Communications to the Editor

[Chem. Pharm. Bull. 31(10)3765—3768(1983)]

SYNTHESIS OF THYSANOLACTONE FROM HYDROXYHOPANONE

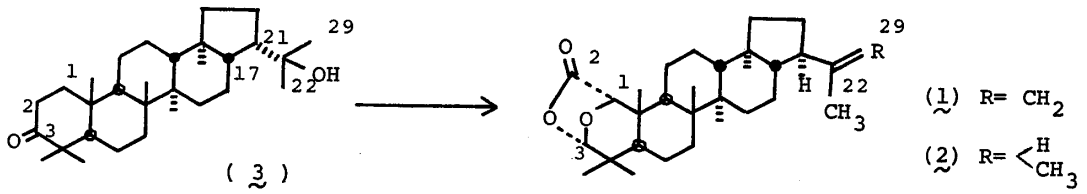
Norio Aimi,* Kazuhiro Kawada and Shin-ichiro Sakai
Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Chiba, Japan

Thysanolactone (1), a novel triterpene from *Thysanospermum diffusum* var. *longitubum*, has been synthesized from the prototype triterpene, hydroxyhopanone (3).

KEYWORDS —— *Thysanospermum diffusum* var. *longitubum*; Rubiaceae; 2,3-seco triterpene; thysanolactone; hydroxyhopanone; partial synthesis; chemical conversion

Thysanolactone (1) was isolated in this laboratory from a Rubiaceous plant, *Thysanospermum diffusum* var. *longitubum*, growing in Okinawa Islands, Japan.[1] Because of the structural novelty, we were interested in synthesizing it by utilizing a simple and easily available natural compound. In a previous paper[2] we reported partial synthesis of the unnatural dihydro derivative (2) from hydroxyhopanone (3).[3] The present communication describes the synthesis of natural thysanolactone (1) from the same starting material (3) in a total yield of 1.1% (19 steps). Hydroxyhopanone (3) has been totally synthesized,[4] and therefore this result leads to a formal total synthesis of natural thysanolactone (1).

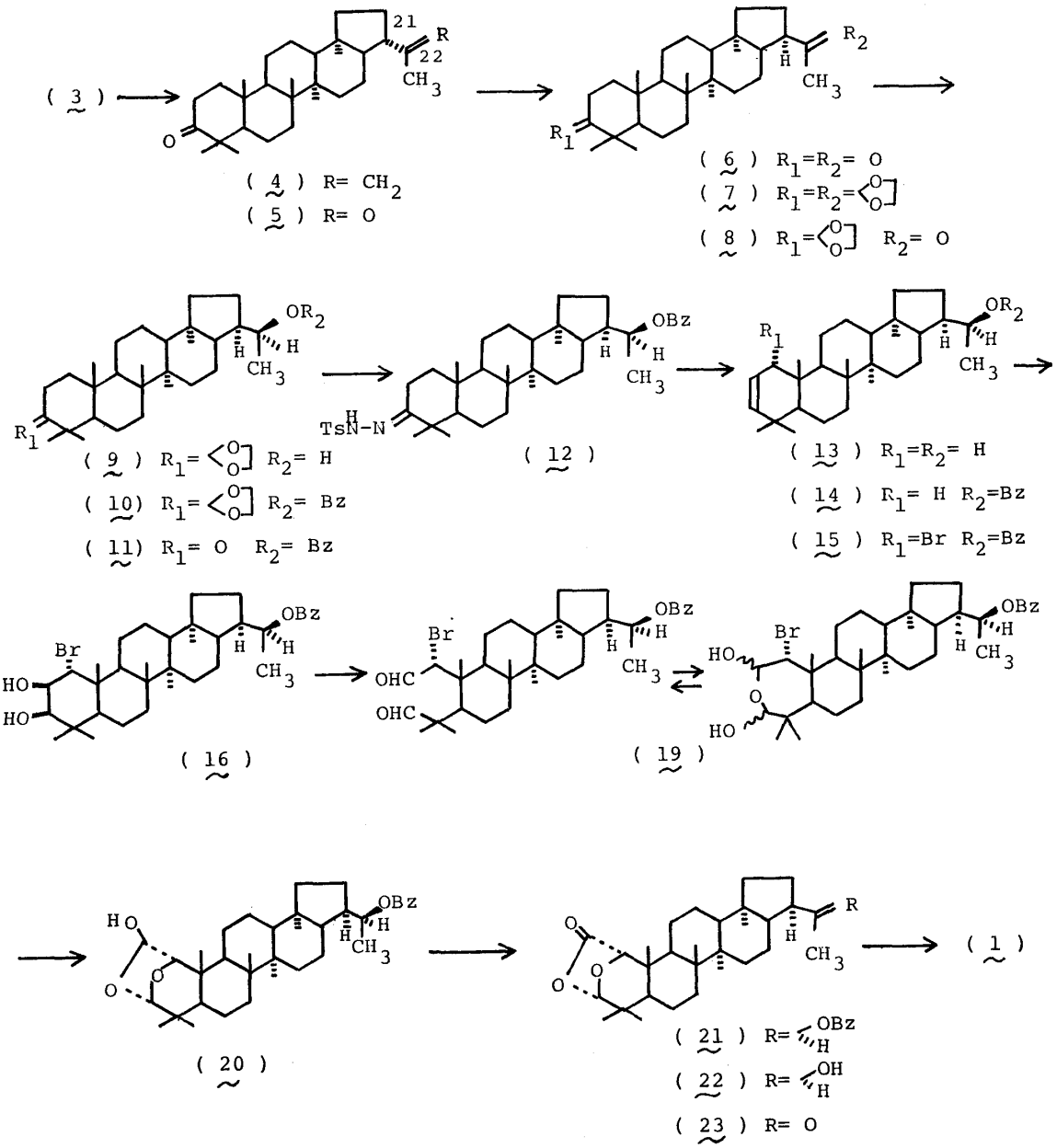
To accomplish this transformation, the side chain on the ring E must be transformed from the 21α dimethylcarbinol group in the starting material (3) to 21β isopropenyl group in thysanolactone (1), besides the structural change of the A ring part. It is well known that the double bond of hopane or moretane derivatives at $\Delta^{22(29)}$ tends to rearrange to the more stable positions such as $\Delta^{21(22)}$ and $\Delta^{17(21)}$. To avoid this unfavorable change we planned the formation of the



(3) (1) R= CH_2 (2) R= $<^{H}_{CH_3}$

terminal double bond to be made at the last step.

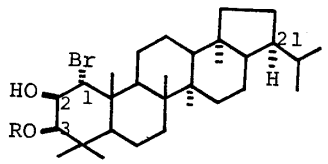
First, 3 was brought to diketone (5) in the known procedures which involve dehydration of the tertiary alcohol, separation of the resulting double bond



isomers, hopenones a ($\Delta^{21(22)}$) and b ($\Delta^{22(29)}$), by use of an $AgNO_3$-SiO_2 column, and ozonolysis of hopenone b. The obtained diketone (5), mp 202° - 204°C and 248° - 255°C (double mp), $[\alpha]_D$ +109° (c=0.28, $CHCl_3$), was treated with dilute sulfuric acid to give the epimer (6), mp 263° - 264°C, $[\alpha]_D$ +30.5° (c=0.27, $CHCl_3$), (97%).[5] Recently, compound 6 has been isolated from an Euphorbiaceous plant as a natural product.[6] The diketal (7), mp 214 - 216°C, was partially hydrolyzed with AcOH in $CHCl_3$-MeOH at room temperature to give the 3-monoketal (8), mp 240° -241°C (69%). The ^{1}H-NMR spectrum of 8 howed the signal due to methyl ketone group at δ 2.15. Reduction of the ketonic carbonyl group was made by use of L-Selectride to give 9, mp 229° - 229.5°C, as a sole product (92%). The (S)-configuration was assigned to $C_{(22)}$ on the basis of the possible and widely accepted reaction mechanism of reduction with bulky hydride reagents.[7]

The protective group at $C_{(3)}$ was removed from compound 10, mp 232° - 234°C, to give 11, mp 184° - 184.5°C, in a quantitative yield. Tosylhydrazone (12), mp 158° - 159°C, was treated with an excess of LDA in THF at 0°C to give an olefin (13), mp 225° - 226.5°C, which was brought to the benzoate (14), mp 195° - 196°C. Allylic bromination of 14 with NBS in the presence of benzoyl peroxide gave an unstable bromide (15), which was submitted to the next reaction without further purification. The α-orientation of the bromine at $C_{(1)}$ was consistent both with the predicted preferential attack of the reagent from the less hindered α-side of the molecule and the outcome of the following reaction steps.

A 2,3-glycol (16), mp 188° - 188.5°C, was obtained from OsO_4 oxidation of 15 with a yield of 47%. In our previous communication, we tentatively assigned the 2α,3α-cis glycol configuration to the closely related compound (17) which was obtained in the same type of reaction in the synthesis of dihydrothysanolactone.[2] Recently, however, we found that benzoylation of 17 in a conventional manner afforded a sole product, in which the $C_{(3)}$-hydroxyl group was benzoylated while the $C_{(2)}$-hydroxyl group remained unacylated; the ^{1}H-NMR spectrum of the product (18) revealed signals due to $C_{(2)}$-H at δ 4.72 (almost at the same position as the starting material (17) (δ 4.50)) as a double doublet with the coupling constants of 3.6 and 2.3 Hz besides $C_{(3)}$-H at 5.50 (d., J=3.6 Hz).[8] This clearly showed that the glycol was 2β,3β-cis diol in which the 2β axial hydroxyl group was highly hindered with two 1,3-diaxial methyl groups at $C_{(4)}$ and $C_{(10)}$. It is most probable that the present compound (16) also possesses the same 2β,3β-glycol configuration.



(17) R= H
(18) R= Bz

Oxidative cleavage of the glycol of 16 with $Pb(OAc)_4$ gave the dialdehyde (19), the ^{1}H-NMR spectrum of which showed that it existed in an equilibrium between the dialdehyde form and the hemiacetal form in $CDCl_3$-D_2O. Treatment of 19 with silver trifluoroacetate in CH_3CN-H_2O gave the expected hemiacetal (20) as an amorphous powder with a yield of 47% from the glycol (16). The configuration of the 1β,3β-epoxide bridge was poved by the ultimate formation of the natural thysanolactone (1). The ^{1}H-NMR spectrum of (20) showed the characteristic signals due to protons on $C_{(1)}$, $C_{(2)}$, and $C_{(3)}$ at δ 3.83, δ 5.43 and δ 5.03, respectively, all in singlet. The observed lack of coupling between $C_{(1)}$-H and $C_{(2)}$-H indicated that the configuration of the $C_{(2)}$ hemiacetal hydroxyl group was β.

Oxidation of 20 with PCC gave the lactone (21) as an amorphous powder (81%), the IR spectrum of which showed the characteristic absorption of the carbonyl at 1795 cm^{-1}. The ^{1}H-NMR spectrum of 21 showed two singlet signals due to $C_{(1)}$-H and $C_{(3)}$-H at δ 4.02 and δ 5.28 as expected.

Removal of the benzoyl group of 21 with lithium hydroxide gave the secondary alcohol (22), mp 240° - 241°C, $[\alpha]_D$ -20.8° (c=0.24, $CHCl_3$), with a yield of 74%. Methyl ketone (23), mp 268° - 269.5°C, $[\alpha]_D$ -40.0° (c=0.22, $CHCl_3$), was obtained through PCC oxidation of 22 with a yield of 92%. The resulting compound (23) was completely identical with the specimen obtained from natural thysanolactone (1) through the stepwise oxidative cleavage of the terminal methylene with OsO_4 and $Pb(OAc)_4$.

The final step of this conversion was introduction of $C_{(29)}$ methylene carbon to 23. Treatment of 23 with methylenetriphenylphosphorane in THF at -18°C to -15°C gave the product, mp 277° - 279°C, $[\alpha]_D$= -17.6° (c=0.14, $CHCl_3$), with a yield of 50%, which was shown to be completely identical with natural thysanolactone (1) (mp, mix. mp, $[\alpha]_D$, IR(KBr), ^{1}H-NMR and MS).

REFERENCES AND NOTES

1) N. Aimi, K. Yamaguchi, M. Takahashi, M. Iwata, S. Sakai, J. Haginiwa and Y. Iitaka, *Tetrahedron*, 37, 983 (1981).
2) N. Aimi, K. Kawada, Y. Nagasato, S. Sakai and J. Haginiwa, *Chem. Pharm. Bull.*, 30, 1098 (1982).
3) J. S. Mills and A. E. A. Werner, *J. Chem. Soc.*, 1955, 3132.
4) Y. Tsuda and M. Hattori, *Chem. Pharm. Bull.*, 15, 1073 (1967).
5) G. V. Baddeley, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.*, 1961, 3891.
6) W-H Hui and M-M Li, *Phytochemistry*, 15, 985 (1976).
7) H. O. House, "*Modern Synthetic Reactions*," 2nd Ed., p. 54, W. A. Benjamin, Inc., Calf., 1972.
8) The experiments of this part were carried out by Mr. Yoshitaka Fukumasu, an undergraduate student of this laboratory.

(Received July 29, 1983)