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A NOVEL ANTILEUKEMIC SESQUITERPENE LACTONE. SYNTHESIS OF RACEMIC ERIOLANIN

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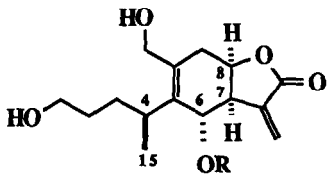
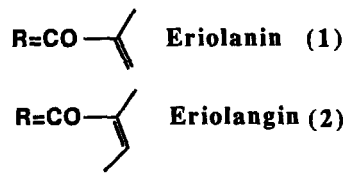
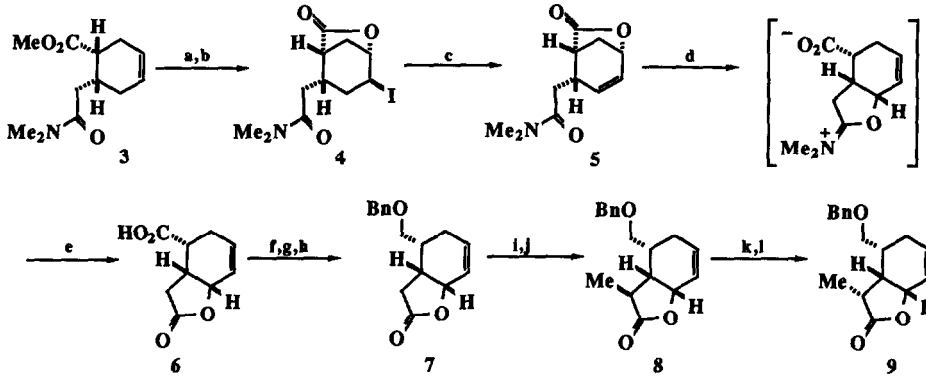
Summary *The synthesis of dl-eriolanin* **1**, *highly oxygenated 1,10-seco-eudesmanolide isolated from the chloroform extracts of* Eriophyllum lanatum *Forbes (Compositae), is reported*

Eriolanin **1** and eriolangin **2** are novel antileukemic 1,10-seco-eudesmanolides which were isolated from *Eriophyllum lanatum* Forbes (Compositae) by Kupchan and coworkers during a search for tumor-inhibitory natural products from plant sources Both eriolanin and eriolangin were found to possess significant in vivo activity against P 388 leukemia in mice and in vitro activity against cell cultures derived from human carcinoma of the nasopharynx (KB) [2] The total synthesis of these natural products has been disclosed by two laboratories [3,4] In this paper we wish to report the synthesis of racemic eriolanin **1** starting from cis-cyclohexene amide **3**



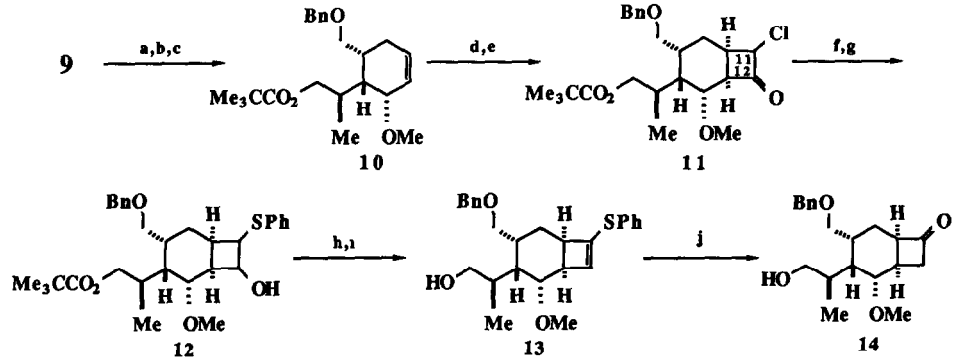


Hydrolysis of ester **3**[5] followed by iodolactonization gave rise to the bicyclic lactone **4**, which in turn was treated with diazabicycloundecene (DBU) in benzene to afford cyclohexene **5** The stereocontrolled functionalization at the C-6 position of **5** was achieved in 86% overall yield via treatment with boron trifluoride etherate and subsequent acid hydrolysis to provide cis-lactone **6** as the sole product. Benzyl ether **7** was easily prepared through the following functional group manipulation, (i) $ClCO_2Et/Et_3N$, (ii) $NaBH_4$, (iii) $BnBr/Ag_2O$ The introduction of the β-oriented C-15 methyl group involves methylation of lactone **7** to **8** followed by a kinetic protonation[6] of the corresponding enolate with trifluoroacetic acid to give the α-oriented methyl lactone **9** in the desired sense (83·17)



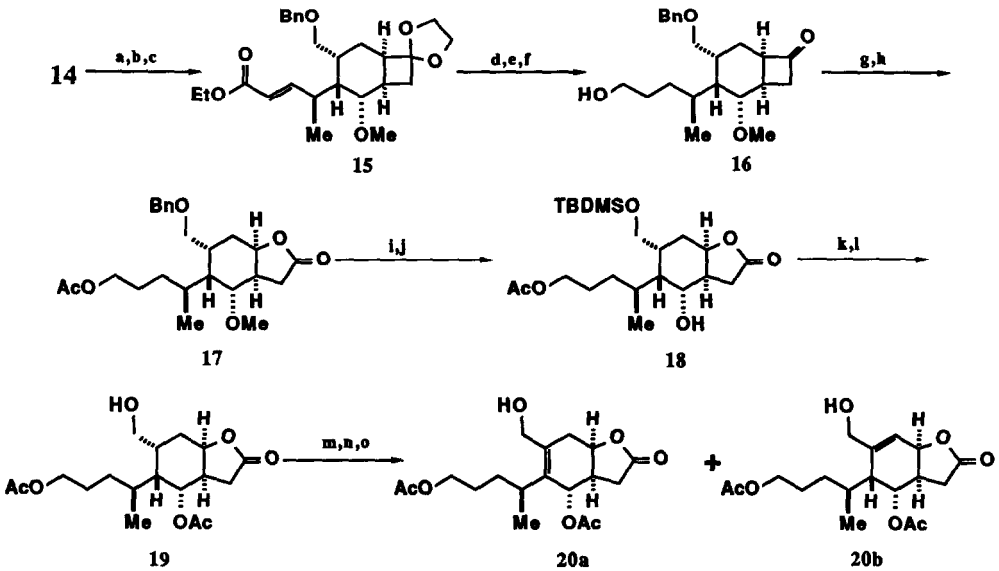
a LiOH/aq.MeOH , b KI_3/aq $NaHCO_3$, quant from 3 ; c DBU/benzene, 92% ;
d BF_3 OEt_2/CH_2Cl_2 ; e 10%HCl/THF/reflux, 86% , f $ClCO_2Et/Et_3N$/THF ;
g $NaBH_4/H_2O$/-20°C, quant. from 6 , h BnBr/$Ag_2O/CHCl_3$, 83% ; i LDA/
THF/-78°C , j MeI/2 5min, 92% from 7 ; k LDA/THF/-78°C , l CF_3COOH, 75%

Reduction of compound **9** with lithium aluminum hydride gave the corresponding primary alcohol Concomitant protection of the primary hydroxyl group with pivaloyl chloride followed by reaction with methyl iodide produced cyclohexene derivative **10**. We then turned our attention to the elaboration of γ-butyrolactone functionality Addition of dichloroketene[7] to **10** took place from the β-face of the olefin system to give rise to cyclobutanone **11** in 44% yield after monodechlorination The regioselectivity of this reaction course was fully confirmed by the chemical transformations of ketene adducts into γ-lactone derivatives and eventually found that a ratio of the C-11 carbonyl compound and its C-12 regioisomer was 5 95 The 1,2-carbonyl transposition[8] of **11** was effectively performed as follows. Treatment of **11** with sodium thiophenolate followed by reduction with sodium borohydride gave cyclobutanol **12** as a mixture of diastereoisomers which without separation was converted to thiovinyl ether **13** in two steps , (i) MsCl/Pyr (ii) t-BuOK/DMSO (59% overall yield). This was then hydrolyzed with mercury(II) chloride in aqueous acetonitrile[9] to afford cyclobutanone **14** in 83% yield



a $LiAlH_4$/THF/-30°C, 83% , b Me_3CCOCl/Py , 95% , c MeI/NaH/THF, 92% , d Cl_3CCOCl
/Zn-Cu/ether/rt,5 5hr ; e Zn/NH_4Cl/MeOH/0°C, 44% from 10 , f PhSNa/MeOH/rt, 74% ;
g $NaBH_4$/MeOH, quant , h MsCl/Py , quant. , i t-BuOK/DMSO, 81% , j $HgCl_2$
/CH_3CN-H_2O(3 1)/40°C,89%

The C_2 homologation of **14** was performed in a straightforward manner in three steps. Acetalization, oxidation, and Wittig reaction provided smoothly α,β-unsaturated ester **15** in 74% yield. The requisite intermediate **16** for ring enlargement was prepared in 97% yield from **15** by reaction with sodium borohydride in the presence of nickle(II) chloride[10] to give the saturated ester, which upon $LiAlH_4$ reduction and acid hydrolysis afforded cyclobutanone **16** Treatment of the resulting **16** with acetic anhydride in pyridine gave the corresponding acetate which was subjected to Baeyer-Villiger reaction[11] to provide γ-butyrolactone **17** in 65% overall yield. Removal of both the benzyl and methyl ethereal moiety was readily accomplished by employing BBr_3 and NaI/15-crown-5[12] to give the crude diol This was then selectively protected by treatment with t-butyldimethylsilyl trifluoromethanesulfonate/2,6-lutidine[13] to afford lactone **18** in 54% yield Subsequent treatment with acetic anhydride in pyridine followed by desilylation with tetrabutylammonium fluoride/benzoic acid gave rise to diacetate **19** in good yield. Introduction of ring olefin by initial pyridinum chlorochromate oxidation[14] followed by treatment with phenylselenenyl chloride in ethyl acetate at 80°C[4] was effected to furnish the unstable aldehydes which were immediately reduced with sodium borohydride in ethanol to give a mixture of the desired alcohol **20a** and its regioisomer **20b** in a ratio of 1.1. Spectral properties of **20a** obtained in this way were identical with those of authentic sample kindly provided us by Professor Schlessinger [4] Since Schlessinger[4] had reported the successful conversion of **20a** into erioranin **1** by a four-step sequence, the present synthesis of **20a** means a formal total synthesis of racemic eriolanin.



a $HOCH_2CH_2OH$/TsOH ; b PCC/MS-3A ; c $Ph_3P{=}CHCO_2Et/CH_2Cl_2$, 74% from 14 , d $NaBH_4/NiCl_2$ $6H_2O$/MeOH , quant. ; e $LiAlH_4$/ether, 97% , f aq acetone/TsOH, quant. ; g Ac_2O/Py., 82% ; h t-BuOOH/10%NaOH/THF, 79% , i BBr_3/15-crown-5/ NaI/CH_2Cl_2 , j TBDMSOTf/2,6-lutidine/CH_2Cl_2, 54% from 17 , k Ac_2O/Py., 83% l n-Bu_4NF/PhCOOH/THF, 92% ; m PCC/MS-4A/CH_2Cl_2 ; n PhSeCl/AcOEt/80°C , o $NaBH_4$/EtOH

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References and Notes.

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2. S. M. Kupchan, R. L Baxter, C.-K. Chiang, C. J. Gilmore, and R. F Bryan, *J Chem Soc , Chem Commun ,* 842 (1973).
3. P. A. Grieco, T. Oguri, S. Gilman, and G. T. DeTitta, *J Am Chem Soc ,* **100**, 1616 (1978); P. A. Grieco, T. Oguri, and S Gilman, *ibid ,* **102**, 5886 (1980)
4. M. R. Roberts and R. H. Schlessinger, *ibid ,* **103**, 724 (1981)
5. T. Wakamatsu, H. Hara, and Y. Ban, *J Org Chem ,* **50**, 108 (1985).
6. S. Takano, J Kudo, M. Takahashi, and K Ogasawara, *Tetrahedron Lett ,* **27**, 2405 (1986)
7. For useful intermediates in organic synthesis, see· (a) C R Clark, J. Lin, and M. Nikaido, *ibid ,* **25**, 2645 (1984); (b) A E Green, M. J. Luche, and J. P. Depres, *J Am. Chem Soc ,* **105** 2435 (1983); (c) R. F Newton and S. M Roberts, *Tetrahedron,* **36**, 2163 (1980); (d) B. M Trost, *Top Curr Chem ,* **43**, 563 (1975); (e) A Hassner, H W. Pinnick, and J M. Ansell, *J Org Chem ,* **43** 1774 (1978); (f) W. T. Brady, *Tetrahedron,* **37**, 2949 (1981)
8. T. Wakamatsu, N. Miyachi, F Ozaki, and Y. Ban, *Heterocycles,* **26**, 1445 (1987).
9. B. M Trost, K.Hiroi, and S. Kurozumi, *J Am Chem Soc ,* **97**, 438 (1975).
10 D. Satoh and T. Hashimoto, *Chem Pharm Bull Japan,* **24**, 1950 (1976)
11. P. A. Grieco, T. Oguri, C -L J. Wang, and E. Williams, *J Org Chem ,* **42**, 4113 (1977).
12. H Niwa, T. Hida, and K. Yamada, *Tetrahedron Lett ,* **22**, 4239(1981).
13. E J. Corey, H. Cho, C Rucker, and D. H. Hua, *ibid ,* **22**, 3455 (1981).
14. J. Herscovic and K Antonakis, *J Chem Soc , Chem Commun ,* 561 (1980).

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