HETEROCYCLES, Vol. 31, No. 9, 1990

SYNTHETIC STUDIES ON NINE-MEMBERED RING DITERPENOIDS: STEREOSELECTIVE CONSTRUCTION OF OPTICALLY ACTIVE 1-OXASPIRO[2.8]UNDECENONE DERIVATIVES

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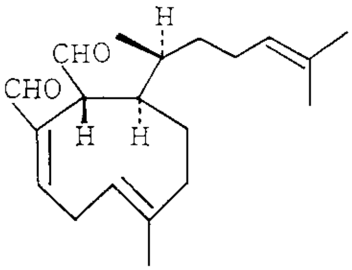
Abstract —— Enantiomeric isomers of 1-oxaspiro[2.8]undecenone derivative (**10**), which are key compounds to synthesize nine-membered ring diterpenoids, were synthesized stereoselectively from optically active monoterpene, limonene, via anionic oxy-Cope rearrangement reaction.

A large number of nine-membered ring diterpenoids have been isolated from marine natural resources,[2] some of which showed interesting biological activities.[3] Stereoselective total synthetic works on several germacrane (ten-membered ring) sesquiterpenoids have recently been accomplished in our group.[4] On these syntheses, monoterpenoids have been used as the starting materials, and Cope rearrangement has been applied to form ten-membered ring. As the extension of these synthetic works, we planned to synthesize nine-membered ring diterpenoids such as dictyodial (**1**)[3] from some monoterpenes utilizing anionic oxy-Cope rearrangement as a key reaction. There have been several synthetic reports on nine-membered ring compounds including caryophyllane-type sesquiterpenoids.[5] A discussion on stereochemistry of thermal oxy-Cope rearrangement of 1,2-divinylcyclopentanol has also been reported.[6] But, no report has been appeared on anionic oxy-Cope rearrangement, on which the reaction proceeds under the mildest conditions among various Cope rearrngements in general. In this paper, we wish to report the stereoselective construction of optically active nine-membered ring compounds with an epoxy ring, 1-oxaspiro[2.8]undecenone derivatives, via anionic oxy-Cope rearrangement reaction of 1,2-divinylcyclopentanol derivatives.

Optically active cyclopentenaldehyde derivative (**2**), which has been prepared from

(+)-limonene following literatures,[7] was transformed into triene (3)[8] by Wittig reaction ($Ph_3P=CH_2$; 87 %). When the triene (3) was treated with m-chloroperbenzoic acid, the endocyclic tetrasubstituted double bond was epoxidized regioselectively (71 % yield) to afford the mixture of diastereomeric epoxides (**4** and **5**). Treatment of the mixture with $LiN(i\text{-}C_3H_7)_2$ in ether afforded a mixture of corresponding triene alcohols (**6** and **7** as almost 4:1 ratio), which could be separated by silica gel column chromatography, in 67 % yield.[9] When each alcohol was treated under Sharpless epoxidation conditions (t-BuOOH and $VO(acac)_2$), the corresponding epoxy alcohols (**8** and **9**) were obtained stereospecifically in 90 % and 60 % yield, respectively.

When the epoxy alcohol possessing trans-divinyl group (**9**) was treated with $KN(TMS)_2$ in DME, the anionic oxy-Cope rearrangement reaction proceeded smoothly at room temperature, and a sole cyclononenone derivative (**10**) was obtained in 54 % yield after 4 h. The structure including stereochemistry of the product was



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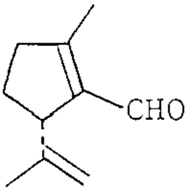

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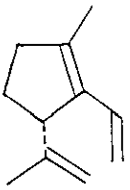

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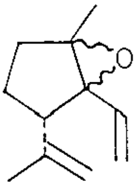
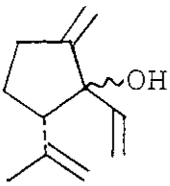


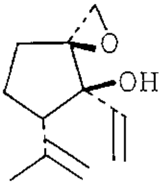
4 β-epoxide

5 α-epoxide



6 β-OH

7 α-OH



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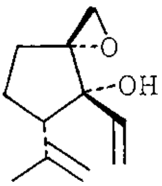

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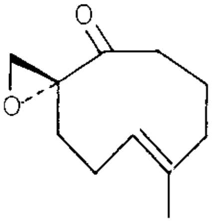

10

determined as **10** by ^1H nmr spectra (COSY, NOESY, and differential NOE). Similarly, treatment of the epoxy alcohol possessing cis-divinyl group (**8**) with $KN(TMS)_2$ in DME afforded the enantiomer of **10** as a sole product in 63 % yield after 2 h. Treatment of **8** with KH and 18-crown-6 in THF also afforded the enantiomer of **10**. No geometrical isomer could be detected.[10] Thus, both enantiomers of **10** became to be available in fairly good yields from (+)-limonene stereospecifically.

Further synthetic work toward natural diterpenoids is in progress.

ACKNOWLEDGEMENTS

We thank Professor Kiyoshi Sakai and Dr. Hiroshi Suemune, Faculty of Pharmaceutical Sciences, Kyushu University, for teaching us the experimental details on the ozonolysis of limonene. We also thank Professor Hajime Nagano, Department of Chemistry, Faculty of Science, Ochanomizu University, and Dr. Kazuhiro Matsushita, JEOL Co. Ltd., for the measurements of nmr spectra.

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8. The spectral data for all the synthetic compounds were in accord with the structures assigned, and only selected data of some compounds are cited.

   8: ^{1}H nmr ($CDCl_3$) δ 1.83 (3H, br s), 2.71 and 2.89 (each 1H, AB quartet, J=4.5 Hz), 4.72 (1H, br s), 4.82 (1H, br s), 5.05 (1H, dd, J=10 and 2 Hz), 5.25 (1H, dd, J=17 and 2 Hz), and 5.75 (1H, dd, J=17 and 10 Hz).

   9: ^{1}H nmr ($CDCl_3$) δ 1.83 (3H, br s), 2.87 (2H, s), 4.87 (1H, br s), 4.93 (1H, br s), 5.11 (1H, dd, J=10 and 2 Hz), 5.25 (1H, dd, J=18 and 2 Hz), and 5.70 (1H, dd, J=18 and 10 Hz).

   10: ^{1}H nmr ($CDCl_3$) δ 1.39 (3H, br s), 2.82 and 2.97 (each 1H, AB quartet, J=4.8 Hz), 5.73 (1H, br t, J=8.1 Hz); no NOE peak could be detected at δ 5.73 on irradiation of δ 1.39; ^{13}C nmr ($CDCl_3$) δ 15.7, 20.7, 27.6, 33.1, 34.8, 39.4, 53.6, 64.4, 128.7, 140.6, and 207.6; ir (neat) 1690 and 1650 cm^{-1}; $C_{11}H_{16}O_2$ (m/z 180.1154); $[\alpha]_D$ +15.0° (c 4.14, CCl_4).

   Enantiomer of **10**: $[\alpha]_D$ −17.2° (c 3.90, CCl_4).

9. The stereochemistry of **4**, **5**, **6**, and **7** was deduced from the relative yields and ^{1}H nmr spectra of **6** and **7**, and was confirmed from the fact that **4** was identical with the product of epoxidation (H_2O_2-NaOH; 57 % yield) and successive Wittig reaction ($Ph_3P=CH_2$; 22 % yield) of **2**.

10. Cope rearrangement of triene alcohol (**6** and **7**) was also attempted under almost the same conditions, but various products were obtained and the objective compound could be isolated in only a poor yield.

Received, 21st June, 1990