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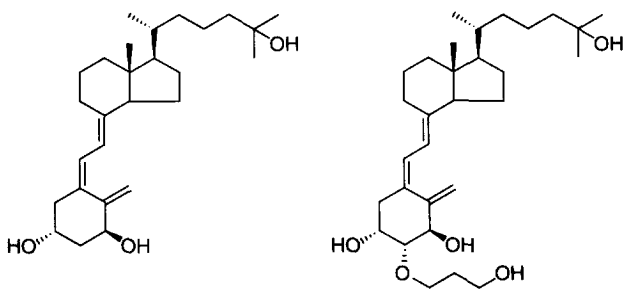
CONVERGENT SYNTHESIS OF 1α,25-DIHYDROXY-2β-(3-HYDROXYPROPOXY)VITAMIN D_3 (ED-71) [1]

Susumi Hatakeyama*, Tatsuhiko Ikeda, Junji Maeyama, Tomoyuki Esumi, Yoshiharu Iwabuchi and Hiroshi Irie
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852, Japan

Akira Kawase and Noboru Kubodera*
Chugai Pharmaceutical Co., Ltd., Tokyo 104, Japan

Abstract: A convergent and versatile synthesis of the potent vitamin D analog, 1α,25-dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3 [**1**] (ED-71) is described.

Introduction: 1α,25-Dihydroxy-2β-(3-hydroxypropoxy)vitamin D_3 (ED-71) [**1**] is an analog of active vitamin D_3, 1α,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) [**2**], bearing a hydroxypropoxy substituent at the 2β-position.[2] ED-71 [**1**] is characterized by highly calcemic activity and long half-life in plasma due to the strong affinity to vitamin D binding protein (DBP) (Fig. 1).[3] Strong preventive and therapeutic effects of ED-71 [**1**] on bone mineral loss in osteoporosis model rats have been observed.[4] Currently, ED-71 [**1**] is undergoing clinical trials in Japan as a promising candidate for the treatment of osteoporosis.



	$1,25(OH)_2D_3$ (2)	ED-71 (1)
VDR	**1**	**1/8**
DBP	**1**	**2.7**
$T_{1/2}$ in Plasma	**short**	**long**

VDR: Vitamin D receptor

Fig. 1 Structure and characters of ED-71

The current synthesis of ED-71 [**1**] involves a linear route using lithocholic acid [**3**] as a starting material and proceeds through the α-epoxide [**4**] as the key intermediate (Fig. 2).[2] The 23-step synthetic method seems, however, to be inconvenient for the synthesis of highly functionalized related compounds such as postulated metabolites. We, therefore, investigated a convergent synthesis of ED-71 [**1**] as a novel and versatile method for the preparation of **1**. For the convergent synthesis of ED-71 [**1**], we first carried out the preparation of the A-ring synthon of **1**, which is characterized by hydroxypropoxy substituent at the C-2 position.

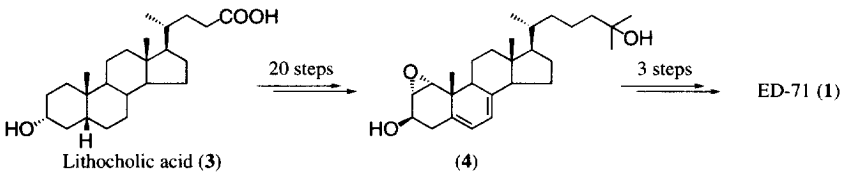


Fig. 2 Linear synthesis of ED-71 from lithocholic acid

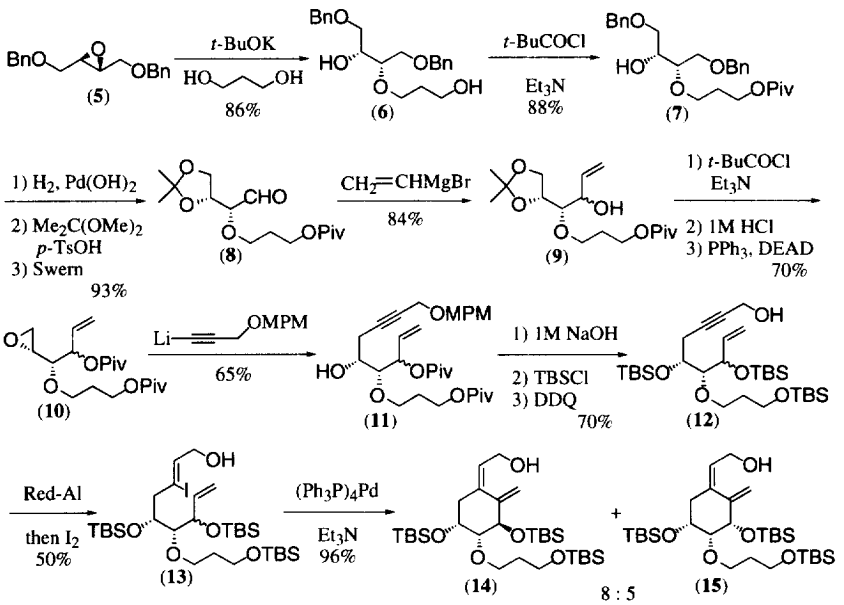


Fig. 3 Synthesis of the A-ring synthon of ED-71

Synthesis of the A-ring synthon of ED-71 [1]: The known C_2 symmetrical epoxide **[5]**[5] was cleaved by 1,3-propanediol in the presence of ^{t}BuOK to give the diol **[6]** in 86% yield. The primary alcohol part in **6** was protected as the pivalate **[7]** (88% yield) which was then converted to the aldehyde **[8]** by debenzylation, acetonide formation and the Swern oxidation in 93% overall yield. The introduction of the vinyl group to the aldehyde **[8]** was achieved by the Grignard reaction of **8** with vinylmagnesium bromide to afford the alcohol **[9]** in an inseparable diastereomixture (84% yield, 3*R*:3*S*=5:8 by NMR). The diastereomeric alcohol **[9]** was transformed to the epoxide **[10]** by the protection of the hydroxy part in **9**, hydrolysis of the acetonide group and the Mitsunobu reaction (70% overall yield). The reaction of the epoxide **[10]** with the lithium acetylide afforded the acetylene **[11]** in 65% yield which was then converted to the iodide **[13]** by hydrolysis, silylation, deprotection giving **12** (70% overall yield), reduction with Red-Al and the subsequent treatment with iodide (50% yield for two steps). The Heck reaction of **13** catalyzed by $(Ph_3P)_4Pd$[6] gave the cyclized alcohols, **[14]**[7] and **[15]**[8] after the separation by column chromatography, almost quantitatively. The alcohol **[14]** is fully substituted with necessary stereochemistry as the A-ring synthon of ED-71 **[1]**, whereas the alcohol **[15]** corresponds to the diastereomer at the C-1 position (Fig. 3).

Convergent synthesis of ED-71 [1]: Having the A-ring synthon **[14]** of ED-71 **[1]**, we next investigated the synthesis of ED-71 **[1]**. The reaction of the hydroxy part in **14** with N-chlorosuccinimide (NCS) and dimethyl sulfide in dichloromethane gave the chloride **[16]** which was then converted to the phosphine oxide **[17]** by the treatment with lithium diphenylphosphide.[9] The Wittig reaction of the phosphine oxide **[17]** and the CD-ring synthon **[19]**, obtained from Inhoffen-Lythgoe diol **[18]**[9] by the known method,[10] provided ED-71 **[1]**, in a satisfied yield, which was completely identical with the authentic material obtained by the linear method in Fig. 2 (Fig. 4).

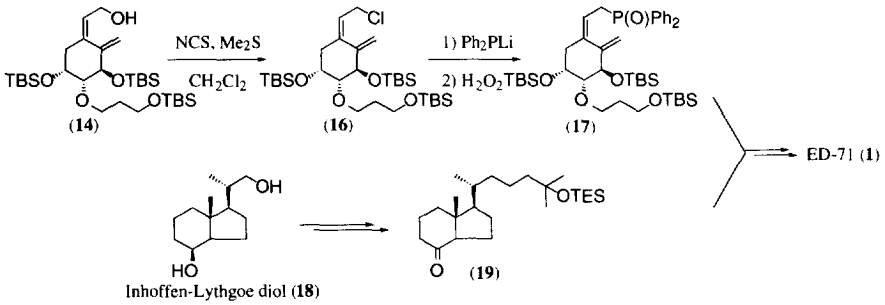


Fig. 4 Convergent synthesis of ED-71

Conclusion: A convergent synthesis of ED-71 has been developed. The main aspect of the synthesis involved transforming the readily available C_2 symmetrical epoxide into the A-ring synthon. The versatility of the convergent route allows for a greater degree of functionalization in the synthesis of highly complicated related compounds than was previously possible, while the linear route has advantages for a large scale production of ED-71 though multistep. The synthesis of postulated metabolites and other highly functionalized derivatives is now made feasible by this route.

Acknowledgment: We are grateful to Professor David Horne, Columbia University, for his helpful discussions.

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7) $[\alpha]_D$ -13.3 (*c* 1.04 $CHCl_3$); IR (neat) 3426, 1469, 1386, 1362, 1257, 1127cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 5.53 (t, 1H, *J*=6.9Hz), 5.26 (br s, 1H), 4.85 (q, 1H, *J*=1.1Hz), 4.25 (d, 1H, *J*=6.9Hz), 4.23-4.14 (m, 3H), 3.72-3.65 (m, 3H), 3.59 (dt, 1H, *J*=9.4, 6.6Hz), 3.19 (dd, 1H, *J*=6.6, 2.0Hz), 2.42 (dd, 1H, *J*=13.0, 7.3Hz), 2.21 (dd, 1H, *J*=13.0, 3.2Hz), 1.78 (m, 2H), 0.90 (s, 9H), 0.89 (s, 9H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.04 (s, 6H).

8) $[\alpha]_D$ +67.2 (*c* 0.89, $CHCl_3$); IR (neat) 3446, 1463, 1260, 1034cm^{-1}; ^{1}H-NMR (500MHz, $CDCl_3$) δ 5.54 (tt, 1H, *J*=5.5, 2.1Hz), 5.35 (t, 1H, *J*=2.3Hz), 4.83 (t, 1H, *J*=2.3Hz), 4.30 (dd, 1H, *J*=8.0, 12.8Hz), 4.14 (qd, 1H, *J*=2.1, 12.8Hz), 3.97 (q, 1H, *J*=2.3, 4.8Hz), 3.80-3.65 (m, 5H), 3.53 (s, 1H), 2.65 (t, 1H, *J*=12.1Hz), 2,13 (dd, 1H, *J*=4.8, 12.1Hz), 1.78 (quint, 1H, *J*=6.6Hz), 0.94 (s, 9H), 0.90 (s, 9H), 0.87 (s, 9H), 0.07 (s, 6H), 0.07 (s. 6H), 0.02 (s, 6H).

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