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ASYMMETRIC TOTAL SYNTHESIS OF STOECHOSPERMOL USING INTRAMOLECULAR (2+2) PHOTOCYCLOADDITION REACTION

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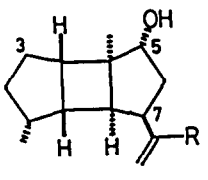
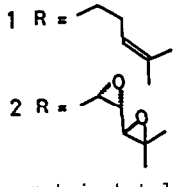
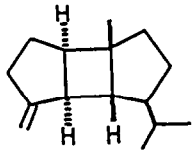
Summary: The first asymmetric total synthesis of stoechospermol, a representative spatane diterpene having cis, anti, cis-tricyclo[5.3.0.0^{2,6}]decane ring system, was achieved. Using the intramolecular asymmetric (2+2) photocycloaddition reaction of the diastereomeric ester **11**, the readily available butenolide **9** was transformed into the optically active dilactone **12a** and **12b**. Subsequent construction of tricyclic carbon ring system and introduction of substituents in a right stereochemistry gave rise to optically pure stoechospermol **1**.

The cis, anti, cis-tricyclo[5.3.0.0^{2,6}]decane ring system is found in spatane diterpenes (such as stoechospermol **1**[1,2] and spatol **2**[3]) and bourbonene sesquiterpenes (such as β-bourbonene **3**[4]) in opposite configurations. The uniqueness in carbon framework of these natural products as well as cytotoxicity found in some spatane diterpenes[3,5] have stimulated us to synthesize these compounds in optically active forms having the desired absolute configurations.[6] The first total synthesis of **1** in racemic form has been reported by Salomon et al using (2+2) photocycloaddition reaction.[7]







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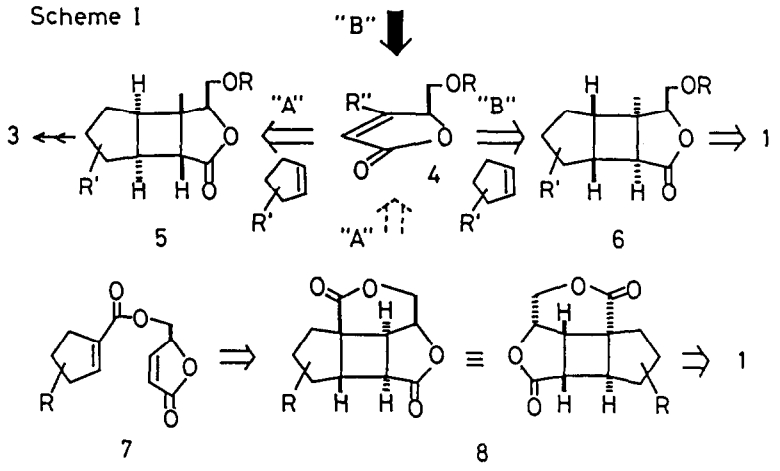
We report here the first asymmetric total synthesis of **1** by the strategy shown in Scheme I, using optically active γ-hydroxymethyl-γ-butenolide derivative **4** (R"=H) as a chiral synthon. We have reported that intermolecular (2+2) photocycloaddition product **5**, obtained by the attack of cyclopentene derivatives to **4** (R"=Me) from the less hindered side ("A"-side), was successfully utilized to the asymmetric total synthesis of **3**.[6,8] The adduct **6** from the hindered side ("B"-side) should thus be a promising intermediate leading to **1**, but this approach was not realized due to the unfavorable stereoselectivity of this process. Therefore, intramolecular version of this (2+2) photocycloaddition from **7** to **8** was examined.

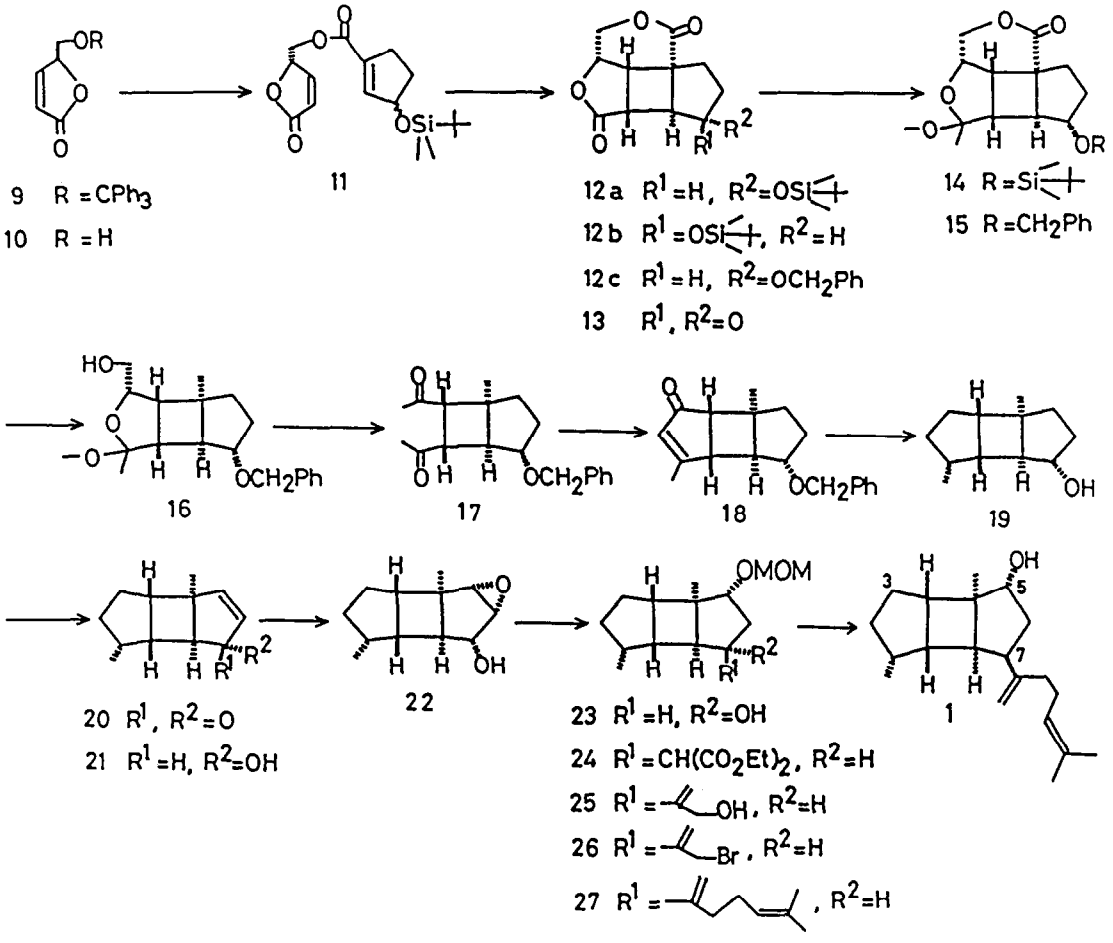
Scheme I



Esterification (DCC-CH_2Cl_2) of chiral butenolide **10**,[10] obtained by acidic detritylation (c. HCl-MeOH) of readily available optically pure butenolide **9**,[11] with the corresponding acid[12] gave the diastereomeric mixture **11** (96%). Upon UV irradiation in acetonitrile, **11** was transformed into a 1:1 mixture of **12a** and **12b** (61%). On the concomitant desilylation and Jones oxidation,[13] both diastereomers gave the same keto-lactone **13**, indicating that regio- and stereoselectivity of this intramolecular cycloaddition reaction was fully controlled by the chiral center of the butenolide portion regardless of that of the cyclopentene portion.

Construction of tricyclic carbon ring system was achieved by transforming **12a** and **12b** into **19** via **15** as follows. Successive treatment of **12a** with methyllithium and trimethyl orthoformate gave acetal **14** (67%), which was converted to **15** (aq. HF-MeOH, then NaH-$PhCH_2Br$-DMF, 57%). On the other hand, **12b** was at first converted into benzyl-lactone **12c** (47%) by the inversion of configuration at C-7,[13,14] and then **12c** was treated with methyllithium and trimethyl orthoformate successively to give **15** (quant). Then, **15** was converted to **16** by DIBAH reduction and following Huang-Minlon reduction (53%). Conversion of **16** to diketone **17** was performed by a sequence of reactions: H_2SO_4-aq. THF, $NaBH_4$-aq. THF, $NaIO_4$-aq. AcOEt, MeLi-ether, then Jones oxidation (67%). Upon treatment with potassium tert-butoxide in tert-butanol, **17** gave **18** (85%), but its possible isomer by another cyclization mode could not be detected.[15] Stereoselective catalytic hydrogenation (5% Pd/C-ether) of **18** and removal of C-3 carbonyl oxygen (N_2H_4-KOH) of the resulting keto-alcohol gave the alcohol **19** (54%) having the desired relative and absolute configuration.

Introduction of C-5 hydroxyl substituent was performed as follows. Successive reaction of **19** with Jones reagent followed by phenylselenation-oxidative elimination[16] gave the enone **20** (42%), which was converted to the allylic alcohol **21** by a sequence of reactions: DIBAH reduction, Mitsunobu reaction,[17] then NaOH hydrolysis (72%). Epoxidation of **21** with m-CPBA in CH_2Cl_2 exclusively gave **22** (81%), in which chiral center at C-5 was properly created reflecting the molecular folding and anchoring effects of the hydroxyl group. Then, **22** was transformed into **23** in four steps (85%).[13]



Now is the stage to introduce alkyl side chain with the right stereochemistry at C-7 position. Thus, **23** was subjected to the reaction of the sodio diethyl malonate in DME by way of its tosylate to **24** (64%), which was reduced to the corresponding allylic alcohol **25** (88%) by modifying Marshall's method.[18] Bromination of **25** to **26**, elongation of the chain and successive reductive desulfurization gave **27**.[13] Deprotection[13] of **27** furnished **1** of mp 64-64.5°C, $[\alpha]_D^{27}$ +38.5° (c=0.47, EtOH), $[\alpha]_D^{22}$ +39.1°(c=1.13, $CHCl_3$) (lit., mp 64-65°C,[1] $[\alpha]_D^{27}$ +21.8° (EtOH),[1] $[\alpha]_D$+29.4° (c=1.07, $CHCl_3$)[2]). Spectroscopic data (NMR, IR, Mass) of **1** prepared here were completely identical with those of the natural product.

Now that the utility of γ-hydroxymethyl-γ-butenolide **10** as a chiral synthon for the asymmetric synthesis of spatane diterpenes has been illustrated, the asymmetric synthesis of spatol **2** is the subject of current studies.

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References and Notes

§ This paper is dedicated to Professor Shun-ichi Yamada on the occasion of his 70th birthday.

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8. Several examples of asymmetric (2+2) photocycloaddition reaction are reported. a) J. J. Partrige, N. K. Chadha, and M. R. Uskokovic, J. Am. Chem. Soc., 95, 532 (1973); b) J. R. Williams and J. F. Callahan, J. Org. Chem., 45, 4475, 4479 (1980); c) S. W. Baldwin and M. T. Crimmins, J. Am. Chem. Soc., 104, 1132 (1982); d) S. Jarosz and A. Zamojski, Tetrahedron, 38, 1447, 1453 (1982).
9. It is shown that the enantiomer of **4** (R"=Me) gave the enantiomer of **5**, which was successfully converted to **20**. Details will be reported elsewhere.
10. All new compounds gave satisfactory analytical and spectroscopic data.
11. K. Tomioka, T. Ishiguro, Y. Iitaka, and K. Koga, Tetrahedron, 40, 1303 (1984).
12. Prepared from methyl cyclopent-2-ene-1-carboxylate (S. B. Jorgensen and A. Berg, Acta Chem. Scand., 20, 2192 (1966)) in four steps (i. m-CPBA; ii. NaOMe; iii. t-$BuMe_2SiCl$, imidazole; iv. aq. NaOH). We are grateful to Prof. T. Ibuka for his advices.
13. The reaction conditions were as follows. **12a → 13**: aq. HF, CrO_3, H_2SO_4, acetone, 69%; **12b → 13**: aq. HF, CrO_3, H_2SO_4, acetone, 49%; **12b → 12c**: i. DIBAH, THF; ii. $HC(OMe)_3$, TsOH, CH_2Cl_2; iii. aq. HF, MeOH; iv. DEAD, PPh_3, $PhCO_2H$, THF; v. aq. NaOH, MeOH; vi. NaH, $PhCH_2Br$, DMF; vii. AcOH-H_2O-THF (1:1:3); viii. CrO_3, H_2SO_4, acetone, 47% overall; **22 → 23**: i. 2-methoxypropene, PPTS; ii. $LiAlH_4$, Et_2O; iii. MOMCl, diisopropylethylamine, CH_2Cl_2; iv. aq. HCl, 83% overall; **25 → 26**: i. MsCl, 2,6-lutidine; ii. LiBr, DMF, 90% overall; **26 → 27**: i. n-BuLi, phenyl prenyl sulfide, THF; ii. Li, $EtNH_2$, 32% overall; **27 → 1**: aq. HCl, MeOH, 71%.
14. Numbering is based on that of **1**.
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