Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 5415–5418
Tetrahedron Letters

The first total synthesis and structural determination of actinopyrone A

Seijiro Hosokawa,* Kazuya Yokota, Keisuke Imamura, Yasuaki Suzuki, Masataka Kawarasaki and Kuniaki Tatsuta*

Department of Applied Chemistry, School of Science and Engineering, Waseda University, 3-4-1 Ohkubo, Shinjuku-ku, Tokyo 169-8555, Japan

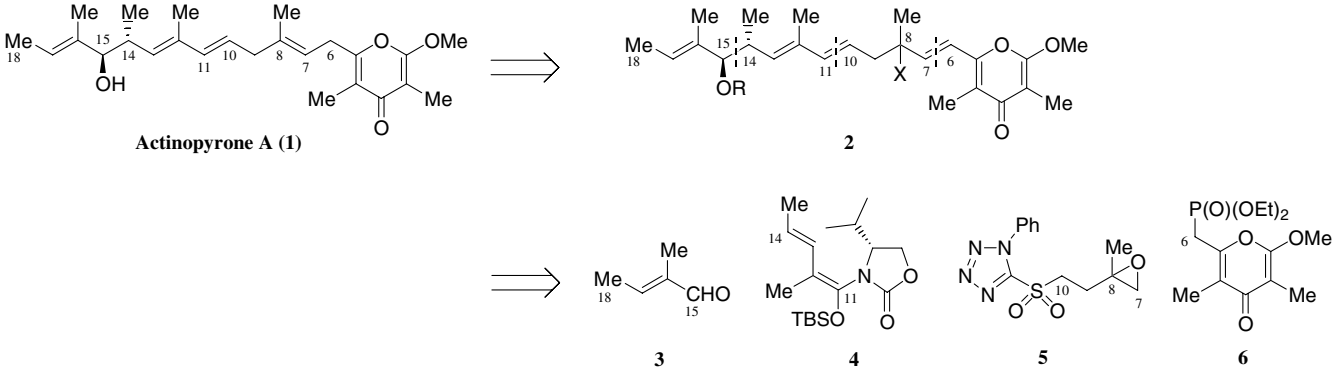
Received 11 April 2006; revised 2 May 2006; accepted 8 May 2006
Available online 12 June 2006

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



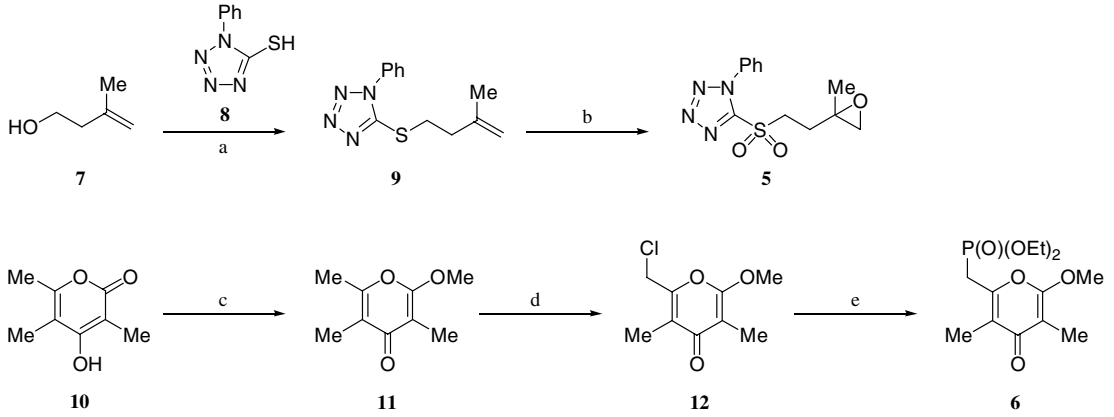
Scheme 1. Retrosynthetic analysis of actinopyrone A (**1**).

Keywords: Actinopyrone A; Total synthesis; Structural determination; Remote stereoinduction; 4-Pyrone; Reductive de-conjugation.
* Corresponding authors. Tel./fax: +81 3 3200 3203 (K.T.); e-mail: tatsuta@waseda.jp

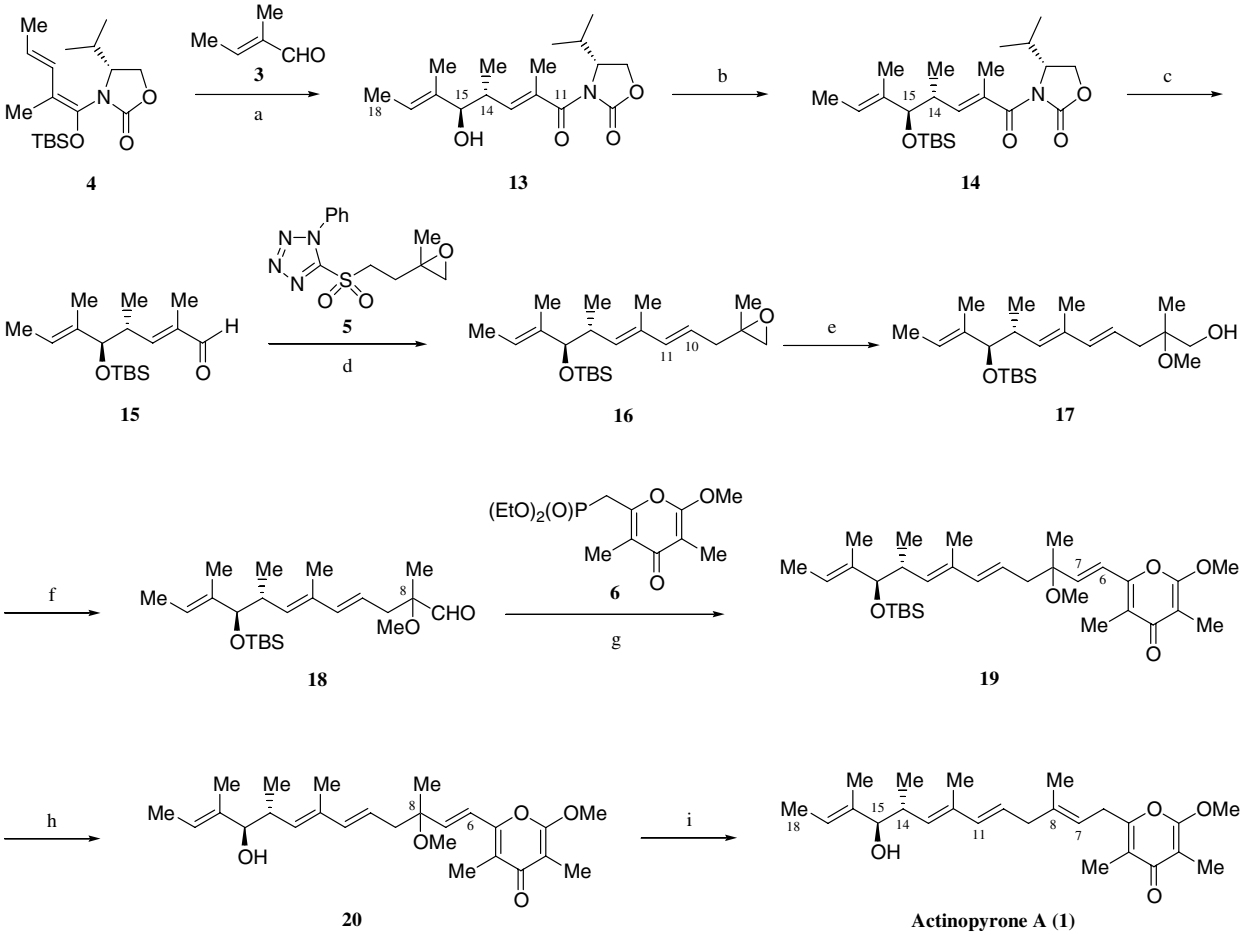
0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.05.028

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

Special thanks to Drs. T. Adachi, A. Kawashima, and Y. Terui in Taisho Pharmaceutical Co. Ltd. to give us an authentic sample of actinopyrone A (**1**) and useful information including spectral data and properties. K.I. thanks JSPS Research Fellowships for Young Scientists. The authors are also grateful for financial support to 21COE 'Center for Practical Nano-Chemistry', Consolidated Research Institute for Advanced Science and Medical Care, and Grant-in-Aid for Scientific Research (A), Scientific Research (C), and Scientific Research on Priority Areas 16073220 from The Ministry of Education, Culture, Sports, Science and Technology (MEXT).

References and notes

1. (a) Yano, K.; Yokoi, K.; Sato, J.; Oono, J.; Kouda, T.; Ogawa, Y.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 32–37; (b) Yano, K.; Yokoi, K.; Sato, J.; Oono, J.; Kouda, T.; Ogawa, Y.; Nakashima, T. *J. Antibiot.* **1986**, *39*, 38–43.
2. Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.; Suzuki, K.; Tanaka, A. . *J. Antibiot.* **2000**, *53*, 844–847.
3. Recently, piericidin A1 possessing the same side chain of actinopyrone A was synthesized. Schnermann, M. J.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 15704–15705.
4. (a) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707–4729; (b) Hosokawa, S.; Ogura, T.; Togashi, H.; Tatsuta, K. *Tetrahedron Lett.* **2005**, *46*, 333–337; (c) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604–13605.
5. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.
6. Selected data; Compound **5**: prisms recrystallized from 2-propanol, mp 88.3–88.7 °C; ^{1}H 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; ^{1}H 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): ^{1}H 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): ^{1}H 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)] ^{1}H 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.

7. (a) Suzuki, E.; Sekizaki, H.; Inoue, S. *J. Chem. Res. Syn.* **1977**, 200; (b) Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1996**, *37*, 2997–3000.
8. Suzuki, E.; Hamajima, R.; Inoue, S. *Synthesis* **1975**, 192–194.
9. In the case of K_2CO_3 as a base, the ratio of 2-O-methylation/4-O-methylation was ~1/1. Hatakeyama, S.; Ochi, N.; Takano, S. *Chem. Pharm. Bull.* **1993**, *41*, 1358–1361.
10. Under the conditions using excess amount (3 equiv) of $MeSO_3F$, 2-O-methylation proceeded selectively, however, starting material **10** did not consumed completely and isolated yield of **11** was 53%. Beak, P.; Lee, J.; McKinnie, B. G. *J. Org. Chem.* **1978**, *43*, 1367–1372.
11. Analogous transformation to a phosphonate via a mesylate: Moses, J. E.; Baldwin, J. E.; Adlington, R. M. *Tetrahedron Lett.* **2004**, *45*, 6447–6448.
12. Crystallographic data (excluding structure factors) for the structures of **14** has been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC 602830. Copies of the data can be obtained, free charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
13. For reduction of γ-acetoxy-α,β-unsaturated ester: Otaka, A.; Yukimasa, A.; Watanabe, J.; Sasaki, Y.; Oishi, S.; Tamamura, H.; Fuji, N. *Chem. Commun.* **2003**, 1834–1835.