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Total synthesis of leustroducsin B via a convergent route

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Abstract—Total synthesis of leustroducsin B was achieved via a convergent route, which includes Julia coupling reaction of segment A with segment B followed by Stille coupling reaction of segment C.

Leustroducsins, isolated from the culture broth of *Streptomyces platensis* SANK 60191 by Sankyo's groups in 1993,[1] are known to show a variety of biological activities. For example, leustroducsin B (**1**) shows induction of a colony-stimulating factor via NF-κB activation and thrombopoiesis.[2] Although a number of inhibitors against serine/threonine protein phosphatases (PPs 1 and 2A) have been isolated,[3] a structurally related natural product, fostriecin, is known to show the most specific inhibitory activity toward PP 2A.[4] It is also known that a hydrated analog of leustroducsin B, leustroducsin H, has potent PP 2A inhibitory activity,[5] which may have a relation to the biological activity, and is of great interest from a viewpoint of structure–activity relationship. These facts make this type of natural products an attractive synthetic target,[6] and several successful syntheses of fostriecin including ours have been reported to date.[7,8] However, only a limited number of syntheses of leustroducsin-type compounds having aminoethyl and ethyl substituents at C-8 and C-4, respectively,[9] were reported: leustroducsin B (**1**) by Fukuyama's group in 2003[10] and phoslactomycin B by Kobayashi's group in 2006.[11]

Taking account of application to studies of chemical biology and medicinal chemistry, particularly focusing on the PP inhibitory activity, we planned a cognate synthetic strategy for these natural products, which is highly convergent and versatile for the synthesis of their analogs as well, and, as a first step, we have already synthesized fostriecin successfully.[8] Herein, we describe the total synthesis of leustroducsin B (**1**) (Fig. 1).

Based on our strategy for fostriecin, we divided a leustroducsin molecule into three segments A, B, and C, as shown in Figure 2. Taking account of the synthesis of various analogs, such as hybrid analogs with fostriecin, we selected aldehyde-based reactions and Pd(0)-catalyzed reactions as a coupling reaction between each segment.[8] Segment A (**2**), a precursor of an ethyl substituted δ-lactone structure, was planned to be synthesized

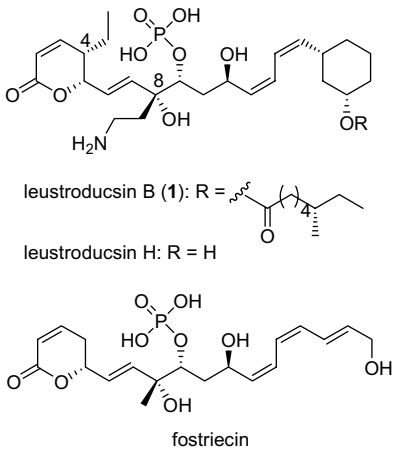

Figure 1. Structures of leustroducsins B, H and fostriecin.

Keywords: Leustroducsin B; Total synthesis; Convergent route; Proteinphosphatase inhibitor.
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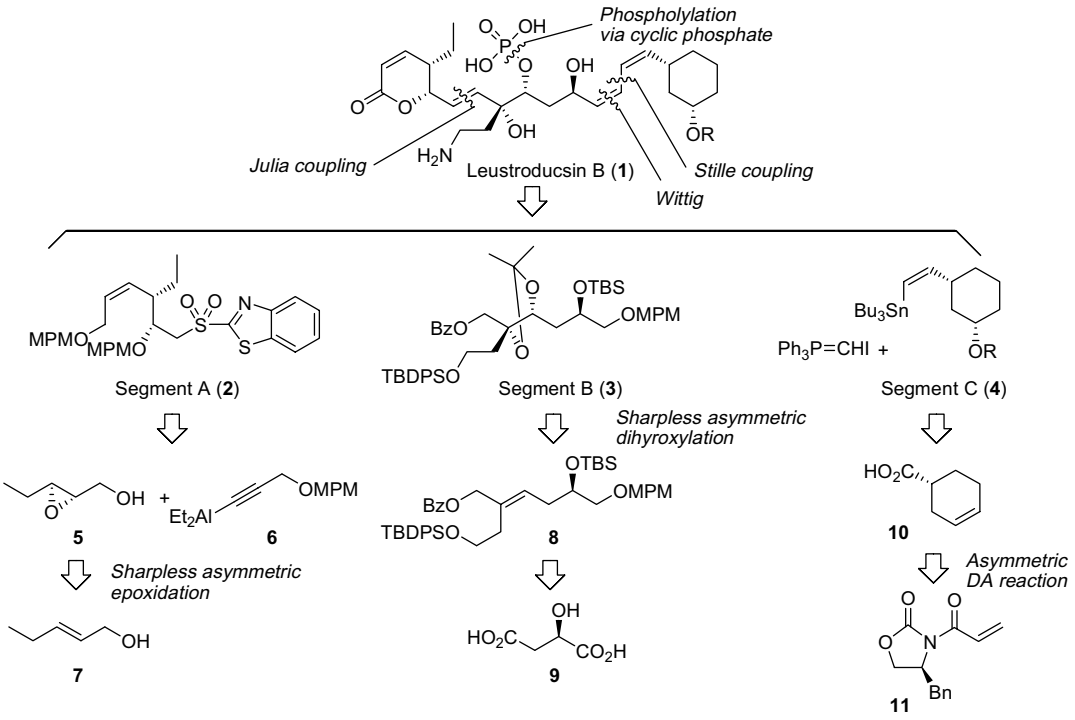
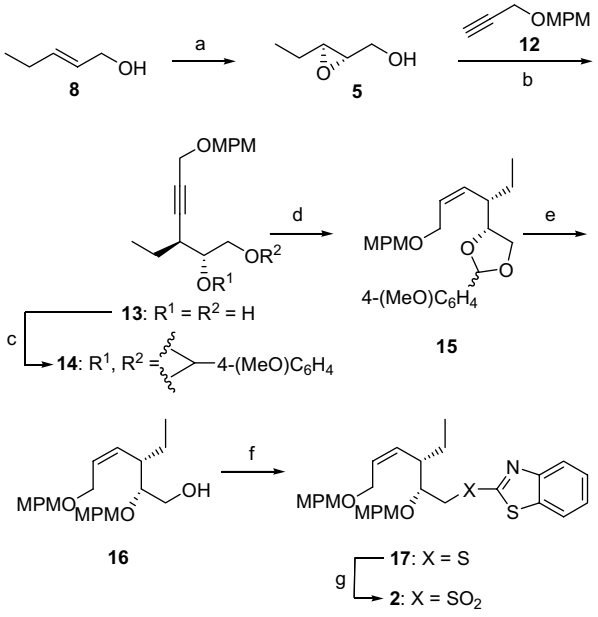


Figure 2. Synthetic strategy for leustroducsin B.

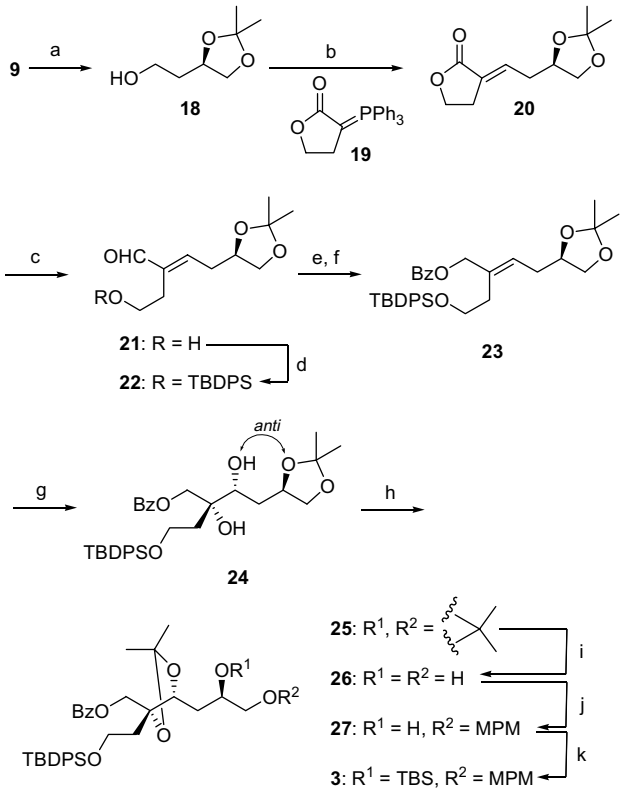
by a combination of Sharpless asymmetric epoxidation[12] and an epoxide cleavage reaction employing an organometallic reagent as key steps. A sulfone functional group was also allowed to be introduced at a suitable position for Julia coupling reaction[13] with segment B (**3**). Segment B (**3**), having an oxyethyl substituent and sequential stereogenic centers, was expected to be synthesized from (*R*)-malic acid (**9**) employing a combination of Wittig reaction and Sharpless asymmetric dihydroxylation.[14] A cyclohexane structure of segment C (**4**) was planned to be synthesized by asymmetric Diels–Alder reaction, and a diene moiety was expected to be constructed by a Pd(0)-catalyzed coupling reaction.[15] According to the strategy, we have synthesized leustroducsin B (**1**) as follows.

Synthesis of segment A (**2**) is shown in Scheme 1. Optically active epoxide **5** prepared by Sharpless asymmetric epoxidation of *trans*-2-pentenol (**8**) was treated with an alkynylaluminum reagent prepared from **12**, giving **13** as a main product. After protection of a diol moiety of **13** with an anisylidene group, partial reduction of an alkyne moiety[10,16] of **14** and regioselective reductive cleavage of the anisylidene group of the resultant olefin **15** afforded primary alcohol **16**, which was transformed into Julia reagent **2** as follows. Treatment of **16** with 2-mercaptobenzothiazole under Mitsunobu conditions[17] afforded sulfide **17**, which was oxidized to give the desired segment A (**2**).

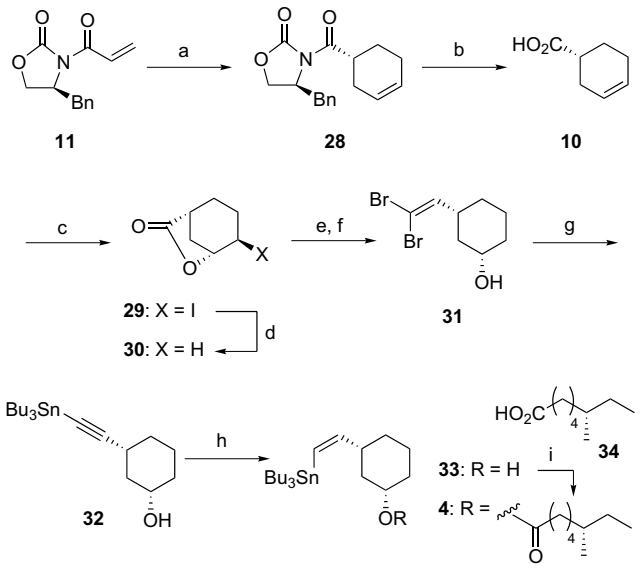


Scheme 1. Synthesis of segment A. Reagents and conditions: (a) $Ti(OPr^i)_4$, L-(+)-DIPT, TBHP, MS4A, CH_2Cl_2, −20 °C, overnight, 82% (95% ee); (b) **12**, *n*-BuLi, then Et_2AlCl, **5**, toluene, −20 °C to rt, 4 h, 39% (regioisomer: 15%); (c) *p*-anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, rt, 2 h, 60%; (d) Zn, $BrCH_2CH_2Br$, $LiCuBr_2$, EtOH, reflux, 22 h; (e) DIBAlH, CH_2Cl_2, −100 °C, 2 h, 62% from **14**; (f) 2-mercaptobenzothiazole, DEAD, Ph_3P, THF, rt, 2 h, 98%; (g) 30% H_2O_2, $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, EtOH, rt, 2 days, 82%.

Segment B (**3**) was synthesized as shown in Scheme 2. Alcohol **18**, which was easily obtainable from (*R*)-malic acid (**9**) according to literature procedures,[8,18] was oxidized and treated in situ with Wittig reagent **19** having a γ-lactone structure, affording **20**. After reduction of **20** with DIBAlH, the resultant primary hydroxyl group of **21** was protected with a TBDPS group to give **22**. An aldehyde group of **22** was converted to a benzoyloxy group according to a usual procedure, then two stereo-



Scheme 2. Synthesis of segment B. Reagents and conditions: (a) see Refs. 8,16; (b) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to 0 °C, 30 min, then **19**, rt, 2 h, 83%; (c) DIBAlH, toluene, −78 °C, 20 min; (d) TBDPSCl, imidazole, DMF, rt, 30 min, 49% from **20**; (e) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 15 min; (f) BzCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 88% from **22**; (g) $(DHQD)_2PHAL$, $K_2OsO_2(OH)_4$, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, *t*-BuOH–H_2O (2:1), rt, overnight, 91% (*anti*-isomer only); (h) 2,2-dimethoxypropane, *p*-TsOH·H_2O, rt, 20 min; (i) $Zn(NO_3)_2{\cdot}6H_2O$, MeCN, 50 °C, 3 h, 93% from **24**; (j) *n*-Bu_2SnO, toluene, reflux, 12 h, then MPMCl, *n*-Bu_4NI, reflux, 1.5 h, 76%; (k) TBSOTf, 2,6-lutidine, CH_2Cl_2, rt, 15 min, quant.

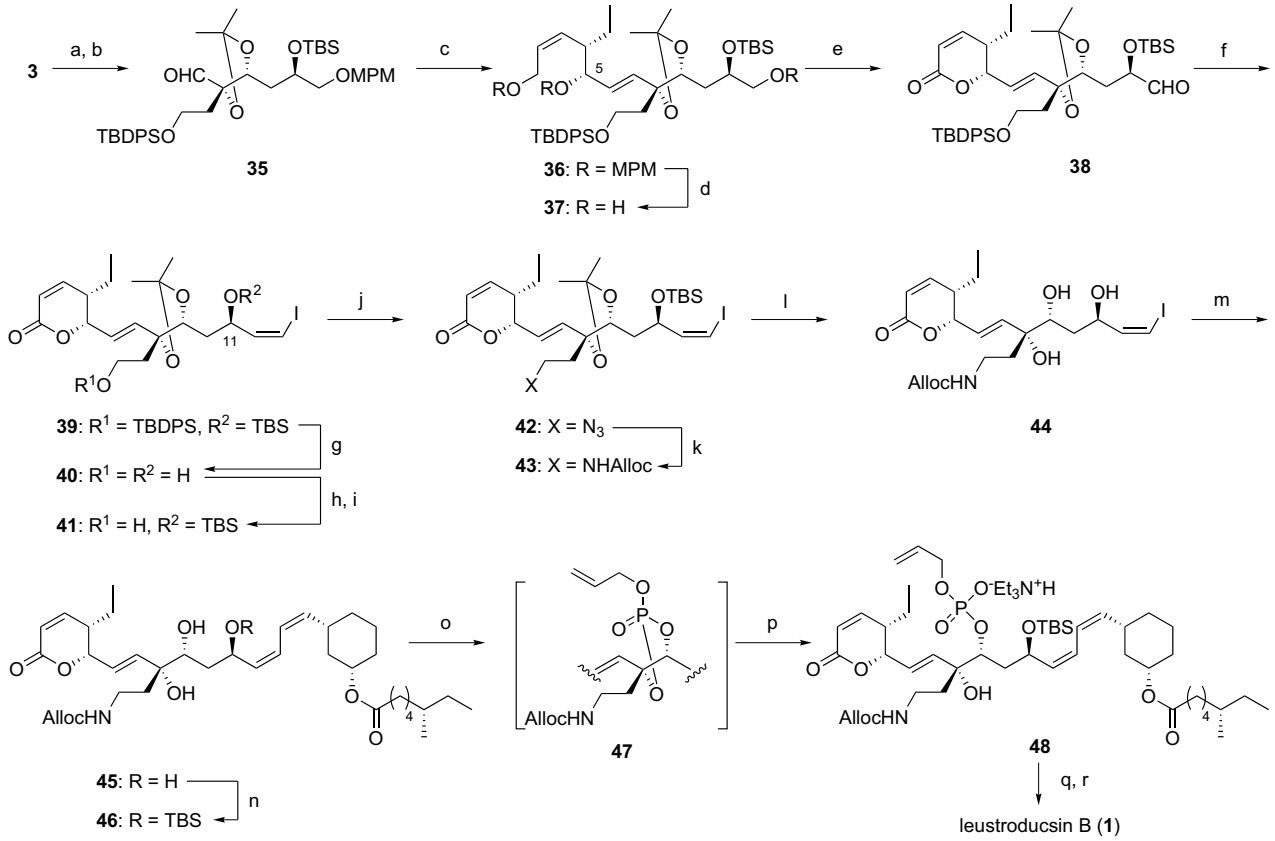


Scheme 3. Synthesis of segment C. Reagents and conditions: (a) 1,3-butadiene, Et_2AlCl, galvinoxyl, CH_2Cl_2, −15 °C, overnight, 63%; (b) 30% H_2O_2, LiOH, THF–H_2O (5:1), rt, 5 h, 67% (94% ee); (c) KI, I_2, $NaHCO_3$, CH_2Cl_2–H_2O (1:2), rt, 24 h; (d) $(TMS)_3SiH$, AIBN, benzene, reflux, 3 h, 76% from **10**; (e) DIBAlH, toluene, −78 °C, 1 h; (f) $Br_2CHP^+Ph_3{\cdot}Br^-$, *t*-BuOK, 1,4-dioxane, 70 °C, 30 min, 71% from **30**; (g) *n*-BuLi, THF, then Bu_3SnCl, −78 °C to 0 °C, 3 h; (h) CpZrHCl, THF, rt, 2 h, 52% from **31**; (i) **34** (94% ee), EDC-MeI, DMAP, Et_3N, CH_2Cl_2, rt, 24 h, 84%.

genic centers at C-8 and C-9 were introduced to **23** by Sharpless asymmetric dihydroxylation, giving diol **24**. Bisacetonide formation and regioselective removal of the terminal acetonide group of **25** by treatment with zinc nitrate gave diol **26**. After selective protection of a primary hydroxyl group of **26** with an MPM group via cyclic stannane, the residual secondary hydroxyl group of **27** was protected with a TBS group to afford segment B (**3**).

Segment C (**4**) was synthesized as shown in Scheme 3. Optically active cyclohexenecarboxylic acid **10** was synthesized by asymmetric Diels–Alder reaction employing optically active oxazolidinone **11**[19] as a starting material to give diastereomerically pure **28**. After hydrolysis, iodolactonization[20] and reduction with a silane afforded lactone **30**, which was reduced with DIBAlH and subsequently treated with Wittig reagent to give dibromide **31**. A dibromoethylene moiety of **31** was transformed into a stannylethylene structure via alkynylstannane **32** by treatment with a base and hydrozirconylation, giving **33**, which was esterified with optically active carboxylic acid **34**[21] to give segment C (**4**).

Segment B (**3**) was coupled with segment A (**2**) at first because of the expectable labile property of the diene moiety and versatility of the acyl side-chain in segment C. Removal of the benzoyl group of **3** followed by oxidation of the terminal hydroxyl group gave aldehyde **35**. Julia coupling reaction of **35** with **3** employing NaHMDS as a base afforded a coupling product **36** in 49% yield, but unexpected epimerization at C-5 took place simultaneously, to result in the formation of a ca. 1:1 diastereomeric mixture.[22] On the contrary, when LiHMDS was used as a base, no epimerization was observed to give a diastereomerically pure **36**, although yield of product **36** was rather low.[23] All MPM groups of **36** were removed by oxidative treatment, and TEMPO oxidation of the resultant triol **37** afforded lactone–aldehyde **38**, which was iodomethylenated by Wittig reaction, affording *cis*-olefin **39**, stereoselectively. As the next step, the hydroxyethyl group of **39** was converted to an aminoethyl group before coupling with segment C (**4**) as follows. After removal of the silyl protecting groups of **39**, the resultant secondary hydroxyl group at C-11 was selectively reprotected with a TBS group, affording **41**. Then the hydroxyl group of **41** was replaced with an azido group, yielding azide **42**, which was reduced and protected with an Alloc group to give **43**. Acidic treatment of **43** removed both TBS and acetonide groups to give **44**, Stille coupling of which with segment C (**4**) afforded **45** having the whole skeleton of leustroducsin B. After selective protection of the hydroxyl group at C-11 with a TBS group, introduction of the phosphate group to the C-9 hydroxyl group of **46** was achieved by partial hydrolysis of cyclic



Scheme 4. Synthesis of leustroducsin. Reagents and conditions: (a) K_2CO_3, MeOH, rt, 4 h, 81% from **27**; (b) TPAP, NMO, MS4A, CH_2Cl_2, 2 h, rt, 95%; (c) segment A (**2**), LiHMDS, THF then **35**, −78 °C to −20 °C, 1 h, 14%; (d) DDQ, wet CH_2Cl_2, rt, 1 h, 79%; (e) TEMPO, DAIB, CH_2Cl_2, rt, 1.5 h; (f) $ICH_2P^+Ph_3{\cdot}I^-$, NaHMDS, HMPA, THF, −100 °C to 0 °C, 30 min, 59% (*Z*:*E* = 4.3:1) from **37**; (g) TBAF, AcOH, THF, rt, overnight, 64%; (h) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 1 h; (i) *p*-TsOH·H_2O, THF–MeOH (1:3), 0 °C, 1 h, 81% from **40**; (j) Ph_3P, DPPA, DEAD, THF, rt, 1 h; (k) Ph_3P, H_2O, THF, rt, 20 h, then pyridine, AllocCl, rt, 20 min, 74% from **41**; (l) MeOH–concd HCl (20:1), rt, overnight; (m) segment C (**4**), $PdCl_2(MeCN)_2$, DMF, rt, 1.5 h, 61% from **43**; (n) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 30 min, 76%; (o) $POCl_3$, pyridine, then allyl alcohol, 0 °C, 2 h; (p) CF_3CH_2OH–H_2O–Et_3N (20:1:1), rt, 1 h, 87% from **46**;[23] (q) HF, pyridine, MeCN, rt, 8 h; (r) $Pd(PPh_3)_4$, Ph_3P, HCO_2NH_4, 50 °C, 7 h, 49% from **48**.

phosphate **47**, producing the desired phosphate **48** as a main product.[24] Eventually, removal of all protecting groups of **48** afforded leustroducsin B (**1**), the physical properties (^1H NMR and $[\alpha]_D$ value) of which were identical to those of the authentic sample[25] (Scheme 4).

In summary, although there still remain some problems to be resolved, we have successfully achieved the total synthesis of leustroducsin B via a convergent route involving a coupling of three segments A, B, and C, which is compatible with our previous total synthesis of fostriecin. The present synthesis proved the versatility and wide applicability of our strategy to the synthesis of various analogs, including hybrid analogs of fostriecin and leustroducsins, which, hence, would open a door for the studies of chemical biology and medicinal chemistry focusing on PPs.

Acknowledgments

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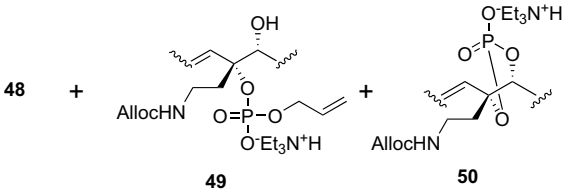
21. Carboxylic acid **34** was prepared by oxidation of the corresponding optically active alcohol (94% ee) which was commercially available from Tokyo Chemical Industry Co., Ltd.
22. To the best of our knowledge, a similar epimerization was reported on the reaction of a sulfone derivative having a tetrahydrofuran ring: Evans, D. A.; Rajapakse, H. A.; Chiu, A.; Stenkamp, D. *Angew. Chem.* **2002**, *114*, 4755; *Angew. Chem., Int. Ed.* **2002**, *41*, 4573.
23. An olefinic by-product, which was produced by elimination of the neighboring MPM group, was obtained in 32% yield. Further optimization of this coupling reaction including utilization of other reactions is in progress, details of which would be described in a full article.
24. A mixture of the hydrated products, C-9 phosphate **48**, C-8 phosphate **49** and cyclic phosphodiester **50**, was obtained in 87% yield from **46**, and the ratio was ca. 71:22:7, respectively. The mixture was employed for the next reaction without separation.



25. The final product **1** was purified at first by preparative TLC with MeOH, then by reversed phase silica gel (C_{18}) column chromatography with H_2O–MeCN (40:1–1:2) as eluant, and showed the following spectral data. ^{1}H NMR (CD_3OD): δ 7.09 (dd, $J = 10$, 5 Hz, 1H), 6.33–6.24 (m, 2H), 6.07 (dd, $J = 16$, 6 Hz, 1H), 6.02 (dd, $J = 10$, 1 Hz, 1H), 5.95 (d, $J = 16$ Hz, 1H), 5.46 (br t, $J = 8$ Hz, 1H), 5.31 (br t, $J = 9$ Hz, 1H), 5.10 (dd, $J = 6$, 4 Hz, 1H), 4.95 (br t, $J = 8$ Hz, 1H), 4.76–4.69 (m, 1H), 4.29 (td, $J = 10$, 3 Hz, 1H), 3.11–2.97 (m, 2H), 2.67–2.54 (m, 2H), 2.28 (t, $J = 7$ Hz, 2H), 2.25–2.15 (m, 1H), 1.96–1.81 (m, 4H), 1.74–1.24 (m, 15H), 1.19–1.03 (m, 3H), 0.96 (t, $J = 8$ Hz, 3H), 0.88 (t, $J = 7$ Hz, 3H), 0.86 (d, $J = 6$ Hz, 3H). $[\alpha]_D^{25}$ +98.8 (*c* 0.0500, MeOH) [lit.[10] $[\alpha]_D$ +99.3 (*c* 0.0500, MeOH)].