Asymmetric Synthesis of Anthracyclinones: Regio- and Stereoselective Synthesis of (−)-7-Deoxydaunomycinone through Direct Asymmetric Introduction of an Alkynyl Unit into C9 Ketone

Hiromichi Fujikata, Hirofumi Yamamoto, Hirokazu Annoura, Makoto Miyazaki and Yasuyuki Kita*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamadaoka, Suita, Osaka 565, Japan. Received December 25, 1989

A new chiral AB-building block (5) for preparing optically active anthracyclinones was synthesized via compound 13a, which was obtained by the stereoselective nucleophilic addition of (trimethylsilyl)ethylmagnesium chloride to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (12) derived from (−)-(2S,3S)-1,4-dimethoxy-2,3-butaneadiol. Synthesis of (−)-7-deoxydaunomycinone [(−)-4] was achieved through a regiospecific condensation of 5 and 4-acetoxy-8-methoxyhomaphthalic anhydride (18). The optical purity (100% ee) of (−)-4 was unambiguously confirmed by high performance liquid chromatographic analysis of (±)-4 and (−)-4 on a chiral column and also by proton nuclear magnetic resonance examination of the methylated compounds, (±)- and (−)-21, using the chiral shift reagent, tris[3-(trifluoromethylhydroxymethylene)acapharato]europium(III) [Eu(tfc)₃].

Keywords asymmetric synthesis; chiral acetal; (−)-(2S,3S)-1,4-dimethoxy-2,3-butaneadiol; stereoselective nucleophilic addition; regiospecific cycloaddition; anthracyclinone; (−)-7-deoxydaunomycinone

The anthracycline antibiotics are of interest as potential antitumor agents against a broad spectrum of human cancers. The daunomycin family (daunomycin, adriamycin, and camminomycin) is one of the most clinically useful groups of drugs, possessing a chiral A ring with a 9-substituted 7,9-cis-dihydroxy functionality as a characteristic structural feature. A large number of studies have been directed toward syntheses of their aglycons, daunomycinone (1), adriamycinone (2), and camminomycinone (3), during the past decade. Recently, much effort has been focused on the syntheses of the optically active aglycons to avoid the complex and wasteful separation of diastereomeric products in the final glycosylation step and also to economize on the use of the valuable sugar moiety. Asymmetric synthesis is one of the choices and many methodologies such as asymmetric reduction, asymmetric epoxidation, asymmetric bromolactonization, and asymmetric osmium tetroxide oxidation have been developed so far, mainly addressed to constructing the chiral tertiary alcohol moiety at the C9 position. Recently we have briefly reported the synthesis of (−)-7-deoxydaunomycinone (4), a late-stage precursor for (+)-daunomycinone (I). Our synthesis includes an effective preparation of a new chiral AB-building block (5), via a novel construction of the C9 (anthracycline numbering) chiral tertiary alcohol moiety through a diastereoselective nucleophilic addition to C9 ketone and a regioselective coupling reaction of 5 with the CD-synthon (18). Here we present a full account of this work.

Synthesis of the Chiral AB Synthon, (6R)-2-Bromo-6-ethyl-6-hydroxy-5,6,7,8-tetrahydro-1,4-naphthoquinone (5) The chiral AB synthon (5) was synthesized from 13a obtained by nucleophilic addition of (trimethylsilyl)ethylmagnesium chloride to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (12).

The acetal (12) was synthesized as shown in Chart 2. The known bromo acid (6) was cyclized under acidic conditions to give the 6-bromo-1-tetralone derivative (7). Demethylation of 7 with aluminum chloride in dichloromethane gave 8, which was subjected to protection reaction of the phenolic hydroxy functions to afford 9. Treatment of 9 under Moriarty's conditions [phenyl iodine(III) diacetate [PhI(OAc)₂]/KOH/Methanol] gave the labile γ-hydroxydimethyloacetel (10), which is easily hydrolyzed on a silica gel column and was used in the subsequent reaction without purification. Transacetalization of 10 with 1.1 eq of (−)-(2S,3S)-1,4-dimethoxy-2,3-butaneadiol in the presence of a catalytic amount of camphorsulfonic acid (CSA) gave the γ-hydroxy acetal (11), which was converted to the chiral acetal (12) by modified pyridinium dichromate (PDC).
The results of nucleophilic addition of organometallics to the chiral 6-bromo-1-oxo-β-tetralone 1-acetal (12) are summarized in Table 1. The reaction of 12 with some Grignard reagents (5 eq), which have alkynyl or alkyl units (R = - - - - TMS, Et, Me) being convertible to the side chains (-COCH₃, -COCH₂OH, Et, Me) observed in natural anthracyclines such as daunomycin, adriamycin, rhodomycin, and feudomycin, was carried out in tetrahydrofuran (THF) (runs 1—3). Extremely high diastereoselectivity (100% ee) was observed in every run. An authentic diastereomeric mixture (13a:13a = 3:1) for comparison with the product in run 1 was obtained by the reaction of 12 with (trimethylsilyl)ethyllum (run 4). The purity of 13b and 13c was determined by proton nuclear magnetic resonance (¹H-NMR) (500 MHz). The stereochemistry of the products was tentatively assigned from our preliminary results and that of 13a and 13b was unambiguously determined by the conversion of 13a to (-)-7-deoxydaunomycinone and by correlation between 13a and 13b.

Conversion of 13a to the bromoquinone (5) was achieved as shown in Chart 3. Detrimethylsilylation of 13a under alkaline conditions afforded 14, which was converted to 15 by acid hydrolysis. Acetylation of 15 was carried out in the presence of a catalytic amount of 4-dimethylamino.pyridine (4-DMAP) to give the triacetate (16). Sodium borohydride (NaBH₄) reduction of 16 in aqueous THF followed by alkaline treatment afforded the triol (17). Without prior acetylation of the C2 alcohol, the reduction of the C1 ketone resulted in the formation of the C1 secondary hydroxy functionality. The triol (17) was relatively unstable and immediately oxidized with ceric ammonium nitrate (CAN) without further purification to give the chiral bromoquinone (5). The complete chiral integrity of the tertiary alcohol moiety during the conversion of 13a to 5 was deduced from the successful synthesis of optically pure (−)-7-deoxydaunomycinone (vide infra).

Synthesis of (−)-7-Deoxydaunomycinone (4) The coupling reaction of 4-acetoxyl-8-methoxyhomaphtholic anhydride (18) with 5 was carried out in the presence of sodium hydride (NaH) in THF. The coupled product 19 was obtained regioselective by [4 + 2] cycloaddition of 18 followed by extrusion of carbon dioxide and hydrogen bromide. Treatment of 19 with mercuric oxide under acidic conditions afforded 20, which was deactylated with aqueous trifluoroacetic acid to give (−)-7-deoxydaunomycinone [(−)-(−)-4] (Chart 4). The melting point (mp) and spectral data (infrared (IR), ¹H-NMR) of (−)-4 were identical with those of authentic (±)-4 prepared earlier by us and the specific rotation of ours was in good agreement with the reported value [mp 232—233.5°C, [α]D 87.5° (c = 0.093, CHCl₃); lit. mp 229—233.5°C, [α]D 87.5° (c = 0.094, CHCl₃)].

The optical purity (100% ee) of (−)-4 was unambiguously confirmed by high-performance liquid chromatographic (HPLC) analysis of (−)- and (±)-4 using a chiral column (Daicel Chiral Cel OA) (Fig. 1) and by ¹H-

---

**Table 1. Nucleophilic Addition of RM to 12**

<table>
<thead>
<tr>
<th>Run</th>
<th>RM</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
<th>Ratio (13a:13c)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMS-MgCl</td>
<td>-23—rt.</td>
<td>96</td>
<td>100:0</td>
<td>13a only</td>
</tr>
<tr>
<td>2</td>
<td>EtMgCl</td>
<td>-78—-23</td>
<td>99</td>
<td>100:0</td>
<td>13b only</td>
</tr>
<tr>
<td>3</td>
<td>MeMgBr</td>
<td>-78—-23</td>
<td>96</td>
<td>100:0</td>
<td>13c only</td>
</tr>
<tr>
<td>4</td>
<td>TMS-Li</td>
<td>-78</td>
<td>81</td>
<td>75:25</td>
<td>13a + 13a</td>
</tr>
</tbody>
</table>
Our asymmetric synthesis is, to our knowledge, the only method so far available for the synthesis of optically active anthracyclonine via asymmetric addition to the C9 (anthracene numbering) ketone and has the following advantages: i) direct asymmetric introduction of the required alkynyl or alkyll units to the C9 position; ii) the use of acetol as a chiral auxiliary, which promises further transformation as a synthetic equivalent of the versatile carbonyl function. Therefore, this methodology should open an effective route to various types of antracycinones, and studies along this line are in progress.146

Experimental

The following instruments were used to obtain physical data: specific rotation, Perkin-Elmer 241 polarimeter; IR spectra, JASCO IRA-1 spectrometer; 1H-NMR spectra, Hitachi R-22 (90 MHz); JEOL JNM-FX 90Q FT-NMR (90 MHz) or JEOL LNM-GX 500 FT-NMR (500 MHz) spectrometer (with tetramethylsilane as an internal standard); low- and high-resolution mass spectra (MS), JEOL JMS D-300 mass spectrometer (with a direct inlet system). A JASCO TRITORAT-II high-pressure liquid chromatography (UV detector) was used for HPLC analysis. E. Merck silica gel (0.063–0.200 mm) and 70–230 mesh ASTM for column chromatography and E. Merck TLC plates pre-coated with Silica gel 60F254 for preparative thin layer chromatography (TLC) (0.5 mm) and TLC detection (0.2 mm) were used. Specific rotation was measured at 20°C in CHCl3, unless otherwise mentioned. All melting points are uncorrected.

6-Bromo-5-hydroxy-8-methoxy-1-oxotetralin (7) A mixture of (19.4 g, 67.1 mmol) and concentrated H2SO4 (80 ml) was stirred for 1 h at 80–90°C under a nitrogen atmosphere. The mixture was cooled to room temperature, diluted with water, and extracted with CH2Cl2. The organic layer was washed with brine, dried over MgSO4, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using CH2Cl2:hexane (1:1) as an eluent to give 7 (75.5 g, 86%). Yellow plates (hexane-CH2Cl2), mp 133–134°C. IR νmax cm⁻¹: 3545, 1678, 1463, 1085. 1H-NMR (CDCl3) δ: 2.00–2.22 (m, 2H, -CH2-), 2.54 (t, 2H, J = 6.4 Hz, -CH2-), 2.94 (t, 2H, J = 6.4 Hz, -CH2-), 3.84 (s, 3H, -OCH3), 5.52 (s, 1H, -OH), 6.97 (s, 1H, aromatic proton). Exact MS Caled for C11H12BrNO2: 255.9756. Found: 255.9753. Caled for C11H12BrNO2: 257.9716. Found: 257.9727.

6-Bromo-5,8-dihydroxy-1-oxotetralin (8) AlCl3 (7.3 g, 55.2 mmol) was added to a stirred solution of 7 (5.0 g, 18.4 mmol) in dry CH2Cl2 (200 ml) at 0°C and the mixture was stirred overnight at room temperature under a nitrogen atmosphere. The reaction was quenched with saturated aqueous oxalic acid at 0°C and the mixture was extracted with CH2Cl2. The organic layer was washed with brine, dried over MgSO4, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using ethane-ether (1:1) as an eluent to give 8 (4.5 g, 96%). Yellow plates (CH2Cl2), mp 153–154°C. IR νmax cm⁻¹: 3547, 1640, 1609, 1445. 1H-NMR (CDCl3) δ: 1.95–2.22 (m, 2H, -CH2-), 2.67 (t, 2H, J = 5.9 Hz, -CH2-), 2.94 (t, 2H, J = 5.9 Hz, -CH2-), 5.29 (s, 2H, -OH X 2), 7.01 (s, 1H, aromatic proton). Exact MS Caled for C11H14BrNO2: 257.9716. Found: 257.9727.

6-Bromo-5,8-dimethoxy-1-oxotetralin (9) A solution of 8 (4.5 g, 17.5 mmol) in dry THF (55 ml) was added dropwise to a stirred suspension of NaNH (2.3 g, 60% in oil, 57 mmol) in dry THF (5 ml) at 0°C under a nitrogen atmosphere. The mixture was stirred for 20 min at room temperature, then chloromethyl methyl ether (5.3 ml, 70 mmol) was added slowly at 0°C, and the resulting solution was stirred for 1 h at room temperature. The reaction was quenched with water and the mixture was extracted with CH2Cl2. The organic layer was washed with brine, dried over MgSO4, and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using ethane-ether (1:1) as an eluent to give 9 (5.8 g, 90%). White plates (CH2Cl2), mp 52–54°C. IR νmax cm⁻¹: 2960, 1680, 1563, 1156. 1H-NMR (CDCl3) δ: 1.95–2.25 (m, 2H, -CH2-), 2.64 (t, 2H, J = 6.8 Hz, -CH2-), 3.06 (t, 2H, J = 6.8 Hz, -CH2-), 3.57 (s, 3H, -OCH3), 3.68 (s, 3H, -OCH3), 5.11 (s, 2H, -OCH2-), 5.23 (s, 2H, -OCH2-), 7.42 (s, 1H, aromatic proton). Exact MS Caled for C11H14BrNO2: 254.0257. Found: 254.0256. Caled for C11H14BrNO2: 254.0249. Found: 254.0248.

6-Bromo-5,8-dimethoxy-2-hydroxy-1-oxotetralin (2S,3S)-1,4-Dimethoxy-2,3-butylen Acetal (11) Ph(OAc)2 (300 mg, 0.71 mmol) was added portionwise to a stirred solution of 9 (245 mg, 0.71 mmol) and KOH
(140 mg, 2.49 mmol) in absolute MeOH (4 ml) at 0°C. The mixture was stirred for 3 h at the same temperature under a nitrogen atmosphere. MeOH was evaporated off under reduced pressure. The residue was diluted with water and extracted with CH₂Cl₂. The organic layer was washed with brine, dried over 22 mmol of MgSO₄, and concentrated under reduced pressure in the presence of a small amount of K₂CO₃ to give a crude product (10), which was used in the next reaction without purification. A mixture of the crude 10, (--)-(2S,3S)-1,4-dimethoxy-2,3-butaneol (130 mg, 0.85 mmol), and a catalytic amount of CSA was stirred for 10 min under reduced pressure (0.5 mm Hg). Dry CH₂Cl₂ (2.5 ml) was added to the resultant residue at room temperature. The reaction was quenched by the addition of the K₂CO₃ (one microscopical funnel) and the inorganic salt was filtered off. The filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (5 ml) and treated with a suitable amount of NaBH₄ for 20 min at 0°C. Usual work-up afforded a crude product, which was purified by silica gel chromatography using hexane-ether (1:4) as an eluent to give 11 (225 mg, 67%) as a diastereomeric mixture. White crystals (hexane, mp 85°C. IR νcm⁻¹: 3425, 2949, 1574, 1461, 1155. ¹H-NMR (CDCl₃, δ): 1.08–2.25 (m, 2H, -CH₂-), 2.65–3.14 (2H, -CH₂-C₆H₅), 3.37, 3.39, 3.44, 3.46, 3.49, 3.60, 3.61 (each 2H, total 12H, -OCH₂-C₆H₅), 4.00–4.75 (2H, -OH), 2.97 and -CH₂OH), 5.16 (m, 1H, aromatic proton). Exact MS Calcd for C₂₁H₂₄Br₂O₃Si: 429.0996. Found: 429.1006.

6-Bromo-5,8-dimethylhexyl-1,2-dioxetarilin (15) (2S,3S)-1,4-Dimethoxy-2,3-butylen) Acetal (12) Activated molecular sieves 3Å (7.0g), PDC (5.6g, 14.82 mmol), and Ac₂O (1.0 ml, 10 mmol) were added to a stirred solution of C₁₂H₁₃O₂Br (43 mmol, 12 g) in dry THF (25 ml) at room temperature. After the resulting mixture was stirred for 2 h at the same temperature under a nitrogen atmosphere. Ether (200 ml) was added to the mixture and the insoluble salt was removed by passage through a short column followed by filtration. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane-ether (1:4) as an eluent to afford 14 (33.9g, 54%). Colored oil. IR νcm⁻¹: 3425, 2925, 1675, 1521, 1474, 1464. ¹H-NMR (CDCl₃, δ): 2.68–3.00 (m, 2H, -CH₂-C₆H₅), 3.04–3.30 (2H, -CH₂-C₆H₅), 3.39, 3.41, 3.50, 3.57 (all 3H, each, -OCH₂-C₆H₅), 4.32 (2H, -OCOCH₂), 4.62 (2H, -OCOCH₂), 4.98, 5.19 (both 2H, aromatic protons), 7.32 (2H, 1H, aromatic proton). Exact MS Calcd for C₂₁H₂₄Br₂O₃Si: 420.0890. Found: 426.0893. Calcd for C₂₁H₂₄Br₂O₃Si: 404.0868. Found: 404.0868.

Nucleophlic Addition of Organometallics to the Chiral Acetal (12) General Procedure: An organometallic reagent (5 mmol) in dry THF was added dropwise to a stirred solution of 12 (1 mmol) in dry THF (10 ml) and the resulting mixture was stirred for 3 h at the same temperature. After completion of the reaction (checked by TLC), the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane-ether (1:4) as an eluent to afford 15 (18.0g, 47). Colored oil. IR νcm⁻¹: 3425, 2925, 1675, 1521, 1474, 1464. ¹H-NMR (CDCl₃, δ): 1.94–2.65 (m, 4H, -CH₂-C₆H₅), 3.04–3.30 (m, 6H, -CH₂-C₆H₅), 3.39, 3.41, 3.50, 3.57 (3H, each, -OCH₂-C₆H₅), 4.30 (2H, -OCOCH₂), 4.62 (2H, -OCOCH₂), 4.98, 5.19 (both 2H, aromatic protons), 7.32 (2H, 1H, aromatic proton). Exact MS Calcd for C₂₁H₂₄Br₂O₃Si: 416.0868. Found: 416.0868.

Hydrogenation of 14 Compound (14) (51.6 mmol) was dissolved in AcOEt (1 ml) and hydrogenated in the presence of a catalytic amount of 5% Pd-C under atmospheric pressure at room temperature. After the completion of the reaction (checked by TLC), the catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using hexane-ether (1:4) as an eluent to give 13 (46.5 mmol, 90%), which was identical with 13 obtained in run 2 by HPLC (97.9%).

(2S)-6-Bromo-2-ethyl-5,8-dihydroxy-1,2-dioxetarilin (15) A solution of 14 (3.59 g, 6.95 mmol) and concentrated H₂SO₄ (1 ml) in 50% aqueous AcOH (500 ml) was refluxed overnight. The resulting mixture was cooled to room temperature, neutralized with NaOH and extracted with ether. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was purified by column gel chromatography using hexane-ether (1:4) as an eluent to give 15 (5.99 g, 77%). Yellow needles (hexane-ether), mp 160–161°C. IR νcm⁻¹: 3548, 3300, 1650, 1649, 1477, 1180, 1013. ¹H-NMR (CDCl₃, δ): 1.95–2.75 (m, 2H, -CH₂-C₆H₅), 2.53 (2H, 1H, -OCH₃), 3.0–3.15 (m, 2H, -CH₂-C₆H₅), 4.11 (m, 1H, -OCH₃), 7.02 (1H, aromatic proton), 7.0 (1H, aromatic proton). Exact MS Calcd for C₁₂H₁₃BrO₄Si: 295.9685. Found: 295.9703. Calcd for C₁₂H₁₃BrO₄Si: 295.9686. Found: 295.9686.

(2S)-6-Bromo-2-ethyl-5,8-triacyloxy-1,2-dioxetarilin (16) A mixture of 15 (330 g, 1.1 mmol), Ac₂O (0.6 ml) and 4-DMAP (10 mg) in pyridine (10 ml) was stirred for 2 h at 50°C under a nitrogen atmosphere. Pyridine was evaporated off under reduced pressure. Then 10% aqueous HCl was added to the residue and the resulting mixture was extracted with ether. The organic layer was washed with brine, dried over MgSO₄, and concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel using hexane-ether (1:2) to give 16 in a quantitative yield. Colorless plates (benzene), mp 170°C. IR νcm⁻¹: 10.0° (ν = 0.655). ¹H-NMR (CDCl₃, δ): 3130, 1778, 1716, 1595, 1455, 1370, 1165. ¹H-NMR (CDCl₃, δ): 2.12, 2.36, 2.39 (all 3H, each, -COCH₃). 2.4–2.72 (2H, -CH₂-C₆H₅), 2.72 (m, 1H, -OCH₃), 2.8–3.1 (m, 2H, -CH₃).
A solution of 4 (15 mg, 0.04 mmol), CH₃I (0.5 ml), and K₂CO₃ (30 mg) in dry acetone (3 ml) was stirred at 60°C for 1 h under a nitrogen atmosphere. The solution was filtered, and the acetone was evaporated off. The residue was puriﬁed by preparative TLC (CHCl₃:acetone = 6:1) to give 21 (9.8 mg, 60%). 1H-NMR (CDCl₃) δ: 1.70–2.00 (m, 2H, -CH₂-), 2.36 (6, 3H, -COCH₃), 2.80–3.20 (m, total 4H, -CH₂- × 2, 3.90, 3.97, 4.00 (all 4 s, total 3H, -OH) × 3, 2.75 (d, 1H, J = 8 Hz, aromatic proton), 7.61 (1H, J = 8 Hz, aromatic proton), 7.80 (1H, J = 8 Hz, aromatic proton). A solution of 21 (1.7 mg) and Eu(fcl)₃ (1 mg) in CDCl₃ (0.15 ml) was used for the ¹H-NMR experiment [JEOL JNM-FX90Q FT-NMR (90 MHz)]; see text and Fig. 2.

References and Notes


8. (−)-(2S,3S)-4,4-Dimethoxy-2,3-butanediol can be readily prepared from L(+)-tartaric acid in four steps: (1) Me₂CO(OMe)₂, MeOH/H₂O, TsOH/cyclohexane [M. Carmack and C. J. Kelly, J. Org. Chem., 33, 2171 (1968)]; (2) LiH₂(Al₂O₃)/reflux; (3) Mel/KOH/DMSO; (4) 95% EtOH/H₂O/reflux.


16. Since the value of the specific rotation of 4 strongly depends on the purity of the solvent (see ref. 15), HPLC analysis and ¹H-NMR spectroscopy were adopted to determine the precise optical purity of (−)(−)‐4.


19. Since the separation of the 11 and the 10-keto compound obtained by hydrolysis of the acetyl moiety of 10 was difficult, NaBH₄ was used to reduce the 10-keto compound; subsequent separation was easy.