereoselective epimerization (Scheme 5) [77]. The starting material is commercially available methyl 2-amino-2,6-dideoxy-α-D-glucopyranoside (**54**), which has been also isolated from natural sources [78].

Reaction of **54** with *o*-benzenedisulfonyl dichloride (**46**) gave the cyclic sulfate **55**, which was submitted to the rearrangement with potassium *t*-butoxide. The ring contraction reaction was quenched immediately after disappearance of **55**, and subsequent oxidation gave carboxylic acid **57** predominantly. The very minor product **58**, which increased prolonged reaction time of rearrangement, was readily separated by silica gel column chromatography. Practically, both compounds could be used for the synthesis without separation, because they were found to be efficiently converted to a single lactone **61** by stereoselective epimerization later on. The synthesis of **61** from each of the two compounds **57** and **58** was realized as follows.

Removal of the *N*-sulfonyl group of **57** by Birch reduction produced the corresponding amino acid **59** in 92% yield. This was transformed to the lactone **60**, which was submitted to epimerization at C_2 and C_3 positions, one of the key operations of this synthesis. After a variety of conditions had been examined, the best result was realized by using DBU in MeOH at room temperature to afford predominantly the desired amino ester **61**. Similarly, the epimer **58** was transformed to **61** through **62** and **63** in 57% overall yield. Hydrolysis of **61** according to the reported procedures [79] led to the hydroxyl acid **64**, which was in turn submitted to the β-lactam formation. For our purpose, a Grignard-mediated cyclization of the silylated derivative seemed most promising [80]. Thus, **64** was silylated with trimethylsilyl chloride and hexamethyldisilazane (HMDS), and subsequent treatment with *tert*-butylmagnesium chloride gave the *bis*-silylated β-lactam **65**. Oxidative decarboxylation [70] of **65** gave exclusively the desired (+)-4-acetoxy-3-hydroxyethyl-2-azetidinone (**44**) with removal of trimethylsilyl groups. Overall, the yield was approximately 32% in 12 steps from **54**.

Utility of amino sugars in syntheses of optically active compounds has been expanded as above. The rearrangement with ring-contraction gave useful intermediary



Scheme 5. Formal total synthesis of (+)-thienamycin.

N-sulfonylamino aldehydes such as **49** and **56** which are ready to be converted to various formations and configurations.

4. The total syntheses of highly oxidized compounds using carbanion–aldehyde coupling

Highly-oxidized compounds containing several stereogenic centers have been challenging target molecules for organic chemists. Stereoselective construction of such compounds requires a well-elaborated synthetic plan including convergent steps with functionalized segments. Herein, we present the total syntheses of luminacins and tetrodecamycin (Fig. 3), in which the carbanion produced from a multi-functionalized segment by hydrogen-alkali metal substitution was coupled with an aldehyde.

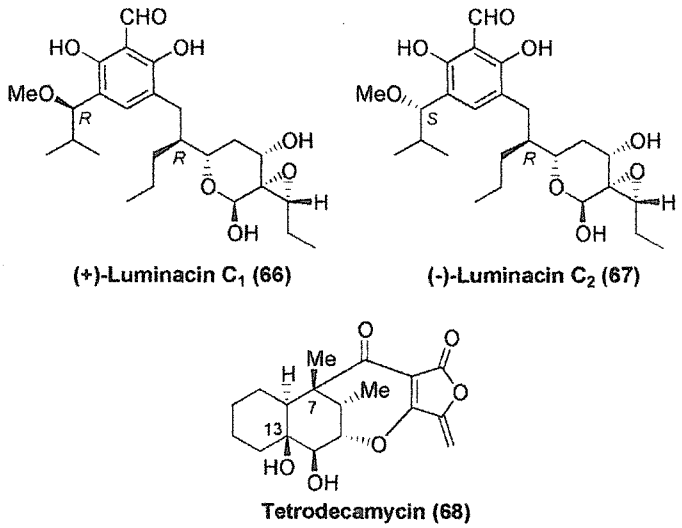


Fig. 3.

4.1. The total synthesis of luminacins C_1 and C_2

Luminacins C_1 and C_2 were isolated from *Streptomyces* sp. as novel angiogenesis inhibitors. Their structures, including the relative configuration of the carbohydrate portion, were determined mainly by NMR studies [81]. As a result, they were found to have the same planar structure as SI-4228 and UCS15A, which were reported to be microbial products showing antimicrobial, immunosuppressive, antitumor and bone resorption inhibitory activities [82,83]. However, the absolute structure of luminacins C_1 and C_2 had remained undetermined until our total

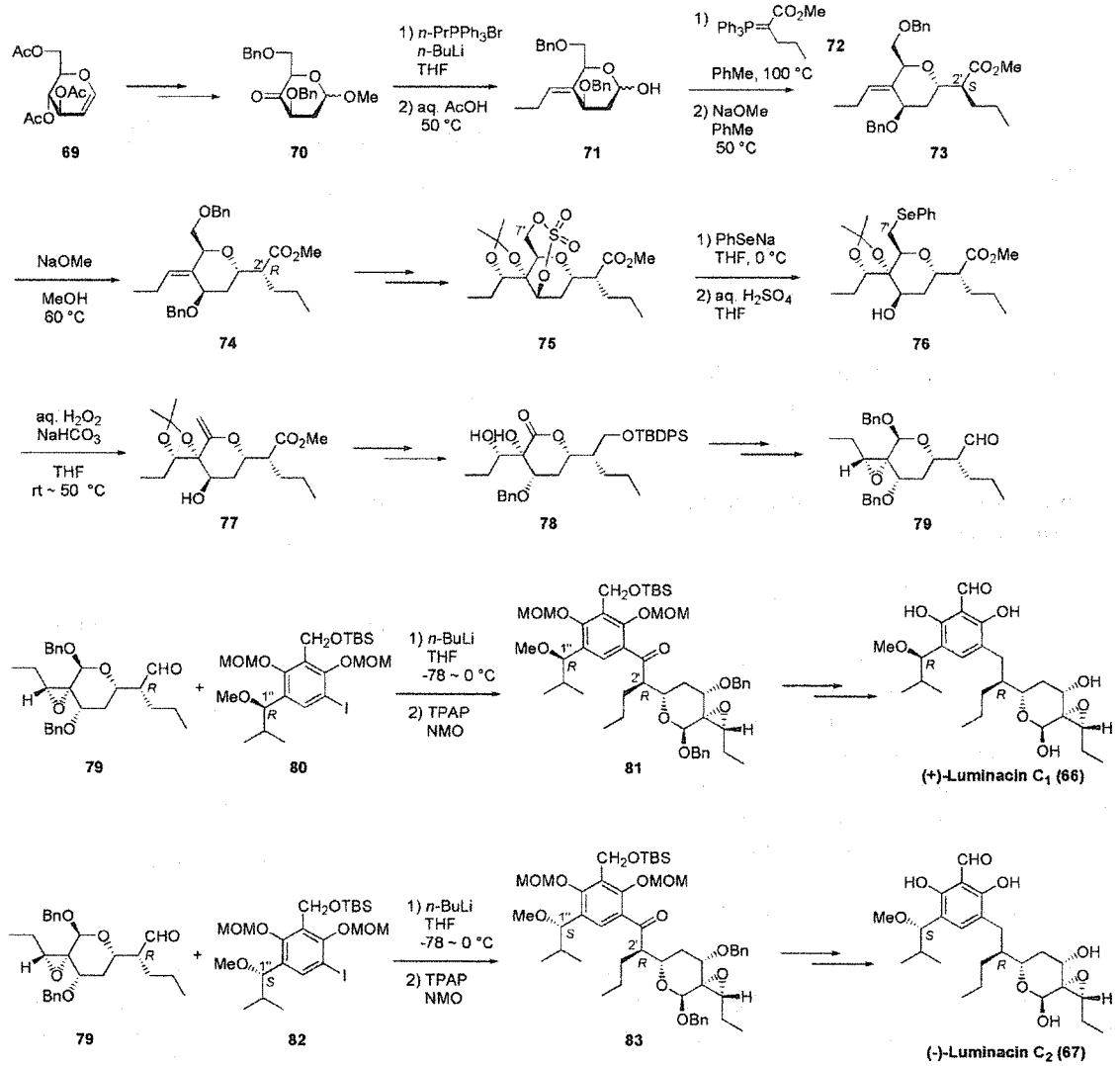
synthesis. The total synthesis of luminacins C_1 and C_2 is described in Scheme 6 [84].

D-glucal (**69**) was transformed to the ketone **70**, which was submitted to Wittig reaction using *n*-$PrPPh_3Br$ and *n*-BuLi and subsequent hydrolysis to afford acetal **71**. Wittig reaction of **71** with **72** was followed by *O*-Michael addition cyclization to give 2′*S*-isomer **73** as a single isomer. The configuration of **73** at $C_{2'}$ was epimerized by treatment with NaOMe in MeOH to obtain **74**. After transformation to cyclic sulfate **75** [85], introduction of the phenylselenyl group at $C_{7'}$ position and removal of sulfate by acidic hydrolysis gave **76**, which was exposed to H_2O_2 to afford the *exo*-olefin **77**. The *exo*-olefin **77** was converted to the diol **78**, which was submitted further manipulation to the aldehyde **79**, the right half of luminacins.

The 2′*R*-isomer **79** was coupled with 1″*R*-isomer **80** to give, after oxidation, (1″*R*, 2′*R*)-isomer **81**, which was converted to (+)-luminacin C_1 (**66**). By the same procedure, coupling of **79** and **82** followed by oxidation gave (1″*S*, 2′*R*)-isomer **83**, which was transformed to (−)-luminacin C_2 (**67**).

4.2. Total synthesis of (−)-tetrodecamycin

(−)-Tetrodecamycin (**68**) was isolated from the culture broth of *Streptomyces* sp. MJ885mF8 to show antimicrobial activities especially against *Pasteurella piscicida* [86,87]. The structure is distinguished by X-ray crystallography as a tetronic acid-containing tetracyclic skeleton, the one cyclohexane ring of which is fully and diversely substituted [88]. Moreover, the quaternary carbons are located at C_7 and C_{13} [89]. The imposing structure and optical medicinal importance of this molecule have attracted a great deal of attention from the other researchers since the disclosure of the structure [90–95], although the total synthesis had not been reported until our synthesis [96].

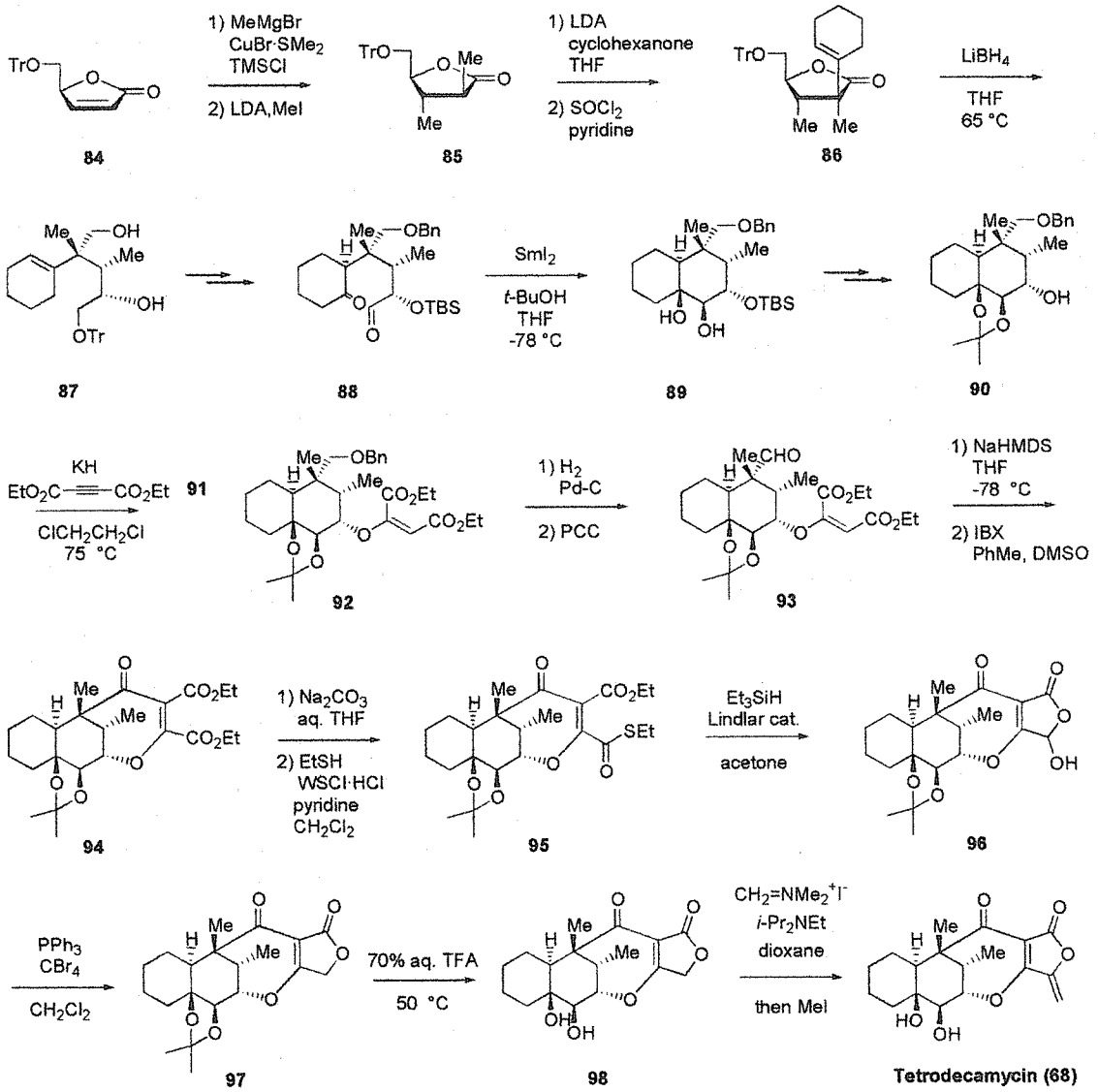


Scheme 6. Total syntheses of luminacins C_1 and C_2.

The total synthesis was initiated with the stereoselective conversion of the carbohydrate derivative **84** (Scheme 7) [20–24,97]. Michael addition and following methylation gave 2,3-dimethyl derivative **85**. Reaction of the lithiated **85** with the cyclohexanone was followed by dehydration to stereoselectively give the quaternary product **86** [20–24], which was submitted to hydride reduction to give diol **87**. After transformation to keto-aldehyde **88**, SmI_2-mediated pinacol coupling proceeded to afford *cis*-diol **89** as a single product [98]. Michael addition of **90** to diethyl acetylenedicarboxylate (**91**) gave the adduct **92**, which was converted to aldehyde **93**. Treatment of **93** with NaHMDS constructed the seven membered ring [99] smoothly and the resulting alcohol was oxidized to ketone **94**. Diester **94** was submitted to regioselective saponification to give monocarboxylic acid, which was transformed to the thioester **95**. Reduction of **95** with Et_3SiH to the corresponding aldehyde [100] accompanied the cyclization to the acetal **96**. Further reduction to lactone **96** was realized by our newly developed method using CBr_4 and PPh_3 [101,102]. Deacetonation of **97** afforded the diol **98**, which, upon treatment with Eschenmoser's reagent [103], underwent introduction of an *exo*-methylene group to give (−)-tetrodecamycin (**68**).

5. The total syntheses of macrolides using intramolecular Diels–Alder reaction

Intramolecular Diels–Alder reaction has been widely used to construct 6-membered ring-fused compounds including a functionalized decalin. The key function for control of stereoselectivity is arrangement of functional groups to lead to the desired transition state as well as stereoselective construction of olefins. Herein are described total syntheses by highly stereoselective intramolecular Diels-Alder reaction using carbohydrates as chiral sources.



Scheme 7. Total synthesis of tetrodecamycin.

5.1. The total synthesis of cochleamycin A

Cochleamycin A (**99**) was isolated by Kirin Brewery group from a cultured broth of *Streptomyces* sp. to show cytotoxicity against P388 leukemia cells and antimicrobial activities [104]. The structure including the relative stereochemistry was elucidated by exhaustive NMR studies to be endowed with a 5-6-10-6 membered tetracyclic core (Fig. 4) [105]. After the isolation, its analog, macquarimicin A (**100**) (Fig. 4) was independently isolated by Abbott group [106]. Not surprisingly, the combination of architectural complexities and bioactivities has engendered considerable interest, resulting in impressive synthetic studies from the groups of Paquette and Tadano using Diels–Alder reactions [107–110]. After our first total synthesis of cochleamycin A [97], Tadano's group reported the total synthesis of macquarimicin A (**100**) [109,110], and Roush's group disclosed his total synthesis of cochleamycin A [111]. Both groups took *transannular* Diels–Alder reactions to construct cochleamycin skeleton, as the formation of a 10-membered ring had been well known to be difficult. We used *intramolecular* Diels–Alder reaction followed by direct constructions of the 10-membered rings. Here, we describe the first total synthesis of cochleamycin A (**99**) accomplished in our laboratory [97].

The first total synthesis of cochleamycin A to determine the absolute structure was achieved as shown in Scheme 8. The lactone **84** was methylated stereoselectively by Michael addition with MeMgBr [112,113] in the presence of $CuBr \cdot Me_2S$ and TMSCl to give **102** as a single isomer. Reduction with $LiAlH_4$ afforded acyclic diol **103**, which was transformed to give the segment **104** in several steps. On the other hand, (*S*)-1,2,4-trihydroxybutane (**105**) was converted to the epoxide **106** [114], which was submitted to introduction of acetylene to afford **107**. **107** was transformed to the other segment, (*E*)-1-iodoalkene **108**.

Coupling of **104** and **108** smoothly proceeded to give the alcohol **109** in quantitative yield. This was selectively reduced to the *cis*, *trans*-diene structure, which was crucial to the construction of the desired *A–B* ring by intramolecular Diels–Alder reaction. Oxidation of the allylic alcohol gave the α,β-unsaturated aldehyde **110**, which was submitted to intramolecular Diels–Alder reaction in the presence of $Yb(fod)_3$ at 140 °C [115]. The desired adduct **111** was obtained as a single product in high yield. This intramolecular Diels–Alder reaction produced four critical stereocenters as expected. **111** was converted to α-bromoester **112**, the precursor of 10 membered ring. The desired cyclization of **112** was accomplished with SmI_2 to give 10-6-5 membered tricyclic product **113** as a single product [116], comprising the fully elaborated structure ready for conversion to the requisite seco-acid **114** (Scheme 5). Each of the four hydroxyl groups of **113** was discriminated from others. Lactonization of **114** was tested under the various conditions to construct *C–D* ring and the best result was realized by using Kita's conditions [117] to afford the δ-lactone **115** which possessed another 10 membered lactone ring. The allylic alcohol of the lactone **115** was oxidized to α,β-unsaturated ketone **116** by exposure to MnO_2. Finally, selective acetylation was accomplished with NaOAc and Ac_2O at 60 °C to afford cochleamycin A (**99**). The synthetic **99** was identical in all respects including the optical rotation with natural cochleamycin A, completing the first total synthesis to establish the absolute structure.

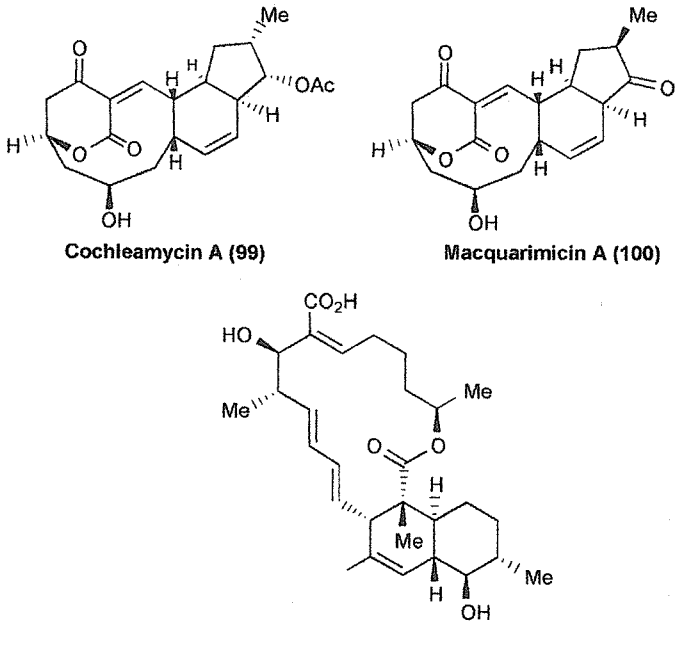
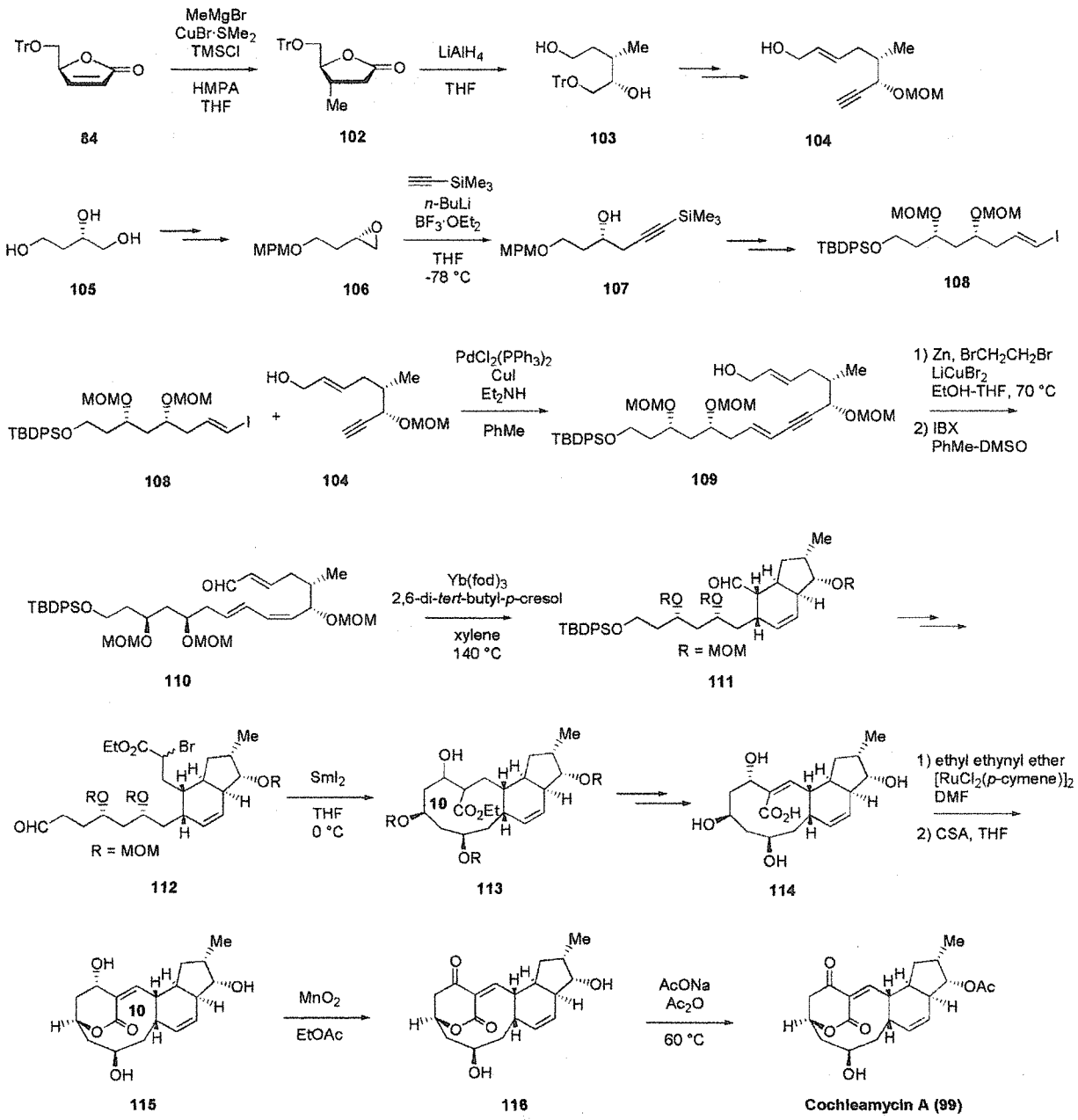


Fig. 4.

5.2. The total synthesis of (+)-tubelactomicin A

Tubelactomicin A (**101**) (Fig. 4) was isolated from the culture broth of *Nocardia*. sp. MK703-102F1 to show strong and specific antimicrobial activities against drug-resistant *Mycobacterium* [118]. The structure was determined by X-ray crystallographic analysis to be the 16-membered lactone fused with a *trans* decalin skeleton. As the morbidity of tuberculosis with the drug resistant strains has increased worldwide, new effective drugs are needed for treatment of *Microbacterium tuberculosis* [119]. The interesting chemical structure, combined with its antitubercular activities, has made (+)-tubelactomicin A an attractive target for synthesis, although the total synthesis has already been accomplished by the Tadano group using intramolecular Diels–Alder reaction [120,121]. Independently, we accomplished the total synthesis of (+)-tubelactomicin A (**101**), which was presented herein (Scheme 9) [122].

The stereochemical array of the northern part was derived from L-arabinose (**117**). Lactone **118** [123] was submitted to the stereoselective methylation and reductive ring opening to give diol **120**, possessing functionality to be the northern part **121**.



Scheme 8. Total synthesis of cochleamycin A.

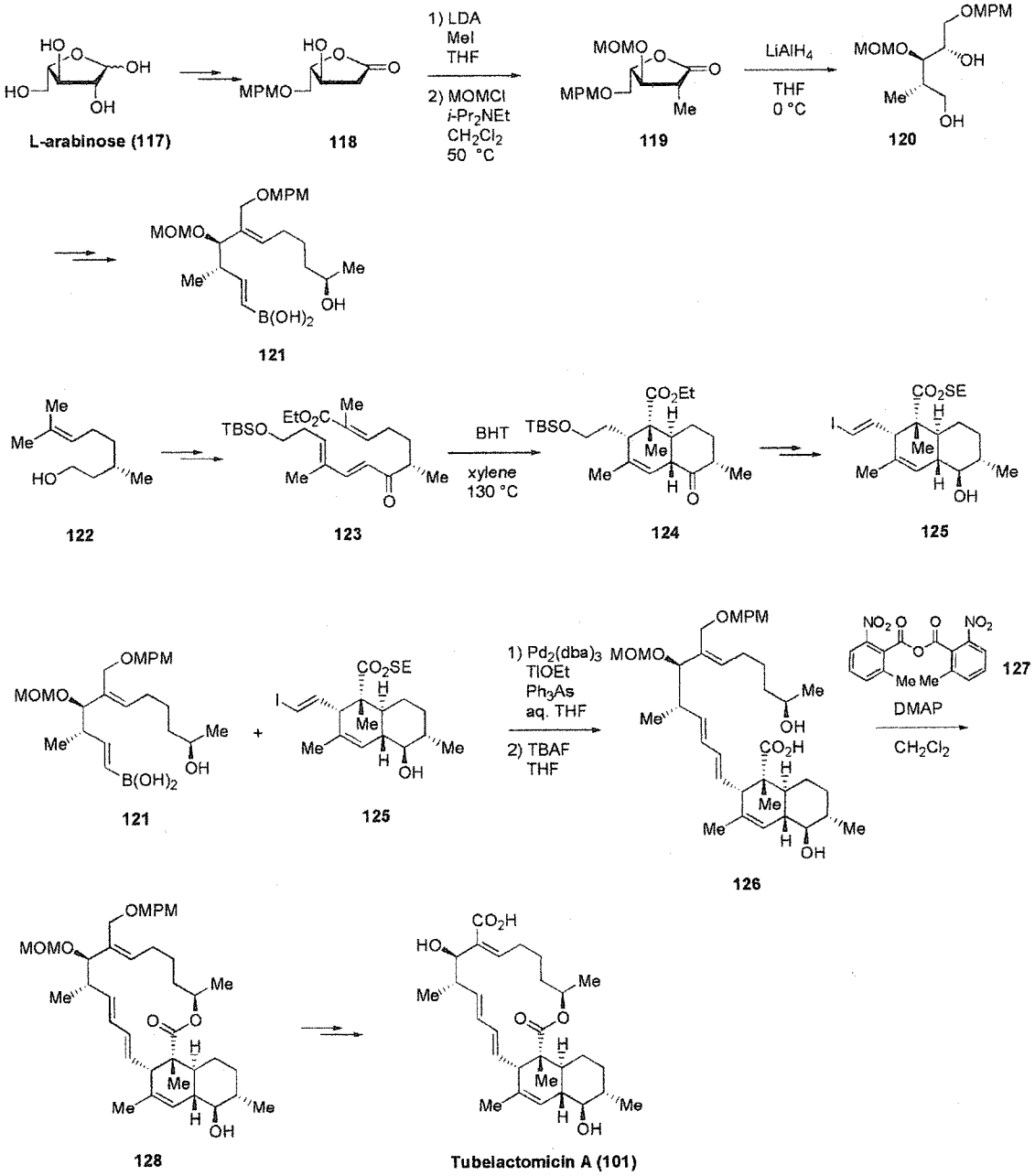
The decalin moiety, the southern part of tubelactomicin A, was constructed by intramolecular Diels–Alder reaction [97,124]. The citronerol **122** was converted the triene **123**. The stereoselective Diels–Alder reaction to construct additional four chiral centers was realized by heating **123** in xylene, which gave **124** as a single product. The decalin **124** was converted to the alcohol **125** to couple with the northern part **121**.

Treatment of the mixture of **121** and **125** under the conditions of Suzuki coupling gave the tetraen product **126** [125]. The seco-acid derivative **126** was submitted to the macrolactonization by Shiina's method [126] to construct lactone **128**. Deprotection and selective oxidation afforded (+)-tubelactomicin A (**101**).

6. Conclusion

Most of the total syntheses that have been completed in our laboratories are the first ever accomplished. The achievement of successful results in research is, of course, of prime importance. Yet, prior to undertaking research, it is essential that the objectives of the research are clearly understood and defined. Hence, it may be no exaggeration to say that the selection of target molecules decides, above all, the value of the research itself in bioactive compounds synthesis.

In one view, the authors believe that the most important is to make utmost efforts towards realizing one's dream, that is, to synthesize a target molecule by one's own



Scheme 9. Total synthesis of tubelactomicin A.

concept and developed strategies. Such effort will certainly produce the "art" as mentioned in the Introduction, in the reactions and/or products.

In short, there is no royal road to success in total synthesis and development of useful bioactive compounds—steady efforts are the only way to achieve that goal.

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