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AN ASYMMETRIC SYNTHESIS OF CIS, ANTI, CIS-TRICYCLO[5,3,0,$0^{2,6}$]DECANES APPLYING γ-HYDROXYMETHYL-γ-BUTYROLACTONE AS A CHIRAL SYNTHON. FIRST ASYMMETRIC TOTAL SYNTHESIS OF (-)-β-BOURBONENE

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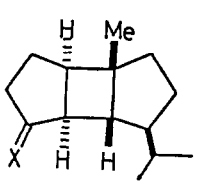
Summary: The asymmetric total synthesis of cis, anti, cis-tricyclo[5,3,0,$0^{2,6}$]decane sesquiterpene β-bourbonene is described The key (2+2) photocycloaddition was carried out applying the optically pure butenolide derivative 6b as a chiral synthon

The cis, anti, cis-tricyclo[5,3,0,$0^{2,6}$]decane system is found in the carbon skeleton of both bourbonene sesquiterpenoids and spatane diterpenoids such as for example, β-bourbonene (1)[1], norbourbonone (2)[2], and spatol (3)[3,4] Spatol, recently isolated from the brown seaweed, is known to be endowed with remarkable biological properties including a potent inhibition of cell replication and β-bourbonene has been the subject of synthetic investigations[5].

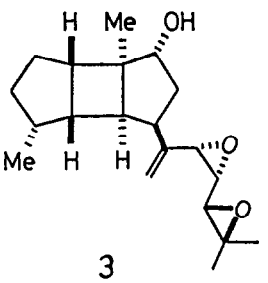
We report herein a total synthesis of (-)-β-bourbonene and (-)-norbourbonone employing an asymmetric (2+2) photocycloaddition reaction and thus record a first, general method of entry into the optically pure tricyclo[5,3,0,$0^{2,6}$]decane series The general approach under consideration involves the asymmetric induction shown in Scheme I wherein the optically active γ-hydroxymethyl-γ-butyrolactone (4) might be expected to be a chiral synthon applicable not only as a chiral source, but also as a building block for the cyclopentenone portion of 5, the promising intermediate leading to 1, 2, and 3

The present approach possesses three attractive features First, both enantiomers (-)-, and (+)-4 are readily available from L-glutamic acid.[6] Second, it is possible to predict the



1 X = CH_2

2 X = O



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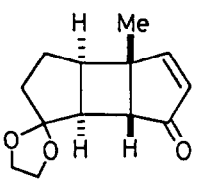

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absolute stereochemistry at the newly created chiral centers on the basis of the least hindered approach.[7,8] Third, the particular applicability of 4 in the chiral synthesis of cyclopentenone series will be illustrated.[9]

Photochemical (2+2) cycloaddition reaction was thoroughly reviewed by Baldwin[8] and reaction between racemic γ-butyl-crotonolactone and 1,1-dimethoxyethylene has been developed by Uda[10], giving two cis-bicyclic 4-5 fused ring compounds in almost nonstereocontrolled manner. Our synthesis begins with the irradiation of a solution of the trityl ether 6a[11], prepared from (-)-4, and cyclopentene in CH_3CN using a low pressure mercury lamp at 20°C under argon, giving two adducts of structure 7a and 8a in the ratio of 60.40 in 37% yield.[12] Improvement in the stereoselectivity was obtained when the pivaloyl ester 6b[13], prepared from 6a in 62% yield in two steps (1) conc HCl/MeOH, (2) t-BuCOCl/pyridine, was used in place of 6a, affording 7b and 8b in the ratio of 72.28 in 74% yield The stereochemistry was assigned based on ^{13}C NMR in which methyl carbon of 7 appeared at higher field (ca 13ppm) than that of 8 (ca 19ppm) due to steric compression Using 6b photocycloaddition was next carried out with cyclopentenone ethyleneketal and was found to afford the adducts of structure 9b, 10b, 11b, and 12b in the ratio of 48 20·16 16 in 62% yield [13,14,15] For the practical purpose the desired major adduct 9b could be easily isolated in 25% yield after short column chromatography on silica gel (AcOEt/n-hexane=1/5) followed by recrystallization (AcOEt/n-hexane)

As demonstrated in the following transformation in which removal of the original chiral center having played its role to create new chiral centers and construction of the cyclopentenone moiety were achieved, the structural features of the photoadduct 9b can be effectively utilized in forming the optically pure cis, anti, cis-tricyclo[5,3,0,$0^{2,6}$]decane nucleus 5. Thus 9b was treated with methyl lithium to give the hemiketal 13 (95% yield) which was then converted to (-)-5[13,16] in 74% overall yield by the sequence of operations. (1) NaOMe in refluxing MeOH, (2) oxidative cleavage of the diol with $NaIO_4$ in aqueous AcOEt, (3) aldol condensation of the corresponding keto aldehyde with NaOH in aqueous ether.

The stage was thus set for the synthesis of (-)-β-bourbonene (1) Hydrogenation of 5 over 10% Pd/C in AcOEt followed by highly stereoselective reduction of the corresponding ketone with $NaBH_4$ in MeOH gave 14 as a single product in 96% yield Tosylation of 14 followed by reaction with sodium diethyl malonate in refluxing DME afforded 15 as a single product in 91% yield. Treatment of 15 with $LiAlH_4$ gave the diol 16[13] in 85% yield Deoxygenation by $LiAlH_4$ reduction of the dimesylate of 16 followed by deprotection (p-TsOH/acetone) afforded (-)-norbourbonone (2) as a crystallin compound in 64% yield.[13] Finally Wittig reaction of (-)-2 according to the known procedure for racemic material[5a] gave (-)-β-bourbonene (1) in 98% yield (10% overall yield from the chiral synthon 6b).[13] Optical rotations, melting point (for (-)-2), and spectral data (IR, NMR, MS) of synthetic (-)-1 and (-)-2 were identical with those of natural products.[1,2,13] Now that utility of γ-hydroxymethyl-γ-butyrolactone as a chiral synthon for the asymmetric synthesis of bourbonane sesquiterpenoids has been illustrated, the asymmetric synthesis of spatane related substances is the subject of current studies

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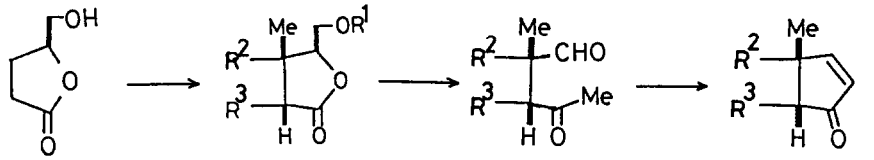
Scheme I



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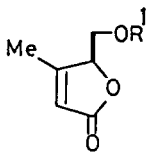

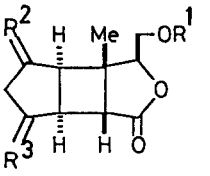

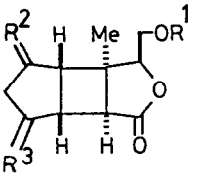

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a $R^1 = CPh_3$

b $R^1 = CO^tBu$

7 $R^2=R^3=H_2$

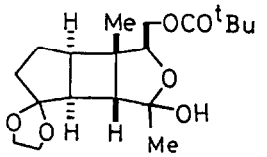
9 $R^2=H_2$ $R^3=O(CH_2)_2O$

10 $R^2=O(CH_2)_2O$ $R^3=H_2$

8 $R^2=R^3=H_2$

11 $R^2=H_2$ $R^3=O(CH_2)_2O$

12 $R^2=O(CH_2)_2O$ $R^3=H_2$



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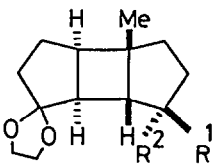

14 $R^1=H$ $R^2=OH$

15 $R^1=CH(CO_2Et)_2$ $R^2=H$

16 $R^1=CH(CH_2OH)_2$ $R^2=H$

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6. Conversion of (-)-4 into (+)-4 was carried out in 60% yield· (1) p-TsCl/pyridine, (2) $PhCH_2$-OLi/THF, (3) hydrogenation over 10% Pd/C in ether. For (-)-4 see reference 7

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12 All new compounds gave satisfactory analytical and spectral data.

13. 6b $[\alpha]_D^{20}$-69.1°($CHCl_3$), mp 65-67°, 9b $[\alpha]_D^{20}$-22.5°($CHCl_3$), mp 126-128°, NMR($CDCl_3$) 1.14(3H,s), 1 20(9H,s), CMR($CDCl_3$) 13.5(CH_3), 26 8(4xCH_3), 13 $[\alpha]_D^{20}$-21.0°($CHCl_3$), mp 94.5-95.0°; 5 $[\alpha]_D^{20}$ -179°($CHCl_3$), mp 49.0°-50 5°, NMR($CDCl_3$) 1.16(3H,s), 6.17(1H,d,J=5Hz), 7.51(1H,d,J=5Hz), 16 $[\alpha]_D^{20}$-30.4°($CHCl_3$), mp 108°, NMR($CDCl_3$) 0 96(3H,s); 2 $[\alpha]_D^{23}$-193°($CHCl_3$), mp 24.5-25.5°, 1 $[\alpha]_D^{20}$-97°(neat), NMR($CDCl_3$) 0.85(6H,d,J=5Hz), 1 00(3H,s), 1.04-2 00(9H,m)

14. Adduct 11b was converted to (+)-5 Head-to-tail isomers 10b and 12b were converted to the known regioisomer of 2^{5a} according to the same procedure for 9b.

15. Irradiation of 6a under the same condition did not afford adducts in practical yield

16 Spectral data of this substance were identical with those of (±)-5, prepared from 3-methyl-2-cyclopenten-1-one and cyclopentenone ethyleneketal in three steps: (1) photoaddition, (2) phenylselenation, and (3) oxidative elimination

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