CHEMISTRY LETTERS, pp. 1391-1392, 1983.

A SIMPLE STEREOSELECTIVE SYNTHESIS OF (1R,3R,5S)-1,3-DIMETHYL-2,9-DIOXA-BICYCLO[3.3.1]NONANE USING REGIOSELECTIVE RING-OPENING OF (R)-β-METHYL-β-PROPIOLACTONE

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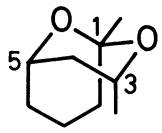
A facile stereoselective synthesis of (1*R*,3*R*,5*S*)-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane was achieved from (*R*)-2-hydroxy-7-octen-4-one, which was easily prepared by the copper-catalyzed reaction of (*R*)-β-methyl-β-propiolactone with vinylmagnesium bromide.

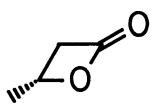
Endo-1,3-dimethyl-2,9-dioxabicyclo[3.3.1]nonane (1) is an interesting biologically active substance isolated from Norway spruce infested by a major timber pest, the ambrosia beetle (*Trypodendron lineatum* Oliv.), and has shown to exhibit an important role for causing host selection of this beetle.[1,2] Although four optically active isomers of *endo*- and *exo*-1 have been recently synthesized from D-glucose in somewhat lengthy steps,[3] the absolute configuration of natural 1 has been unknown yet. We wish to report here a fairly simple stereoselective way to synthesize an *endo*-enantiomer, [1*R*,3*R*,5*S*]-isomer using the regioselective ring opening reaction of (*R*)-β-methyl-β-propiolactone (2).

Previously, the S_N2 type copper-catalyzed reaction of optically active β-methyl-β-propiolactone with Grignard reagents, accompanying the ring-fission between the β-carbon and the ether oxygen, has been shown to provide an efficient method for the synthesis of optically active natural products *via* chiral 3-substituted butyric acid derivatives.[4] On the contrary, in the present synthesis the regioselective reaction of lactone 2 with vinylmagnesium bromide at the acyl carbon is utilized for the synthesis of the key starting material, *i.e.*, (*R*)-2-hydroxy-7-octen-4-one (3), which seems to be formed by the Michael addition of vinylmagnesium bromide to the initial ring-opening product, (*R*)-5-hydroxy-1-hexen-3-one.

The lactone 2 was easily prepared[4] from (*S*)-(+)-3-bromobutyric acid (98% ee; $[M]_{546}^{25}$ +114.2° (c 2.3, 2M $HClO_4$), lit.[5] $[M]_{546}^{25}$ +116.5°) in a yield of 70%; $[\alpha]_D^{22}$ +28.8° (c 4.3, $CHCl_3$)(95% ee).[6] When vinylmagnesium bromide (2 eq) was added to a mixture of 2 and copper(I) iodide (2 mol%) in THF-Me_2S (20:1) at -10 °C and the reaction mixture was stirred for 1 h at the same temperature, the desired (*R*)-



1



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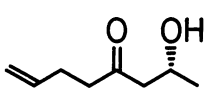
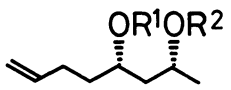


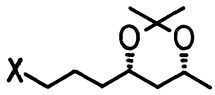
3

hydroxy ketone[7] 3 was isolated in a high yield of 89% by distillation; $[\alpha]_D^{22}$ -57.2° (c 2.27, $CHCl_3$); bp 80 °C/0.3 mmHg (kugelrohr); NMR (CCl_4) δ 1.15 (3H, d, J = 6 Hz), 2.3 - 2.5 (6H, m), 3.7 (1H, s), 4.0 - 4.4 (1H, m), and 4.8 - 6.0 (3H, m).

Next key step for construction of the *endo*-isomer 1 was stereoselective reduction of 3 to *erythro*-7-octene-2,4-diol (4), which was easily achieved by the procedure reported by Narasaka and Pai.[8] Thus, treatment of 3 with tributylborane and subsequent reduction with $NaBH_4$ furnished *erythro*-diol 4 (*erythro*:*threo* = 94:6). *Erythro*-4 was isolated by silica gel TLC (AcOEt:hexane = 2:1) in 85% yield; $[\alpha]_D^{22}$ -15.0° (c 1.14, MeOH).[9]

Treatment of 4 with 2-methoxypropene gave acetonide (5) (93%); bp 95 °C/15 mmHg (kugelrohr); $[\alpha]_D^{24}$ -12.05° (c 1.33, $CHCl_3$). The acetonide was converted to alcohol (6) by hydroboration (90%), and oxidized by pyridinium dichromate (PDC) in CH_2Cl_2 to give aldehyde (7) (60%). Treatment of 7 with methylmagnesium bromide in THF at 0 °C furnished secondary alcohol (8) (quant.), which was oxidized by PDC in DMF to ketone (9) in 86% yield. Ketone 9 was smoothly converted to bicyclononane 1 by the reported procedure;[3] bp 160 °C/120 mmHg (Kugelrohr); $[\alpha]_D^{24}$ -32.4° (c 0.25, pentane), lit.[3] $[\alpha]_D^{27}$ -37.3°.





4: R^1, R^2 = H

5: R^1, R^2 = 

6: X = CH_2OH

7: X = CHO

8: X = $CH(OH)CH_3$

9: X = $COCH_3$

References

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3) H. Redlich, B. Schneider, R. W. Hoffmann, and K. J. Geueke, *Justus Liebigs Ann. Chem.*, 1983, 393.
4) T. Sato, T. Kawara, A. Nishizawa, and T. Fujisawa, *Tetrahedron Lett.*, 21, 3377 (1980); T. Fujisawa, T. Sato, T. Kawara, and K. Ohashi, *ibid.*, 22, 4823 (1981); T. Sato, K. Naruse, and T. Fujisawa, *ibid.*, 23, 3587 (1982).
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6) Although optical rotation of (*S*)-β-methyl-β-propiolactone was determined recently by NMR spectroscopy as α_D - 27.8 ± 1.6° (neat, dm) [A. Leborgne, M. Moreau, and N. Spassky, *Tetrahedron Lett.*, 24, 1027 (1983)], the optical purity of lactone 2 was determined by the optical rotation of (*R*)-(-)-ethyl 3-hydroxybutyrate obtained by the reaction of lactone 2 with ethyl alcohol in the presence of a catalytic amount of sodium ethoxide; $[\alpha]_D^{24}$ -40.7° (c 1.09, $CHCl_3$), for the (*S*)-isomer, lit. $[\alpha]_D^{25}$ +43° (c 0.93, $CHCl_3$) [H. Hungerbühler, D. Seebach, and D. Wasmuth, *Helv. Chim. Acta*, 64, 1467 (1981)].
7) The absolute configuration of 3 was tentatively assigned as *R* by considering the reaction mechanism of the nucleophilic attack to the acyl carbon.
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(Received June 27, 1983)