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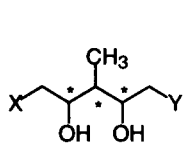
Enantioselective Preparation of 1-Benzyloxy-3-methyl-6-heptene-2,4-diols: Total Synthesis of (+)-Prelactone C

Tomoyuki Esumi, Hiroko Fukuyama, Reiko Oribe, Kaori Kawazoe, Yoshiharu Iwabuchi, Hiroshi Irie, and Susumi Hatakeyama*

Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan

Abstract: A concise method leading to all stereoisomers of 1-benzyloxy-3-methyl-6-heptene-2,4-diol from (2*E*,5*E*)-1,7-dibenzyloxy-2,5-heptadiene-4-ol has been developed. The first synthesis of (+)-prelactone C, a δ-lactone isolated from the concanamycin-producing *Streptomyces sp.*, has been achieved utilizing (2*S*,3*S*,4*R*)-1-benzyloxy-3-methyl-6-heptene-2,4-diol as a chiral building block.

Enantiomerically pure compounds of the general structure **1** are useful chiral building blocks in the synthesis of various natural products, in particular, macrolide antibiotics having polypropionate chain structures.[1] We envisioned that this type of chiral building blocks would be obtained from epoxy alcohol **2** by regio- and stereoselective introduction of methyl group followed by sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) promoted reductive cleavage of the benzyloxy group which we have developed recently.[2] We now report a concise method for the preparation of all stereoisomers of 1-benzyloxy-3-methyl-6-heptene-2,4-diol (**1**; X = -CH=CH$_2$, Y = OBn) and the first synthesis of (+)-prelactone C (**3**),[3] a δ-lactone isolated from the concanamycin-producing *Streptomyces sp.*,[4] utilizing one of the stereoisomers as a chiral building block.



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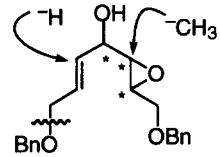

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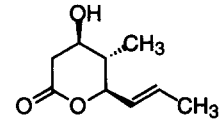

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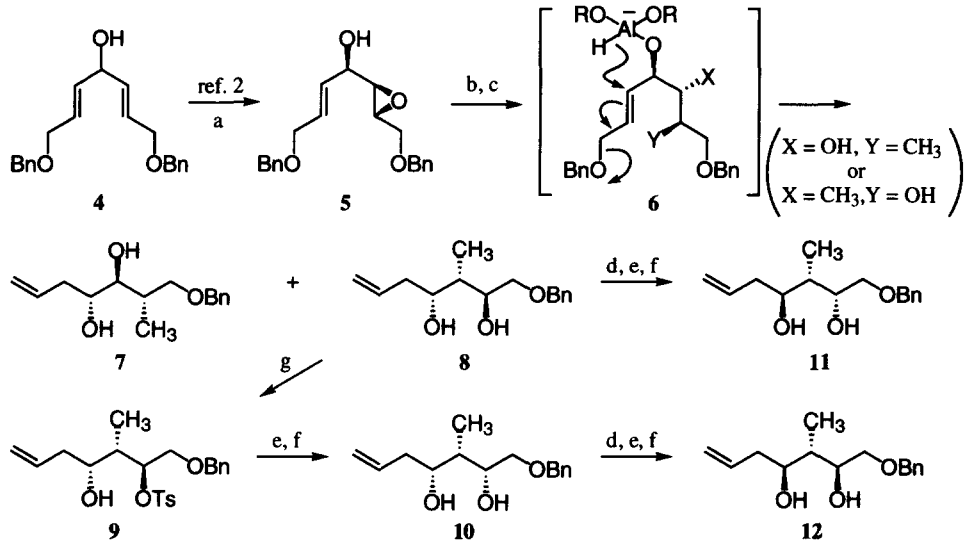
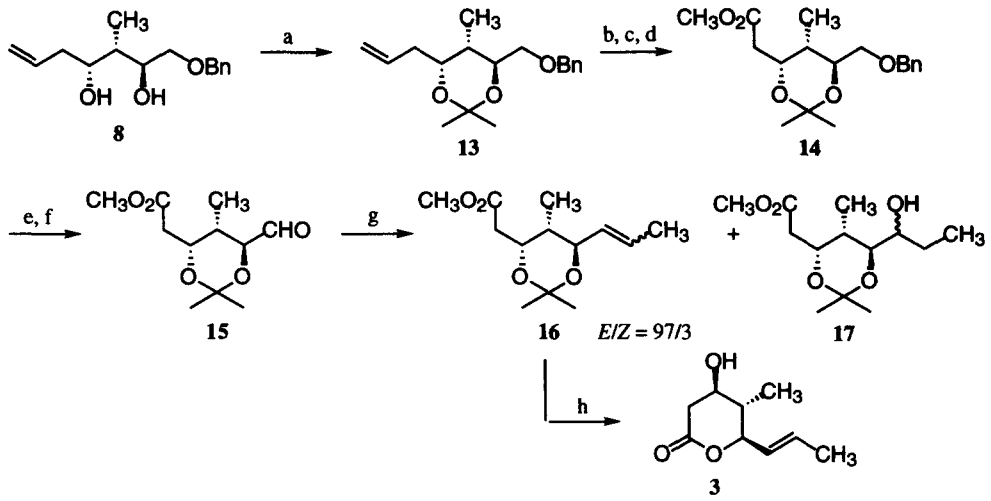
σ-Symmetrical (2*E*,5*E*)-1,7-dibenzyloxy-2,5-heptadien-4-ol (**4**) was first converted into the optically pure epoxy alcohol **5** by catalytic Katsuki-Sharpless asymmetric epoxidation[5] using D-diisoprppyl tartrate according to the established procedure.[2, 6, 7] After examination of nucleophilic methylation of **5** under various conditions,[8] we eventually found that reaction of **5** with methylmagnesium bromide in the presence of copper(I) cyanide caused regio- and stereoselective opening of the epoxide to give a 14:86 mixture[9] of the corresponding 1,2- and 1,3-diols. Interestingly, Me_2CuLi[8a] or $Me_2CuCNLi_2$[10] resulted in poorer regioselection (ca. 1:1). Without separation, treatment of the mixture of diols with Red-Al® in boiling toluene allowed reductive cleavage of the benzyloxy group as in **6** to give 1,2-diol **7**,[11,12] $[\alpha]^{20}_D$ +2.9° (*c* 1.17, CH_3OH), and 1,3-diol **8**,[13] $[\alpha]^{18}_D$ +6.2° (*c* 1.04, CH_3OH), in 11% and 61% overall yields from **5**, respectively. In order to prepare the other diastereoisomers of **8**, we then examined inversion[14] of its hydroxy groups. The C-2 hydroxy group

of **8** was found to be selectively tosylated under usual tosylation conditions to give monotosylate **9**[15] which, upon reaction with cesium acetate[16] followed by methanolysis, afforded 1,3-diol **10**, $[\alpha]^{21}_D$ +6.3° (*c* 1.04, CH_3OH), in 73% overall yield. Two hydroxy functionalities of **8** and **10** were also found to be inverted *via* the corresponding dimesylate to give **11**, $[\alpha]^{26}_D$ −1.4° (*c* 0.87, CH_3OH), and **12**, $[\alpha]^{26}_D$ +2.6° (*c* 1.69, CH_3OH), respectively by the same procedure described above although the yields were moderate (40%).[17] At this stage we could develop a method for the preparation of all possible stereoisomers of **1** starting with **4** because the antipodes of four 1,3-diols **8**, **10**, **11**, and **12** should be also available if the enantiomer of **5** is used as a starting material.



Scheme 1. (a) D-DIPT (9 mol%), Ti(O^{i}Pr)4 (7 mol%), ^{t}BuOOH (2equiv.), 4A molecular sieves, CH_2Cl_2, −25 °C (b) CH_3MgBr (12 equiv.), CuCN (6 equiv.), THF, −20 °C; (c) Red-Al® (3 equiv.), toluene, reflux; (d) MsCl, Et_3N, DMAP (cat.), CH_2Cl_2; (e) CsOAc (16 equiv.), 18-crown-6 (5 equiv.), benzene, reflux; (f) K_2CO_3, CH_3OH; (g) *p*-TsCl, Et_3N, DMAP (cat.), CH_2Cl_2.

The synthetic utility of the above-mentioned compounds was exhibited by the first synthesis of (+)-prelactone C (**3**) employing **8** as a chiral building block. Thus, the 1,3-diol **8** was first converted to acetonide **13**, $[\alpha]^{20}_D$ +3.6° (*c* 1.00, $CHCl_3$), in 97% yield. Upon successive osmylation, $NaIO_4$ oxidation, $NaClO_2$ oxidation, and esterification, **13** gave ester **14**, $[\alpha]^{21}_D$ −15.2° (*c* 0.71, $CHCl_3$), in 80% overall yield. Debenzylation of **14** followed by Swern oxidation gave aldehyde **15**[18] which was subjected to Takai's (*E*)-selective olefination[19] using *gem*-dichromium reagent generated by the reaction of 1,1-diiodoethane[20] with $CrCl_2$. In this particular case, the olefination proceeded with excellent *E*-selectivity to produce olefin **16** as a 97:3 *E/Z* inseparable mixture in 50% overall yield from **14** although this reaction also gave alcohol **17** in 31% yield. Finally, acid treatment of **16** gave (+)-prelactone C (**3**) quantitatively which was purified by $AgNO_3$ impinged preparative TLC in order to remove a trace amount of its *Z*-isomer. The synthetic substance exhibited spectral properties (^1H and ^{13}C NMR, IR, MS) and specific rotation, $[\alpha]^{18}_D$ +58.9° (*c* 0.71, CH_3OH) {lit.[3] $[\alpha]^{20}_D$ +57.6° (*c* 0.5, CH_3OH)}, in accord with those reported.[3] As a result, the present synthesis of (+)-prelactone C (**3**) from **8** made the absolute structure of natural prelactone C unambiguous.[21]



Scheme 2. (a) $(CH_3O)_2C(CH_3)_2$, PPTS (cat.),CH_2Cl_2; (b) NMO, OsO_4 (cat.), THF-H_2O (4:1), then $NaIO_4$; (c) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (4:1); (d) CH_2N_2, Et_2O; (e) H_2, $Pd(OH)_2$ (cat.), EtOH; (f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 to 25 °C; (g) $CrCl_2$ (20 equiv.), CH_3CHI_2 (5 equiv.), DMF (20 equiv.), THF; (h) AcOH-H_2O (4:1).

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(11) All new compounds reported herein exhibited satisfactory spectral data(^1H and ^{13}C NMR, IR, HR MS).

(12) Selected ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) data are following. **7**: ^1H NMR δ 0.98 (d, 3H, *J* = 7.1 Hz), 2.07 (m, 1H), 2.28 (m, 1H), 2.34-2.46 (m, 1H), 2.82 (br d, 1H, *J* = 6.4 Hz), 3.15 (br d, 1H, *J* = 5.4 Hz), 3.45-3.58 (m, 1H), 3.55 (d, *J* = 5.4 Hz), 3.56 -3.69 (m, 1H), 4.51 (s, 2H), 5.11 (br d, 1H, *J* = 11.1 Hz), 5.12 (br d, 1H, *J* = 18.3 Hz), 5.88 (ddt, 1H, *J* = 11.1, 18.3, 7.4 Hz), 7.20-7.40 (m, 5H); ^{13}C NMR δ 14.6, 34.5, 37.1, 72.2, 73.1, 73.6, 77.6, 127.8, 128.0, 128.6, 135.4, 137.5. **8:** ^1H NMR δ 0.91 (d, 3H, *J* = 7.2 Hz), 1.75 (dquint, 1H, *J* = 2.1, 7.2 Hz), 2.16 (br dt, 1H, *J* = 5.4, 15.0 Hz), 3.02 (br s, 1H), 3.23 (br s, 1H), 3.48 (dd, 1H, *J* = 7.5, 9.6 Hz), 3.57 (dd, 1H,

J = 3.6, 9.6 Hz), 3.83 (hept, 1H, J = 3.6 Hz), 3.93 (m, 1H), 4.81 (s, 2H), 5.35 (dd, 1H, J = 1.8, 10.2 Hz), 5.38 (dd, 1H, J = 1.8, 17.4 Hz), 6.08 (ddt, 1H, J = 6.9, 10.2, 17.4 Hz), 7.52-7.66 (m, 5H); ^{13}C NMR δ 10.7, 38.6, 38.7, 71.5, 72.9, 73.4, 73.8, 117.3, 127.9, 135.5, 137.8. **10**: ^{1}H NMR δ 0.92 (d, 3H, J = 7.2 Hz), 1.67 (tq, 1H, J = 2.1, 7.2 Hz), 2.19 (dt, 1H, J = 7.5, 14.1 Hz), 2.30 (dt, 1H, J = 7.5, 14.1 Hz, 2.85 (br s, 1H), 2.91 (br s, 1H), 3.46 (dd, 1H, J = 4.8, 9.3 Hz), 3.51 (dd, 1H, J = 7.2, 9.3 Hz), 3.90 (ddt, 1H, J = 1.8, 6.0, 7.8 Hz), 4.04 (ddt, 1H, J = 4.8, 7.2, 9.6 Hz), 4.52 (d, 1H, J = 11.7 Hz), 4.58 (d, 1H, J = 11.7 Hz, 5.10 (br d, 1H, J = 10.2 Hz), 5.12 (br d, 1H, J = 19.5 Hz), 5.79 (ddt, 1H, J = 7.5, 10.2, 19.5 Hz), 7.28-7.40 (m, 5H); ^{13}C NMR δ 5.9, 38.3, 39.5, 72.6, 73.5, 74.6, 74.8, 111.7, 127.8, 127.9, 128.6, 135.2, 137.9. **11**: ^{1}H NMR δ 0.95 (d, 3H, J = 7.2 Hz), 1.74 (dquint, 1H, J = 2.1, 6.6 Hz), 2.24 (dt, 1H, J = 8.1, 14.1 Hz), 3.49 (dd, 1H, J = 4.2, 9.6 Hz), 3.55 (dd, 1H, J = 7.8, 9.6 Hz), 3.61-3.70 (m, 1 H), 4.14-4.22 (m, 1 H), 4.57 (dd, 2H, J = 12.0, 17.4 Hz), 5.13 (dt, 1H, J = 1.5, 10.2 Hz), 5.14 (br d, 1H, J = 15.6 Hz, 5.77-5.94 (m, 1H), 7.28-7.38 (m, 5H); ^{13}C NMR δ 11.8, 39.1, 40.0, 71.3, 72.5, 73.5, 74.2, 118.0, 127.8, 127.9, 128.5, 135.0, 138.0. **12**: ^{1}H NMR δ 0.83 (d, 3H, J = 7.2 Hz, 3 H), 1.75 (hept, 1H, J = 7.2 Hz, 1 H), 2.15 (dt, 1H, J = 6.9, 8.1 Hz), 2.35-2.47 (m, 1H}, 3.20 (br s, 1H), 3.35 (br s, 1H), 3.46 (dd, 1H, J = 7.2, 9.6 Hz), 3.63 (dd, 1H, J = 3.0, 9.6 Hz, 1 H), 3.72 (br dt, 1H, J = 3.0, 5.1 Hz), 3.81 (br t, 1H, J = 7.2 Hz), 4.54 (d, 1H, J = 12.3 Hz), 4.59 (d, 1H, J = 12.3 Hz), 5.13 (br d, 1H, J = 11.1 Hz), 5.14 (d, 1H, J = 15.3 Hz), 5.83-5.97 (m, 1H), 27.28-7.40 (m, 5H) ; ^{13}C NMR 12.7, 39.0, 40.7, 72.8, 73.5, 74.7, 117.9, 127.8, 127.9, 135.0, 137.9.

(13) The relative stereochemistries of 1,3-diols **8**, **10**, **11**, and **12** were confirmed by ^{1}H NMR analysis (vicinal coupling constants and NOE) of the corresponding acetonides and the chemical shift correlation of their ^{13}C resonances of the acetonide carbons to the empirical rule: Cf.: Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945-948; Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099-7100.

(14) Mitsunobu's method did not give any satisfactory results. Mitsunobu, O. *Synthesis* **1981**, 1-28.

(15) The 4-tosyloxy isomer was not detected in this particular case.

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(17) The inversion reactions of the dimesylates were rather sluggish unlike the reaction of **9** so that the corresponding dienes and trienes were also produced by competitive elimination reactions (< 15%).

(18) Usual aqueous work-up led to almost complete hydration of the resulting aldehyde. So the aldehyde was isolated by the following nonaqueous work-up (i. dissolving the reaction mixture into *n*-hexane; ii. removing the precipitates by suction filtration through Celite; iii. evaporation in vacuo).

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