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SYNTHESIS OF (+)-ASPERDIOL, A MARINE ANTICANCER CEMBRENOID[1]

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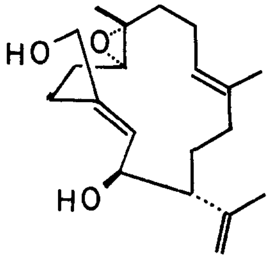
Abstract: The synthesis of (+)asperdiol (1), an anticancer cembrenoid from marine organisms, was achieved starting from allyl alcohol (3a); the synthetic route was summarized in scheme 1.

Asperdiol (1), a cembrenoid discovered from marine organisms, possesses a unique chemical structure and exhibits an anticancer activity[2]. The structure including absolute configuration has been firmly established by X-ray crystallographic analysis. The interesting profile of anticancer activity of asperdiol has prompted our intense interest into the synthesis of this cembrenoid.



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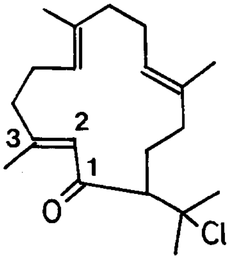

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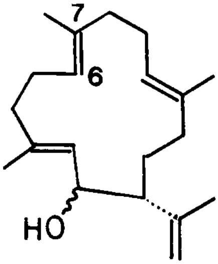
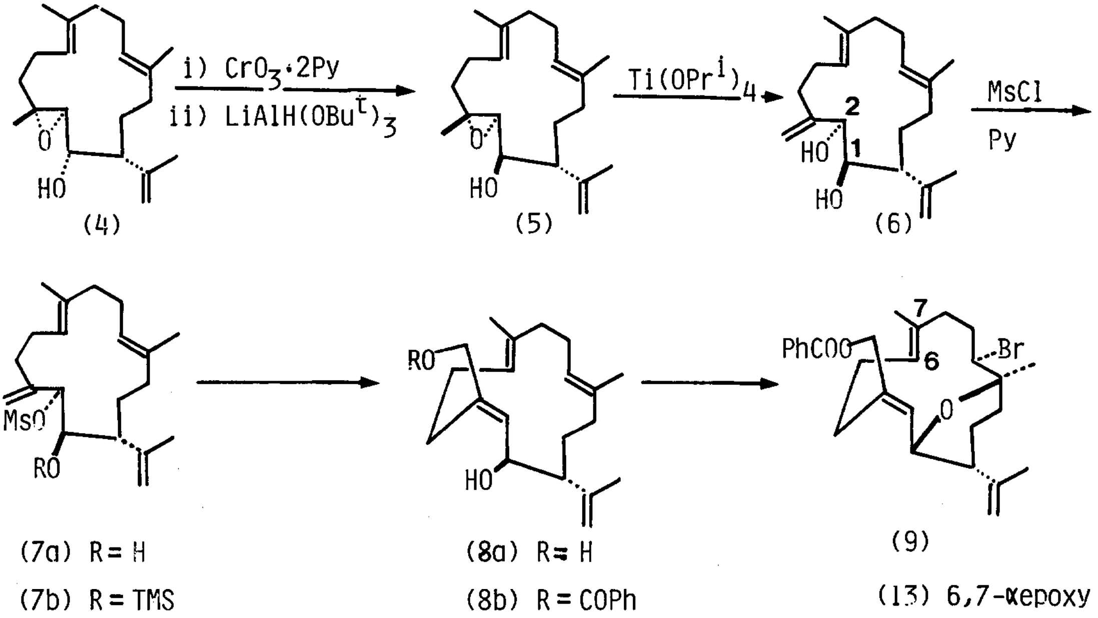


(3a) α OH
(3b) β OH

We have already executed an efficient construction method of chloro ketone (2) of the cembrenoid skeleton by simple operation with satisfactory yield[3]. It seemed to us expectable thoroughly to derive the asperdiol from the derivative (3a or b)[4], readily available from the ketone. Of particular interest in synthesizing 1 from 3 is the selective introduction of hydroxyl group onto the C_3-Me with simultaneous inversion of geometry at C_2-C_3 double bond. Regio- and stereoselective epoxidation of C_6-C_7 double bond should also be elaborated in our synthesis. In this paper, we delineate the synthesis of asperdiol involving as a key step the allylic rearrangement of 6 via its mesylate as shown in scheme 1. In addition, the rearranged product (8) has been converted into bromo ether (9) to introduce the required epoxide ring at C_6-C_7 double bond.

By virtue of the presence of hydroxyl group, 3a was easily convertible to epoxy alcohol (4) in 78% yield by Sharpless reagent[5] under controlled conditions[6]. Treatment of 4 with Collins reagent (room temp., 7 min) followed by stereoselective reduction from less hindered *α*-side gave the isomeric alcohol (5) exclusively in 91% yield from 4. The relative stereochemistry of C_3-Me with respect to C_1-OH of 4 and 5 was confirmed by comparison of chemical shift of the methyl groups in the PMR spectra, in which the former appeared at 1.27 ppm while the latter showed at 1.35 ppm, respectively. Although 5 was unreactive at room temperature, heating of 5 in toluene containing tetraisopropyl orthotitanate[7] at 90°C overnight effected the epoxide ring opening. The rearrangement proceeded regioselectively as expected, leading to allyl alcohol (6) in 93% yield[8].



Scheme 1
Synthetic Route to Asperdiol

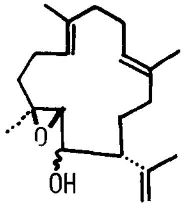
Since we were not able to envision a complete satisfactory model of the transition state to anticipate the stereochemistry of the allylic rearrangement of 6, the isomeric alcohol (11a) was also prepared as follows and its rearrangement was examined at the same time. Application of the Sharpless epoxidation to trans alcohol (3b) afforded epoxy alcohol (10a) (C_3-Me; 1.17 ppm) in 83% yield. It was then transformed to the isomeric alcohol (10b) (C_3-Me; 1.40 ppm) in 66% yield by successive reactions, Collins oxidation followed by reduction with $LiAlH(OBu^t)_3$. 10b was similarly converted into 11a in 60% yield[9] by treatment with $Ti(OPr^i)_4$ under the same conditions[10].

For the subsequent solvolysis reaction, it was necessary to bias the regioselection of mesylation in favor of C_2-OH group of the diols, 6 and 11a. By the action of mesyl chloride at -20°C in the presence of triethylamine, 6 and

11a gave the corresponding mesylates (7a and 11b) with high position-selectivity in each case; none of the position-isomeric mesylates could be detected in the reaction mixture. Highly hindered nature of the C_1-OH group in each compound is to be expected in view of the steric effect of the neighboring isopropenyl group.

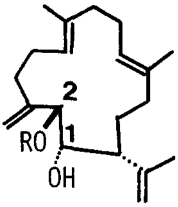
Solvolysis of the mesylates (7a and 11b) was examined under several conditions to aim the stereospecific rearrangement. When 7a was treated with potassium carbonate in aqueous dioxane, 8a was isolated in 22% yield. The latter mesylate (11b) gave the isomeric diol (12) in 45% yield under the same conditions. The geometry of the newly formed double bond of the products was based on observation of 7% NOE between C_2-H and C_3-CH_2OH group in 8a while no NOE was observed between these protons in 12. It was thus revealed that the solvolysis proceeded stereoselectively although we could not account for the specificity. Since the low yield of the solvolysis seemed to be caused by participation of C_1-OH group, the hydroxyl group of 7a was first protected quantitatively as its trimethylsilyl ether by the action of trimethylsilyl chloride in the presence of triethylamine and dimethylamino pyridine at -20°C. The resulting ether (7b) was exposed to benzoic acid in the presence of 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) and catalytic amounts of sodium iodide in DMF at 70°C[11]. The allylic rearrangement took place smoothly to afford benzoate (8b) as a sole isolable product in 55% yield. Hydrolysis of the benzoate gave the free diol (8a), indicating that the rearrangement proceeded stereospecifically under the different conditions.

Now all that is required to make asperdiol is the introduction of epoxide ring selectively at C_6-C_7 double bond. Elaboration of the selective oxidation was achieved through the six membered bromo ether (9), provided smoothly in 55% yield from the benzoate (8b) by the action of 2,4,4,6-tetrabromocyclohexadienone (TBCO)[12]. The final stage of our synthesis was straightforward from 9, which was subjected to oxidation with m-chloroperbenzoic acid at -20°C for 2 days to result in the formation of two isomeric epoxides in 3:1 in 55% yield[13].



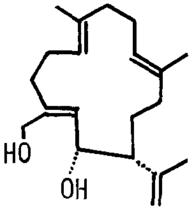
(10a) βOH

(10b) αOH



(11a) R=H

(11b) R=Ms



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Since the Dreiding model suggested that α-side of 9 was less hindered as compared with β-side, the major product (13) was allowed to react with zinc in refluxing ethanol to regenerate the C_{10}-C_{11} double bond. After hydrolysis with potassium hydroxide in refluxing dioxane, the epoxy diol (1) was obtained in 64 % yield from 13. It exhibited the identical CMR and PMR spectra with those reported for asperdiol[14].

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8. When the isomer (4) was treated with $Ti(OPr^i)_4$ under the same conditions, a mixture of 14, 15, and 16 were obtained in 45, 17 and 6% yields, respectively. C_3-Me of 15 and 16 appeared at 10.33 and 18.14 ppm in the CMR spectra, indicating the geometry of each compound.
9. The yield was not optimized.
10. The isomeric epoxy alcohol (10a) gave 17 (C_3-Me; 11.44 ppm) in 89% yield when treated with $Ti(OPr^i)_4$ under the same conditions.
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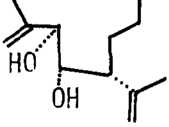

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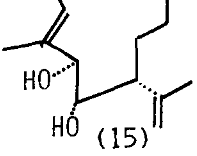

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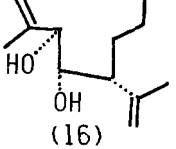

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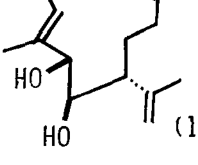

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