Synthetic Study on Telomerase Inhibitor, D8646-2-6: Synthesis of the Key Intermediate Using Sn(OTf)2 or Sc(OTf)3 Mediated Aldol-Type Reaction and Stille Coupling

Akira KANAI, a Yoshifumi TAKEDA, a Kouji KURAMOCHI, b Atsuo NAKAZAKI, a and Susumu KOBAYASHI*a

a Faculty of Pharmaceutical Sciences, Tokyo University of Science (RIKADAI); and b Department of Applied Biological Science, Faculty of Science and Technology, Tokyo University of Science (RIKADAI); 2641 Yamazaki, Noda, Chiba 278–8510, Japan. Received December 12, 2006; accepted December 19, 2006; published online December 22, 2006

The synthesis of the key intermediate (4) in the proposed route to D8646-2-6 is described. The aldol reaction of the carbohydrate-containing pyrone 7 with the aldehyde 6 was accomplished by using LiHMDS and Sc(OTf)3 or Sn(OTf)2. The stepwise dehydration reaction of the aldol adduct 14, followed by Stille coupling with vinyl stannane 5 which contained phosphonate gave the desired 4.

Key words aldol-type reaction; carbohydrate-containing pyrone; stille coupling; scandium triflate; tin triflate; vinyl stannane which contains phosphonate

In 2002, the Mitsubishi Pharma group reported the isolation of a telomerase inhibitor, D8646-2-6 (1) from the culture broth of fungus Epicoccum purpurascens.1) The compound has a unique C3-pyranosyl 4-hydroxy-2-pyrone moiety 2) and conjugated polyene unit.3—7) However the structure of 1 including the relative and absolute stereochemistry has not been fully elucidated yet. The potent biological activity and structural complexity of this compound prompted us to initiate synthetic studies toward 1. In our preceding paper, we have reported the construction of the C-glycosyl 4-hydroxy pyrone moiety of 1. Comparison of the NMR spectra of the C3-galactopyranosyl 4-hydroxy-2-pyrone moiety 2 with those of natural 1, demonstrated that the carbohydrate moiety of the latter compound to be C3-galactopyranoside (Fig. 1).8)

Our synthetic strategy toward the total synthesis of 1 is shown in Chart 1. Due to the labile nature of the polyenic side chain, our synthetic strategy involved an initial aldol condensation of the pyrone moiety with the side chain unit (C8—C12), followed by the elongation of the remaining side chain unit. Since the stereochemistry at C21 and C23 was not determined, we envisaged that phosphonate 4 would serve as a versatile key intermediate for the synthesis of D8646-2-6 and its stereoisomers. Horner-Wadsworth-Emmons reaction was successfully utilized by Cha and co-workers in the total synthesis of citreoviridin9) which contains polyene conjugated with pyrone ring. Phosphonate 4 could be synthesized by Stille coupling10) of triene 15 with vinyl stannane which contains phosphonate.11) Although there have been some reports concerning the aldol-type reaction and alkylation of pyrones,12—24) the application of this approach to a carbohydrate-containing compound is unprecedented. Since oxygenated functionalities of substrates might influence on the reactivity of carbanion, the reactivity of such carbohydrate-bearing pyrones as well as its synthetic utilities is quite interesting. Herein, we report the synthesis of the key intermediate 4 using aldol-type reaction of carbohydrate containing pyrone 7 followed by stepwise dehydration and Stille coupling with vinyl stannane 5 which contains phosphonate group.

The feasibility of the key aldol-type reaction was evaluated through model systems. The aldol reaction of 725—27) with (2E,4E)-hexa-2,4-dienal by the simple treatment with LiHMDS to give 8 in only 6% yield and 62% of 7 was recovered (Chart 2).

However, the aldol-type reaction of 4-methoxy-6-methyl-2-pyrrone 9 with (2E,4E)-hexa-2,4-dienal proceeded smoothly under the same conditions to afford the aldol product 10 in 87% yield. These results indicated that the carbohydrate moiety greatly influenced the aldol-type reaction. We reasoned that the highly oxygenated functional group of 7 might decrease the reactivity of the pyrone-stabilized carbanion through the coordination to the lithium ion or by steric

Fig. 1. Structure of D8646-2-6 and C3-Pyranosyl 4-Hydroxy-2-pyrone Moiety

Chart 1. Synthetic Strategy of D8646-2-6

* To whom correspondence should be addressed. e-mail: kobayash@rs.noda.tus.ac.jp © 2007 Pharmaceutical Society of Japan
hidrance.

We next examined a variety of additives in the above aldol-type reaction (Table 1). The addition of LiCl did not affect the yield of the aldol products 8 and 11 (entry 1). However, the addition of Me2AlCl, TiCl(OiPr)3, Sc(OTf)3, SnCl4 or Sn(OTf)2, improved the yield of the products (entries 2, 4, 6, 8, 9). When Me2AlCl or TiCl(OiPr)3 was used, the major product was 8 (entries 2, 4). On the other hand, the dehydrated product 11 was obtained as a major product using Sc(OTf)3 or Sn(OTf)2 as an additive (entries 6, 9). The addition of SnCl4 slightly improved the yield of the aldol products with almost 1:1 ratio of 8 and 11 (entry 8). Using 3 eq of LiHMDS, no significant improvement was achieved with Me2AlCl or TiCl(OiPr)3 as an additive (entries 3, 5). However, we found that the aldol reaction proceeded smoothly when LiHMDS (3 eq) and Sc(OTf)3 or Sn(OTf)2 (1 eq) were used in the reaction (entries 7, 10).

We tentatively speculate that scandium(III) and tin(II) might coordinate to both carbonyl oxygen of the aldehyde (activation of an electrophile) and ether oxygen of galactose moiety (proximity effect). We also believe that Sc(OTf)3 or Sn(OTf)2 stabilize the alkoxide derivative of the aldol-type product by the formation of the stable scandium(III) or tin(II) alkoxide.

Table 1. Aldol-Type Reaction of Pyrone Moiety 7 with (2E,4E)-Hexa-2,4-dienal

<table>
<thead>
<tr>
<th>Entry</th>
<th>LiHMDS (eq)</th>
<th>Additive (1.0 eq)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>LiCl</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Me2AlCl</td>
<td>35 Trace</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Me2AlCl</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>TiCl(OiPr)3</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>TiCl(OiPr)3</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Sc(OTf)3</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>3</td>
<td>Sc(OTf)3</td>
<td>54</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>SnCl4</td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>Sn(OTf)2</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>3</td>
<td>Sn(OTf)2</td>
<td>69</td>
</tr>
</tbody>
</table>

With the aldol adduct 8 in hand, direct dehydration was next investigated. When the aldol adduct 8 was subjected to a conventional dehydration conditions using CCl3COCl and Et3N,28) the desired triene 11 was obtained in 57% yield as a 2:1 mixture of E and Z isomers, in addition to alcohol 12 (10%) and trichloroacetate 13 (4%) (Table 2, entry 1 and Chart 3).29)

The formation of alcohol 12 and trichloroacetate 13 might be explained by the rearrangement shown in Chart 3. Similar sigmatropic rearrangement of allylic trichloroacetimidate was also reported by Overman.30,31) We also examined other direct dehydration methods such as TFAA–Et3N, Tf2O and HfCl4(THF)2 to afford the triene 11 in low to moderate yield (Table 2, entries 2—4). Finally we found that the stepwise method involving an initial acetylation (Ac2O–pyridine, DMAP) followed by elimination with DBU afforded the best result (74%) (entry 5).

The present Sc(OTf)3 or Sn(OTf)2 mediated aldol-type reaction was successfully applied to the synthesis of the key intermediate of D8646-2-6. Pyrone 7 was reacted with (2E,4E)-5-bromopenta-2,4-dienal 633,34) using LiHMDS and Sc(OTf)3 or Sn(OTf)2 to give the aldol product 14 in 85% or 83% yield, respectively (Chart 4). It should be emphasized that no reaction occurred without Sn(OTf)2 or Sc(OTf)3. Aldol adduct 14 was then subjected to a stepwise elimination described above (Ac2O–pyridine and DMAP) followed by elimination with DBU afforded the best result (74%) (entry 5).

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With the triene 15 in hand, we next examined Stille coupling of 15 with vinyl stannane 5 which is bearing phospho-
addition of Sn(OTf)\(_2\) or Sc(OTf)\(_3\). Using a combination of carbohydrate-bearing pyrone with aldehyde proceeded by the ion mixture, the coupling product was obtained in 63\% yield.

Experimental

IR spectra were recorded on a JASCO FT/IR-410 spectrometer using NaCl plate. Optical rotations were recorded using CHCl\(_3\) or MeOH as solvents on a JASCO P-1030 digital polarimeter. 1H-NMR spectra (600 MHz, DMSO-\(d_6\)) are in hertz (Hz). Optical rotations were recorded using poly(ethylene glycol) as internal standard.

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Aldol Condensation of Pyrone Moiety 7 with 2E,4E-Hexa-2,4-dienal Sn(OTf)\(_3\) Mediated Aldol Reaction To a stirred solution of pyrone moiety 7 (2.0 g, 3.00 mmol) in dry THF (30 ml) at 78 °C. After being stirred for 30 min, 2E,4E-hexa-2,4-dienal (0.7 ml, 6.0 mmol) and Sn(OTf)\(_3\) (1.2 g, 2.8 mmol) were added successively at −78 °C. After the reaction mixture was stirred for additional 2.5 h, it was allowed to warm up to the room temperature. Then it was poured into saturated aqueous NH\(_4\)Cl. After the mixture was filtered through Celite\(^\text{®}\), the product was extracted with EtOAc. The organic phase was washed with 1 N HCl, and it was neutralized with saturated aqueous NaHCO\(_3\). The organic extract was washed with Brine, dried with Na\(_2\)SO\(_4\), then filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 2 : 1 benzene/EtOAc) to afford aldol adduct 8 (1.48 g, 69\%) as a pearl yellow foam and triene 11 (0.09 g, 3\%) as a yellow foam.

Sc(OTf)\(_3\) mediated aldol reaction was carried out with the same procedure described above to afford aldol adduct 8 (54\%) and triene 11 (20\%).

\((E,3,5,5E)-1-(4-Benzoylpyrroliz-3(2,3,4,6-tetra-O-benzyl-\beta-D-galactopyranosyl)-1,3,5-heptatrien-1-ol)\) To a stirred solution of aldol adduct 8 (0.46 g, 0.55 mmol) in dry CH\(_2\)Cl\(_2\) (6 ml) at room temperature under argon was dropwise added LiHMDS (9.0 ml, 1.0 M solution in THF, 9.00 mmol). After being stirred for 30 min, vinyl 15 (2.0 g, 3.00 mmol) in dry CH\(_2\)Cl\(_2\) (6 ml) at room temperature. Then it was poured into saturated aqueous NH\(_4\)Cl. After the mixture was filtered through Celite\(^\text{®}\), the product was extracted with EtOAc. The organic phase was washed with Brine, dried with Na\(_2\)SO\(_4\), then filtered, and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, 2 : 1 benzene/EtOAc) to afford aldol adduct 9 (0.33 g, 74\%) as a yellow foam.

The stereochemistry of compound 11 was determined by 1H-NMR analysis in DMSO-\(d_6\) at 100 °C.

Chart 4. Application of the Methodology for the Preparation of the Triene 15

Chart 5. Stille Coupling of Triene 15 with Vinyl Stannane 5 which Contains Phosphonate

Stille coupling of 15 with vinyl stannane 5 did not proceed in the presence of Pd(PPh\(_3\))\(_4\) as catalyst precursor, desired coupling product 4 was obtained in 42\% yield and reductive product 16 in 12\% yield in the presence of Pd(dba),. When AsPh\(_3\) was added in the reaction mixture, the coupling product was obtained in 63\% yield without accompanying an undesired 16.

In conclusion, we found that the aldol-type reaction of carbohydrate-bearing pyrone with aldehyde proceeded by the addition of Sn(OTf)\(_3\), or Sc(OTf)\(_3\). Using a combination of this methodology, followed by stepwise dehydration reaction and stille coupling, we were able to achieve the synthesis of a key intermediate 4. Further investigation toward the total synthesis of D8646-2-6 (1) is currently in progress.
5.35 (0.5H, d, J = 12.7 Hz), 5.92—5.97 (1H, m), 6.20—6.26 (1H, m), 6.27 (0.5H, d, J = 15.2 Hz), 6.28 (0.5H, d, J = 15.4 Hz), 6.32—6.37 (1H, m), 6.63—6.67 (1H, m), 6.64 (0.5H, s), 6.66 (0.5H, s), 7.01—7.45 (2.6H, m).

1H-NMR (100 MHz, CDCl3, mixture of rotamers): δ 16.6, 67.8, 69.1, 70.3, 70.8, 72.3, 72.5, 72.8, 73.4, 74.0, 74.2, 74.4, 74.6, 75.0, 75.5, 75.7, 77.2, 77.6, 83.5, 85.5, 95.7, 96.4, 102.9, 103.6, 120.9, 126.6, 127.1, 127.4, 127.5, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 131.4, 134.4, 135.3, 135.3, 137.1, 137.3, 138.0, 138.0, 138.7, 139.0, 139.2, 139.3, 139.5, 139.6, 139.9, 160.3, 161.5, 163.3, 164.3, 167.6, 168.3. HR-ESI-MS m/z: Calcd for C28H28O7Na [M + Na]+ 933.5354, Found 933.5349.

1E,3E,5E)-6-Bromo-1-(4-benzoyl-3-(2,3,4,6-tetra-O-benzyl-α-D-galactopyranosyl)-2-pyrene)-1,3,5-hexatriene (15) The aldehyde reaction of pyrnone 7 with aldehyde 6 was carried out with the same procedure described above.

The stereochemistry of compound 15 was determined by 1H-NMR analysis in DMSO-d6 at 100 °C.

R′0.4 (15:1 benzene–CH2CL2). [α]22D 5.1° (c = 1.38, CHCl3). IR (neat) cm−1: 3060, 3029, 2869, 1701, 1537, 1397, 998, 744, 699. 1H-NMR (600 MHz, DMSO-d6, mixture of rotamers): δ 3.45—3.56 (2H, m), 3.68—3.74 (2H, m), 4.06 (1H, m), 4.25 (0.5H, d, J = 11.6 Hz), 4.37—4.50 (4H, m), 4.55—4.60 (2H, m), 4.65 (0.5H, d, J = 12.2 Hz), 4.73—4.79 (2H, m), 4.84 (0.5H, d, J = 12.9 Hz), 4.89 (0.5H, d, J = 12.7 Hz), 5.09 (0.5H, d, J = 13.1 Hz), 5.22 (0.5H, d, J = 13.1 Hz), 5.28 (0.5H, d, J = 12.7 Hz), 5.33 (0.5H, d, J = 12.7 Hz), 6.37 (0.5H, d, J = 15.3 Hz), 6.38 (0.5H, d, J = 15.3 Hz), 6.53 (0.5H, dd, J = 11.0, 14.9 Hz), 6.54 (0.5H, dd, J = 10.9, 14.8 Hz), 6.62 (1H, dd, J = 10.8, 14.8 Hz), 6.70 (0.5H, s), 6.71 (0.5H, s), 6.85 (0.5H, d, J = 13.4 Hz), 6.86 (0.5H, d, J = 13.4 Hz), 6.95 (0.5H, dd, J = 10.8, 13.4 Hz), 6.96 (0.5H, dd, J = 10.6, 13.3 Hz), 6.99—7.43 (2.6H, m). 13C-NMR (100 MHz, DMSO-d6, mixture of rotamers): δ 69.3, 70.2, 70.7, 71.3, 72.1, 72.5, 72.6, 73.1, 73.9, 74.0, 74.1, 74.5, 74.6, 75.0, 75.7, 76.9, 77.1, 84.3, 84.5, 97.7, 98.2, 102.9, 103.2, 113.3, 134.4, 140.0, 127.2, 127.3, 127.7, 127.4, 127.5, 127.6, 127.7, 127.9, 127.9, 128.1, 128.1, 128.2, 128.4, 128.4, 128.7, 132.2, 133.0, 135.2, 135.0, 135.5, 135.6, 135.8, 136.0, 137.5, 138.3, 138.9, 139.0, 139.0, 139.2, 139.3, 139.4, 139.5, 139.6, 160.3, 163.4, 167.8, 168.3. HR-ESI-MS m/z: Calcd for C28H28O7Na [M + Na]+ 903.2508, Found 903.2509.
29) The reaction was monitored by TLC analyses before it was quenched, alcohol 12 was major product, however after being quenched, triene 11 was major product. Alcohol 12 has correlation of terminal methyl proton and methine proton of carbon bearing hydroxyl group in the COSY spectrum.
33) Aldehyde 6 was prepared from pyridinium-1-sulfonate according to the literature, see: Becher J., *Org. Synth.*, 59, 79—84 (1979).
35) Attempted direct dehydration of 14 with CCl3COCl and Et3N gave the desired triene 15 only in 30% yield due to competitive retro aldol reaction.