TOTAL SYNTHESIS OF (±)-DIPLOPHYLLIN USING INTRAMOLECULAR CYCLIZATION OF ω-FORMYL-β-ALKOXYCARBONYLALLYLSILANE[1]

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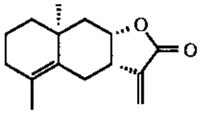
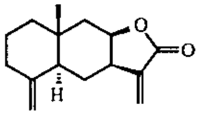
Abstract- ω-Formyl-β-ethoxycarbonylallylsilane derivative (**15**) was prepared from methyloctalone in several steps. Intramolecular cyclization of the allylsilane (**15**) was effected by BF_3-OEt_2 to give hydroxy esters (**17** and **18**) in good stereoselectivity at C-7. The hydroxy ester (**17**) was converted into (±)-diplophyllin (I) with *p*-TsOH in an excellent yield.

Eudesmanolide sesquiterpene, possessing α-methylene-γ-butyrolactone moiety, is widely distributed class of natural products with interesting biological activities.[2] The moiety of α-methylene-γ-butyrolactone plays an important role for the activities.[3] Diplophyllin (I) was reported as a major component of each essential oil from the liverworts *Diplophyllum albicans* and *D. taxifolium.*[4] The enantiomer of diplophyllin was obtained on acid isomerization of (+)-isoalantolactone (II).[4] Both compounds, isoalantolactone[5] and diplophyllin, have a moderate cytotoxicity against KB cell.[4]

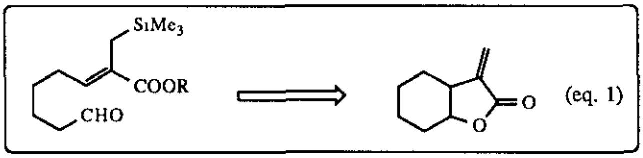


Diplophyllin (I)



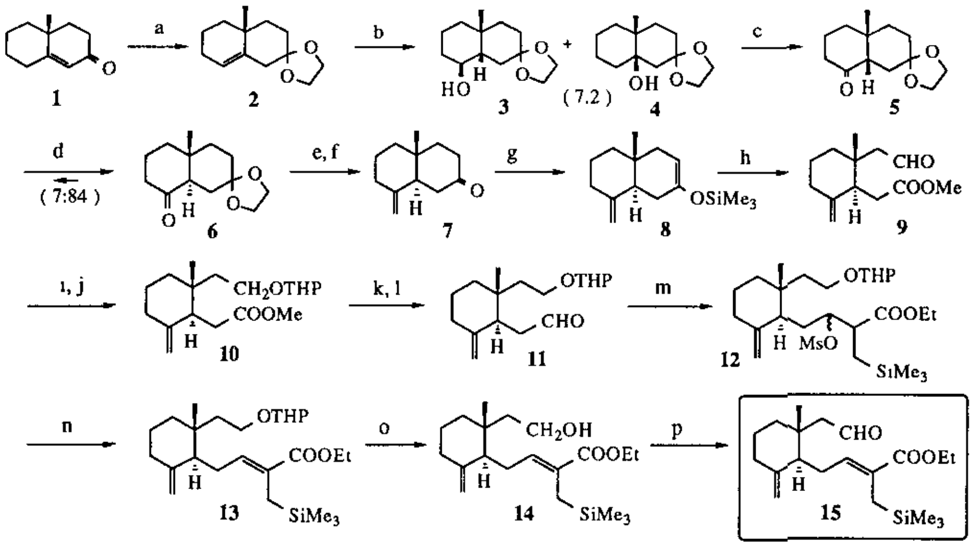
Isoalantolactone (II)

We have reported a facile synthesis of α-methylene-γ-butyrolactones fused to carbocycles employing the intramolecular Hosomi-Sakurai reaction of ω-formyl-β-alkoxycarbonylallylsilanes (eq. 1).[6,7] This method is very useful to synthesize the terpenoid lactones having α-methylene-γ-butyrolactone moiety. We also reported a facile and stereoselective synthesis of *cis*- and *trans-p*-menthanolides from optically active formylated allylsilane derivative using this cyclization method.[8] We would like to report the first total synthesis of (±)-diplophyllin utilizing our intramolecular cyclization method.



(eq. 1)

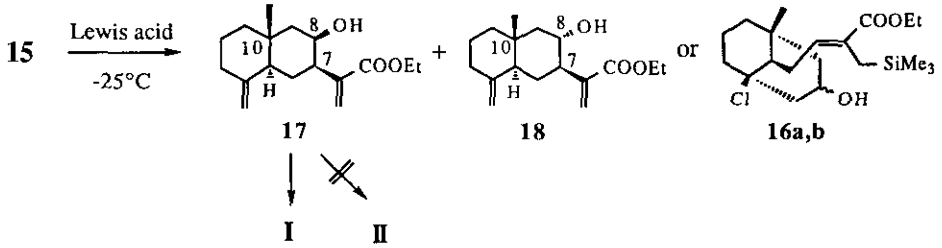
Formyl-allylsilane (**15**) was synthesized starting from the known methyloctalone (**1**) which was derived from 2-methylcyclohexanone and methyl vinyl ketone.[9,10] The conversion of the octalone (**1**) into the decalone (**7**) was already reported by Marshall *et al.*[11] We synthesized the decalone (**7**) by the Marshall's method[9] with partial modification. The α,β-unsaturated carbonyl group of the (±)-methyloctalone was protected as ethylene ketal with the double bond migration, and then hydroboration-oxidation afforded *cis*-fused hydroxy ketals (**3** and **4** in a ratio of 7:2) in 75% yield. Swern oxidation of the major component (**3**) gave *cis*-fused decalone (**5**) in 94% yield. *trans*-Fused decalone (**6**) was expected to be more stable than *cis*-isomer (**5**) by 1.6 kcal/mol (*trans*/*cis* ≈ 96:4) from the MM2 calculation. Treatment of the *cis*-isomer with NaH in refluxing THF gave the *trans*-isomer and *cis*-isomer in respective 84 and 7 % isolated yields. Treatment of the *trans*-isomer (**6**) with the methylenephosphorane, derived from triphenylmethylphosphonium iodide and nBuLi in THF, followed by 80% acetic acid afforded the methylene derivative in 79% yield, whose physical and spectral data were coincident with the reported data of the authentic decalone (**7**).[11] Regioselective proton removal of **7** was effected with an excess of LDA and the resulting carbanion was quenched with chlorotrimethylsilane to give



a) $(CH_2OH)_2$, *p*-TsOH / benzene, reflux (76%), b) B_2H_6/THF then H_2O_2, NaOH (75%), c) Swern oxidation (94%), d) NaH/THF, reflux (84%), e) Ph_3PCH_2I,nBuLi/THF (94%), f) 80% AcOH (84%), g) LDA,TMSCl/THF (96%), h) 1. O_3,pyridine/CH_2Cl_2, -100°C, 2. Me_2S, 3. CH_2N_2 (37%), i) $NaBH_4$ (94%), j) DHP,PPTS (95%), k) LAH/ether (86%), l) Swern oxidation (94%), m) 1, $TMS(CH_2)_2COOEt$, LDA/THF,-78°C (87%), 2, MsCl, Et_3N (95%), n) DBU/benzene, reflux (74%), o) PPTS/EtOH (77%), p) Swern oxidation (96%)

silyl enol ether (**8**) in an excellent yield. It is not easy to distinguish the two double bonds, *exo*-methylene and the enol ether, on ozonolysis. When **8** was treated with ozone in CH_2Cl_2 in a presence of pyridine at -100 °C and then with ethereal diazomethane,[12] aldehyde (**9**) was obtained in 37% yield after chromatographic separation. Successive sodium borohydride reduction, THP-protection, lithium aluminum hydride reduction and Swern oxidation of the aldehyde (**9**) gave aldehyde (**11**) in good yield in each step. Coupling reaction of the enolate of ethyl β-trimethylsilylpropionate (LDA in THF at -78°C) with the aldehyde (**11**) gave adducts, which were then treated with methanesulfonyl chloride and triethylamine gave mesylate (**12**). Elimination of methane sulfonic acid from **12** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in refluxing benzene selectively gave Z-allylsilane (**13**).[13] Removal of the protecting group (THP) followed by the Swern oxidation of the allylsilane (**13**) gave the desired cyclization precursor (**15**) in good yield.

Intramolecular cyclization of **15** with titanium tetrachloride in CH_2Cl_2 at -25°C was smoothly proceeded.[14] The resulting products (**16a** and **b**; 37% and 52% yields respectively) were not the expected hydroxy esters nor the lactone, but [3.3.1]nonane derivatives (**16a** and **b**)[15] which should be come from the intramolecular reaction of the *exo*-methylene group and the formyl function. This undesired cyclization reaction should arise from the presence of a good nucleophile (Cl^-) in the Lewis acid. Therefore, we use boron trifluoride ether complex as a Lewis acid instead of titanium tetrachloride for the cyclization reaction to give *trans*-hydroxy ester (**18**) and *cis*-hydroxy ester (**17**) in 30.6 and 25% yields, respectively. The stereochemistry of these hydroxy esters was determined by the ^{1}H-nmr analysis, especially the coupling pattern of the C-8 proton signals [**17**; δ 4.04 (br q,*J*=4 Hz), **18**; δ 3.90 (td,*J*=11,5 Hz)].[16] Lactonization of the *cis*-isomer (**17**) was performed with *p*-toluenesulfonic acid in refluxing benzene for 30 min not to give (±)-isoalantolactone (±-**II**) but (±)-diplophyllin (±-**I**), accompanying isomerization of the double bond, quantitatively. The ^{1}H-nmr data of the synthetic (±)-diplophyllin[17] are coincident with those of the natural diplophyllin reported by Ohta *et al.*[4] A synthesis of the optically active octalone (**1**) had already been reported by Pfau *et al.*,[10] therefore, the total synthesis of natural diplophyllin is expected to be achieved by our strategy.



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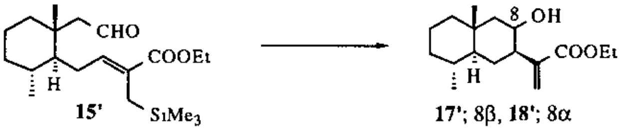
REFERENCES AND NOTES

1. This paper forms "Studies on the Terpenoids and Related Alicyclic Compounds XLVI". Part XLV: K. Nishitani, T. Konomi, K. Okada and K. Yamakawa, *Heterocycles*, **1994**, *37*, 679.

2. H. Yoshioka, T. J. Mabry and B. N. Timmermann, "Sesquiterpene Lactones," University of Tokyo Press, Tokyo, **1973**. N. H. Fischer, E. J. Oliver and D. Fischer, *Fortschr. Chem. Org. Naturst.*, **1979**, *38*, 47; B. M. Fraga, *Nat. Prod. Rep.*, **1992**, *9*, 217; **1993**, *10*, 397.
3. S. M. Kapchan, *Pure Appl. Chem.*, **1970**, *21*, 227; E. Rodriguez, G. H. N. Towers and J. C. Mitchell, *Phytochemistry*, **1976**, *15*, 1573; G. Schlewer, J. L. Stampf and C. Benezra, *J. Med. Chem.*, **1980**, *23*, 1031; J. M. Cassady and M. Suffness, "Anticancer Agents Based on Natural Product Models," ed. by J. M. Cassady and J. D. Douros, Academic Press, New York, **1980**, pp, 201-267, and references cited therein.
4. Y. Ohota, N. H. Andersen and C. -B. Liu, *Tetrahedron*, **1977**, *33*, 617.
5. J. Kallen, *Chem. Ber.*, **1873**, *6*, 1506. Synthesis; H. Minato, I. Horibe, *J. Chem. Soc., Chem. Commun.*, **1965**, 531; *J. Chem. Soc.*, C, **1967**, 1575.
6. K. Nishitani and K. Yamakawa, *Tetrahedron Lett.*, **1987**, *28*, 655; **1991**, *32*, 387; K. Nishitani, Y.Nakamura, R. Orii, C. Arai, and K. Yamakawa, *Chem. Pharm. Bull.*, **1993**, *41*, 822.
7. Kuroda and co-workers have reported a similar reaction independently; C. Kuroda, S. Shimizu and J. Y. Satoh, *J. Chem. Soc., Chem. Commun.*, **1987**, 286; *J. Chem. Soc., Perkin Trans.* 1, **1990**, 519; C. Kuroda, S. Shimizu, T. Haishima and J. Y. Satoh, *Bull. Chem. Soc. Jpn.*, **1993**, *66*, 2298.
8. K. Nishitani, H. Fukuda and K. Yamakawa, *Heterocycles*, **1992**, *33*, 97.
9. J. A. Marshall and W. I. Fanta, *J. Org. Chem.*, **1964**, *29*, 2501; C. H. Heathcock and J. E. Ellis, *Tetrahedron Lett.*, **1971**, 4995; R. A. Moss and D. J. Smudin, *J. Org. Chem.*, **1976**, *41*, 611.
10. M. Pfau, G. Revial, A. Guingant and J. d'Angelo, *J. Am. Chem. Soc.*, **1985**, *107*, 273.
11. J. A. Marshall, M. T. Pike and R. D. Carroll, *J. Org. Chem* , **1966**, *31*, 2933.
12. G. Slomp, Jr. and J. L. Jonson, *J. Am. Chem. Soc.*, **1958**, *80*, 915.
13. The geometry of the α,β-unsaturated ester moiety was determined by its ^{1}H-nmr spectrum showing triplet signals at δ 6.50. H. M. R. Hoffmann and R. Henning, *Helv. Chim., Acta*, **1983**, *66*, 828.
14. Cyclization of the model compound (**15'**) with $TiCl_4$ gave excellent yield of **17'** and **18'** in 2:3, however, with TBAF gave only 22% yield of **18'**. Many spots other than **17** and **18** were observed on a TLC plate when tried TBAF for the cyclization of **15** on a few mg scale reaction.



15' **17'**; 8β, **18'**; 8α

15. Spectral data; ms; *m/z* 386, 388 [M$^+$], ir; 1720, 1710 cm^{-1}, ^{1}H-nmr; **16a**; δ 0.03 (9H, s) 0.90 (3H, s), 1.28 (3H, t , *J*=7 Hz), 4.16 (2H, t, *J*=7 Hz), 4.16 (1H, m), 6.62 (1H, t, *J*=6 Hz), **16b**; δ 0.00 (9H, s), 0.90 (3H, s), 1.26 (3H, t, *J*=7 Hz), 4.16 (2H, q, *J*=7 Hz), 4.43 (1H, m), 6.63 (1H, t, *J*=6 Hz).
16. C-10 Methyl proton signal of **17** (δ 0.96) appeared at a lower field than that of **18** (δ 0.80), which showed *cis*-relationship between the C-10 methyl group and the C-8 hydroxyl group of **17**.
16. ^{1}H-Nmr spectral data; 1.08 (3H, s), 1.65 (3H, br s), 4.48 (1H, q, *J*=7 Hz), 5.56, 6.22 (each 1H, d, *J*=3 Hz).

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