Tetrahedron Letters,Vol.25,No.3,pp 333-336,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

ASYMMETRIC TOTAL SYNTHESIS OF ANTILEUKEMIC SESQUITERPENE (+)-IVALIN

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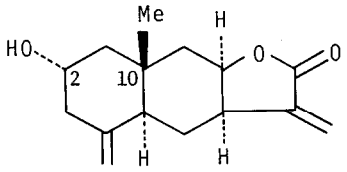
Summary: The one-pot double alkylation reaction of a chiral α,β-unsaturated imine (6) with isopropenyl Grignard reagent followed by methyl iodide has been shown to proceed highly asymmetrically. Subsequent stereoselective transformation of the derived adduct (10) has culminated in a first asymmetric total synthesis of the optically pure eudesmane sesquiterpene (+)-ivalin (1).

The development of methodology for the effective asymmetric synthesis is an area of fruitful and challenging current research.[2] As a part of our program directed toward the development of new stereoselective reactions, we have reported a highly efficient enantioselective and diastereoselective synthesis of 1,2-disubstituted cycloalkanecarboxaldehydes based on the controlling of the substrate conformation by virtue of chelation.[3] As a touchstone for demonstration of this new method, antileukemic eudesmane sesquiterpenes such as ivalin (1), isoalantolactone (2), etc., which have been targets of considerable synthetic efforts,[4] appear particularly interesting because of their model characters for a variety of biologically active natural products.[5]



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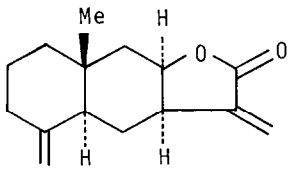

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Herein, we wish to report the first asymmetric total synthesis of (+)-ivalin (1),[6] a representative of the class of antileukemic eudesmane sesquiterpene lactones.[7] Our approach involves elaboration of optically active 10, followed by the construction of 10-methyl decalin unit 16.

The substrate (6) for the asymmetric synthesis was prepared as follows. The ketalization of 3[8] proceeded smoothly to give the ester 4.[9] Reduction of 4 followed by PCC oxidation afforded 5. The chiral α,β-unsaturated aldimine (6) ($[\alpha]_D^{20}$-88.6° (benzene), mp 51-53°C) was prepared by the condensation of 5 with L-t-leucine t-butyl ester,[10] a highly effective chiral auxiliary reagent in the

present asymmetric synthesis.

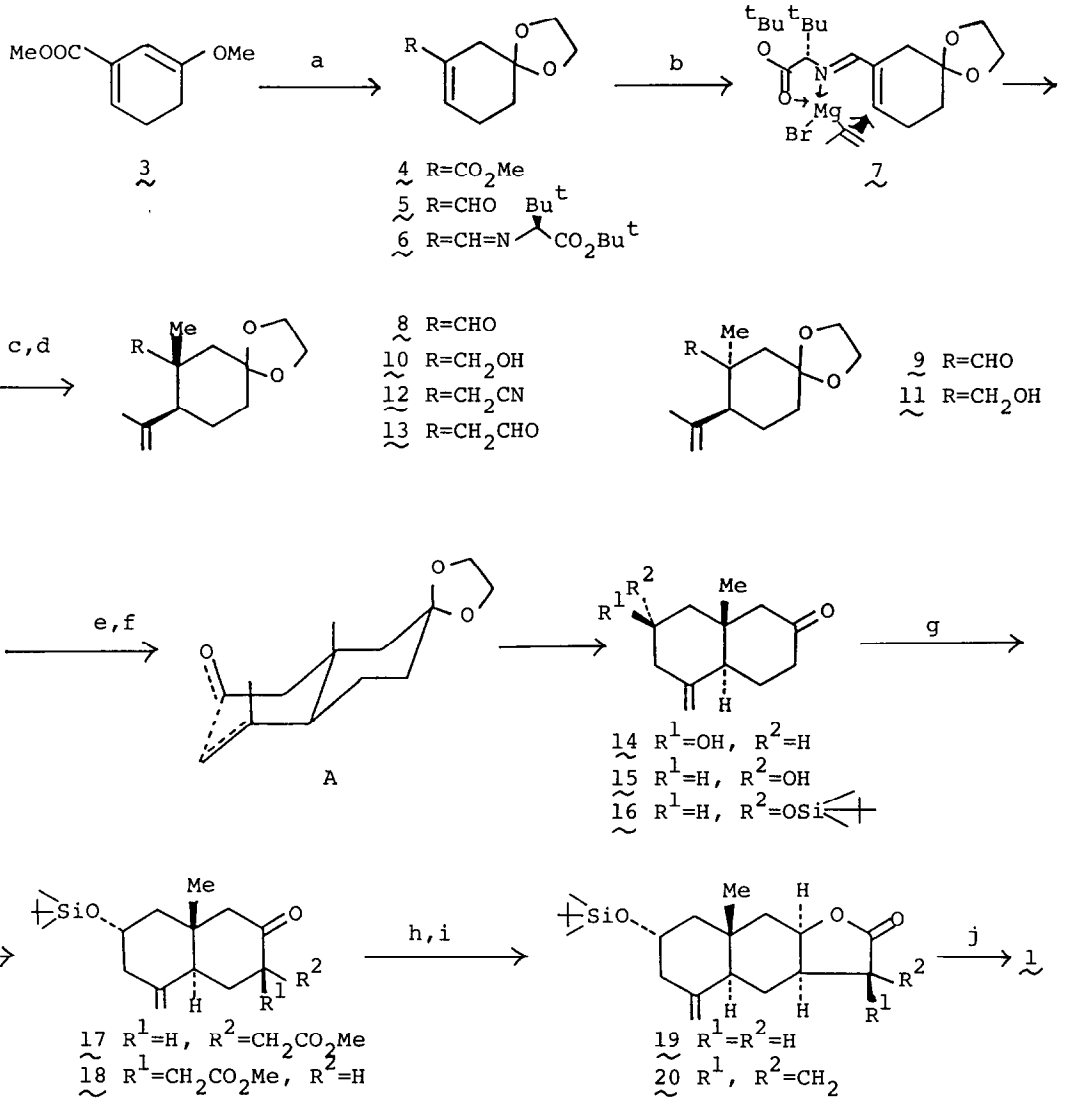
The asymmetric tandem double alkylation via 1,4-addition of 6 with isopropenylmagnesium bromide followed by methylation afforded, after hydrolysis, a mixture of products (8 and 9).[11] Without separation this mixture was subjected to $NaBH_4$ reduction to give a mixture of easily separable products. Purification by silica gel column chromatography (n-hexane-benzene-ethyl acetate/7:3:3) afforded trans-10 (35%) and cis-11 (22%).[12] Relative configuration of 10 and 11 was determined by ^{13}C NMR analysis of the corresponding 8 and 9. Angular methyl signal of 8 appeared at 11.0 ppm while that of 9 at 22.6 ppm, indicating that 8 had the axial angular methyl group.[3] Although the diastereoselectivity was somewhat lower, enantioselectivity was found to be as high as 95% by converting 10 into the crystalline 12 of $[\alpha]_D^{20}$+19.0° ($CHCl_3$), mp 39-41°C. Repeated recrystallization of 12 from n-hexane afforded the optically pure 12 of the constant optical rotation ($[\alpha]_D^{20}$+20.1° ($CHCl_3$), mp 42-43°C) in a good recovery yield. This means that the present asymmetric synthesis afforded 10 in 95% e.e. The absolute configuration of 10, predicted by the mechanism as shown in 7, was proved by converting it into natural (+)-ivalin (1).

The optically pure 12 was then reduced with DIBAH to give 13 in 88% yield. The aldehyde-olefin cyclization of 13 with $SnCl_4$ resulted in the concomitant deprotection of the ethylene ketal group to give predominantly the decalin unit 14 ($[\alpha]_D^{20}$-10.0° ($CHCl_3$), mp 100-102°C) in 61% yield.[13] The axial orientation of the hydroxy group in 14 was suggested by NMR analysis. Thus C2-H appeared at δ 4.20 (half width 11 Hz) corresponding to be axial orientation of C2-OH. The predominant formation of 14 was attributed to the favorable transition state A in which the developing six membered carbocycle could attain the chair conformation.

Stereoinversion of the hydroxy group was then carried out by the reaction of the corresponding mesylate with KO_2[14] to give the requisite 15 (C2-H δ 3.80 (half width 20 Hz)). 15 was then converted to the silyl ether 16 ($[\alpha]_D^{20}$-28.7° ($CHCl_3$)) in 20% overall yield (from 14).

The stage was thus set for the construction of the lactone ring. Reaction of the enolate anion of 16 with methyl bromoacetate afforded regioselectively and stereoselectively the ester 17. Epimerization of 17 with t-BuOK gave the thermodynamically more stable ketoester 18 in 76% yield. Reduction of 18 with $NaBH_4$ followed by acidic work-up gave rise to the lactone 19 ($[\alpha]_D^{24}$+18.6° ($CHCl_3$), mp 104.0-107.5°C) in 81% yield.

Hydroxymethylation and subsequent mesylation followed by treatment with DBU[15] afforded the α-methlene γ-butyrolactone 20 ($[\alpha]_D^{25}$+95.4° ($CHCl_3$), mp 111-113°C) in 37% overall yield. Deprotection gave the optically pure (+)-ivalin (1) of $[\alpha]_D^{23}$ +140° ($CHCl_3$) (lit.,[6] $[\alpha]_D^{23}$+142° ($CHCl_3$)). Optical rotation, spectral data (NMR, IR, MASS), melting point (131-134°C (lit.,[6] 130-132°C, 131-134°C)), mixed melting



a) ethylene glycol, $BF_3 \cdot OEt_2$ in CH_2Cl_2; $LiAlH_4$ in ether; PCC in CH_2Cl_2; L-t-leucine t-butyl ester in benzene (77%)
b) isopropenylmagnesium bromide in THF, then MeI-HMPA; aq. citric acid; $NaBH_4$ in MeOH (10(35%), 11(22%))
c) MsCl-Hünig base in CH_2Cl_2; NaCN in HMPA (83%)
d) DIBAH in ether (88%)
e) $SnCl_4$ in CH_2Cl_2 (61%)
f) MsCl-Hünig base in CH_2Cl_2; KO_2-18-crown-6 in DMSO-DME; TBDMSCl-imidazol-DMAP in DMF (20%)
g) LDA-$BrCH_2CO_2Me$ in THF; t-BuOK in THF (61%)
h) $NaBH_4$ in MeOH; 10% aq. HCl (81%)
i) LDA-HCHO in THF; MsCl-Hünig base-pyridine in CH_2Cl_2; DBU in benzene (37%)
j) aq. HF-CH_3CN (78%)

point, and tlc behavior of the synthetic (+)-ivalin were completely identical with those of the natural specimen.

The first asymmetric total synthesis of (+)-ivalin demonstrated above holds a great promise for the asymmetric synthesis of other biologically potent eudesmane sesquiterpenes.

Acknowledgement: The authors are grateful to Professor Akio Karube, Akita Technical College, Japan, for a gift of natural (+)-ivalin.

References and Notes

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9. Satisfactory spectral and analytical data were obtained for all new compounds.
10. Optically pure L-t-leucine is commercially available from Daiichi Pure Chemicals Co., LTD., Japan.
11. Chiral auxiliary reagent L-t-leucine t-butyl ester was recovered without any loss of optical purity for reuse.
12. A product not having been methylated was also isolated.
13. Only a trace amount of 15 was detected by tlc analysis.
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(Received in Japan 7 October 1984)