Tetrahedron Letters Vol. 21, pp 5033 - 5036 0040-4039/80/1222-5033$02.00/0

STEREOCONTROLLED SYNTHESIS OF CLERODIN HOMOLOG

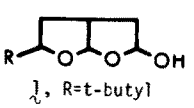
—— A SYNTHETIC APPROACH TO STRUCTURE-ACTIVITY RELATIONSHIPS ——

Yasuhiro Kojima and Natsuki Kato*

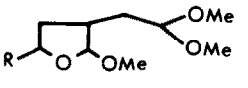
Department of Agricultural Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

Summary: In order to elucidate the structure-activity relationships of the antifeeding diterpenes having a neo-clerodane skeleton, clerodin homolog 5 was stereoselectively synthesized through 18 steps via a key intermediate 11. Perhydrofuro[2,3-b]furan ring in the synthesized homolog was more unstable than that of the natural product, and gave a tri-MeOH adduct 3 in a similar behavior to that of the model compounds 1 and 2.

In order to elucidate the structure-activity relationships of the antifeeding substances[1] having a neo-clerodane skeleton[2a], such as clerodin[2b], clerodendrin A[2c], and caryoptin[2d], we have recently reported both the synthesis[3,4] of perhydrofuro[2,3-b]furan derivatives (1 and 2), which have partial structures of natural products, and their antifeeding activities[4] for the larvae of Spodoptera litura F. which were 1/10 ∿ 1/20 fold only, compared with those of the natural products. As one of some reasons for the latter result, it was assumed that the model compounds, 1 and 2, had more unstable perhydrofuro[2,3-b]furan ring[4] than that of the natural products: quantitative experiments of 1 with MeOH gave a tri-MeOH adduct 3 at room temperature, whereas clerodin was only



1, R=t-butyl
2, R=phenyl



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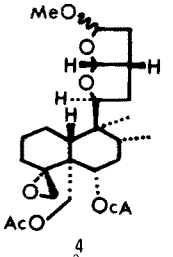

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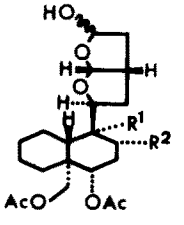
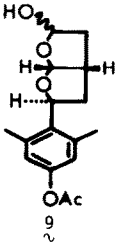


5, $R^1=R^2=H$
6, $R^1=CH_3$, $R^2=H$
7, $R^1=H$, $R^2=CH_3$
8, $R^1=R^2=CH_3$



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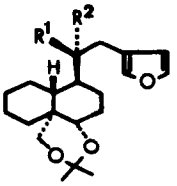
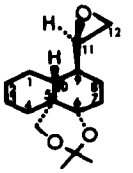
converted into a mono-MeOH adduct 4 under the same condition. The unstability of the model compounds may be attributed to the flexibility and easiness of the free rotation of the perhydrofuro[2,3-b]furan rings as compared with those of the natural products. Then, we planned to synthesize clerodin homologs (5 ~ 8) and an ortho-di-substituted phenyl compound 9, in which the free rotation and flexibility of their perhydrofuro[2,3-b]furan rings would be sterically controlled.

In this paper, we wish to report the stereocontrolled synthesis of clerodin homolog 5. Since the transformation of a furan alcohol 10 to 5 could be carried



10, R^1=OH, R^2=H
26, R^1=H, R^2=OH



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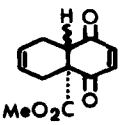

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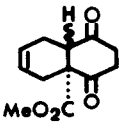

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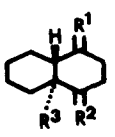
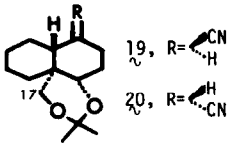


14, R^1=R^2=O, R^3=COOMe
15, R^1=O, R^2=H,OH, R^3=COOMe
16, R^1=O, R^2=H,OH, R^3=CH_2OH

17, R^1=O, R^2=H,OTHP, R^3=CH_2OTHP
18, R^1=CN,H, R^2=H,OTHP, R^3=CH_2OTHP



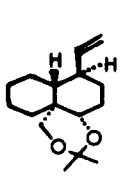
19, R=CN,H
20, R=H,CN

out with a methodology recently reported by us[3,4], an epoxy acetonide 11 which possessed five asymmetric carbons was chosen as a key intermediate for the stereocontrolled synthesis of 5.

We commenced a preparation of the key intermediate 11 via Diels-Alder reaction with methyl gentisate readily attained by methylation of gentisic acid (MeOH, H_2SO_4, reflux). Diels-Alder reaction of a p-quinone, prepared by silver oxide oxidation[5] of methyl gentisate, with butadiene ($SnCl_4$, CH_3CN, 0°) gave a mixture of cis- and trans-adducts 12 (90.8% from methyl gentisate) in a ratio of 4 : 1, which was converted into a dihydro derivative 13 by the reduction with Zn-AcOH (60°, 2hr, 97.2%). Epimerization of 13 by $NaOCH_3$ (MeOH, -20°) improved the ratio of the cis- and trans-decalin derivatives to 1 : 3.3. Since the mixture was difficult to separate on TLC, it was transferred to the next reaction without separation. Catalytic hydrogenation (H_2, 10%Pd/C, EtOAc, rt) of the derivatives gave a mixture of a trans-diketo ester 14 and its cis-isomer in 98.8% yield with a ratio of 3 : 1, which were separated by silica gel column chromatography. Partial reduction of 14 by $NaBH_4$ (dioxane-iso-PrOH-H_2O, rt) afforded only the desired C^6-α-alcohol 15 in 87.8% yield, and the β-configuration of C^6 proton was proved from the coupling constants, J=12.0 and 4.0 Hz,

of its signal at δ3.96. The alcohol 15 was then transformed into a trans keto diol 16 by treatment with ethylene glycol (p-TsOH, benzene, 90.5%) followed by reduction with $LiAlH_4$ (Et_2O, 0°, 88.0%) and finally deketalization[6] with p-TsOH (80%AcOH-H_2O, rt, 65.8%)[7].

Elongation of C_2 unit at a C^9 position in 16 was initiated by transformation into a tetrahydropyranyl ether 17 by using dihydropyrane (p-TsOH, CH_2Cl_2, 0°, 89.0%). Treatment of 17 with TosMIC[8] (tert-BuOK, DME-tert-BuOH, rt) afforded a nitrile derivative 18 in 74.7% yield, which was converted into a single product, nitrile acetonide 19, by treatment with p-TsOH in MeOH followed by the protection with dimethoxypropane (p-TsOH, acetone, 0°, 91.0% from 18). α-Configuration of a nitrile group in 19 was proved from a deshielding effect to C^{17}-methylene protons by the nitrile group. Treatment of 19 with LDA afforded a mixture of 19 and its epimer 20 (19 : 20=3 : 2). The C^{17}-methylene protons of 19 and 20 appeared as doublet signals at δ3.68 and 3.80 and δ3.86 and 4.45, respectively. The low-field shift of the latter might be attributed to the alignment on the same side, i.e., α-configuration, of the C^{17}-methylene and nitrile groups. A nitrile acetonide 19 was then transformed into a vinyl acetonide 21 in 75.5% yield by treatment with DIBAH (toluene, -78°) followed by Wittig reaction with methylene triphenylphosphorane (THF, -78° to 0°). Reaction of 21 with m-CPBA (Na_2HPO_4, CH_2Cl_2, rt) gave an epoxy acetonide 22 in 81.0% yield, which was a mixture of a key intermediate 11 bearing a desired configuration with respect to the C^{11} position and its epimer 23 in a ratio of 92 : 8[9]. Recently we developed the method to determine the configuration and conformation by combination of empirical force-field calculation and lanthanide induced shift experiment[3]. The determination[10] of the relative configuration with respect to the C^{11} position of 22 was achieved by applying the method to two diastereo-



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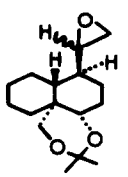

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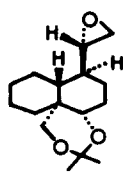

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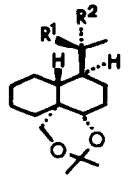
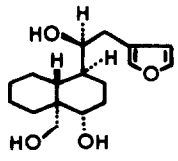


24, R^1=OH, R^2=H
25, R^1=H, R^2=OH



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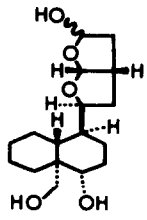

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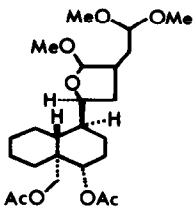

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mers, 24 and 25, which were derived by the reduction of 22 with $LiAlH_4$.

Transformation of the epoxy acetonide 11 to a final product 5 was initiated by the reaction of it with lithium di(3-furyl)cuprate·2furyllithium-Me_2S complex[11] (Et_2O, 0°), yielding a desired furan alcohol 10 and its epimer 26 with respect to the C^{11} position in a ratio of 92 : 8, with a quantitative yield. Treatment of a furan derivative 10 with 80%AcOH-H_2O afforded a furan triol 27 in a quantitative yield. The triol 27 was then transformed into a perhydrofuro-[2,3-b]furan derivative 28 having a natural form in 77.0% yield by a sequence similar to that previously developed for the synthesis of the model compounds, 1 and 2[3,4]. Acetylation of 28 (Ac_2O, Py, rt) followed by acid work-up gave a final product 5 in a quantitative yield. The clerodin homolog 5 was unexpectedly converted into only a ring opening product, tri-MeOH adduct 29, by the reaction with MeOH (p-TsOH, rt). This behavior in 5 agreed with that of the perhydrofuro[2,3-b]furan rings in 1 and 2[4]. It was suggested that C^8 and/or C^9 methyl groups in the neo-clerodane diterpenes may considerably bring a very subtle contribution to the stability of the perhydrofuro[2,3-b]furan ring. Furthermore, the magnitude of the stability of the ring may be apparently correlated to the potency of their biological activities[12]. According to these concepts, the synthesis of the clerodin homologs (6 ~ 8) is currently under way.

References and Footnotes

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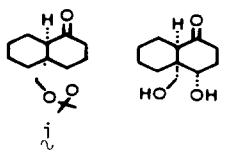
2. a) D. Rogers, G.G. Unal, D.J. Williams, S.V. Ley, G.A. Sim, B.S. Joshi, and K.R. Ravindranath, Chem. Comm., 97 (1979). b) D.H.R. Barton, H.T. Cheung, A.D. Cross, L.M. Jackmann, and M. Martin-Smith, J. Chem. Soc., 5061 (1961). c) N. Kato, M. Shibayama, and K. Munakata, J. Chem. Soc. Perkin I, 712 (1973). d) S. Hosozawa, N. Kato, and K. Munakata, Phytochemistry, 13, 308 (1974).
3. Y. Kojima, N. Kato, and Y. Terada, Tetrahedron Lett., 4667 (1979).
4. Y. Kojima and N. Kato, Agr. Biol. Chem., 44, 855 (1980).
5. K. Brunner, Monatsh., 34, 913 (1913).
6. When acetone was used in the place of 80%AcOH-H_2O as a solvent, a keto acetonide 4 with cis ring junction was obtained in 91.0% yield.
7. A cis-keto diol 11 was obtained together with 16 in 13.2% yield. Epimerization of 11 by KOH in MeOH afforded a trans derivative 16 accompanied by cis derivative 11 in a ratio of 5 . 1 in 90.0% yield.
8. O.H. Oldenziel and A.M. van Leusen, Tetrahedron Lett., 1357 (1973); O.H. Oldenziel, D. van Leusen, and A.M. van Leusen, J. Org. Chem., 42, 3114 (1977).
9. Since the ratio of the epoxy acetonide 11 and its epimer 23 could not be determined directly on NMR, the ratio of the alcohol 24 and 25 was used instead of that.
10. A detailed report concerning the work will be presented subsequently.
11. Y. Kojima and N. Kato, Tetrahedron Lett., in press.
12. On the result of biological test for the various derivatives of the clerodin homolog 5 and phenyl perhydrofuro[2,3-b]furan derivatives, it was proved that the stereocontrol of their perhydrofuro[2,3-b]furan rings was correlated to the potencies: Y. Kojima and N. Kato, J. Chem. Soc. Japan, submitted.



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(Received in Japan 5 September 1980)