Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8189-8192, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01743-3

A Total Synthesis of Antibacterial Clerodane, 16-Hydroxycleroda-3,13(14)Z-dien-15,16-olide

Hisahiro Hagiwara,* Kazuhiro Inome and Hisashi Uda

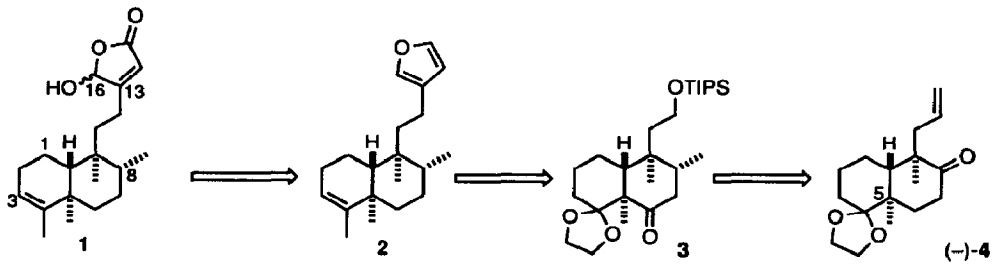
Institute for Chemical Reaction Science, Tohoku University
Katahira, Aoba-ku, Sendai 980, Japan

Abstract:*The total synthesis of an antibacterial clerodane, 16-hydroxycleroda-3,13(14)Z-dien-15,16-olide, is described and its absolute stereochemistry has been determined.*

Clerodane diterpenoids are one of the main groups in natural products, involving more than 800 congeners.[1] Some of the clerodanes have prominent bioactivity such as insect antifeedant, but bioactivity of other clerodanes are mostly unexplored. In spite of their popularity in nature, there are only two successful total syntheses of optically active clerodanes.[2] 16-Hydroxycleroda-3,13(14)Z-dien-15,16-olide **1**, isolated from *Acritopappus longifolius*,[3] *Polyalthia longifolia* [4] or *Oremna oligotricha* [5] whose twigs have been used as chewing sticks in southern Ethiopia, has comparable antibacterial activity with streptomycin against a number of Gram-positive bacteria.[5] Though the relative stereochemistry of the acetate of **1** was determined by X-ray crystallography,[4a] the absolute stereochemistry has not been rigorously established. We delineate herein a first total synthesis of **1**, starting from (5*R*,9*R*,10*R*)-(–)-4 (99%ee) (clerodane numbering) whose enantiomer has been synthesized and used as a starting block of some biologically active terpenoids in this laboratory.[6]

Our retrosynthetic analysis is described in Scheme 1. We envisioned the γ-hydroxybutenolide moiety of **1** could be generated by photo-oxygenation of furan **2** which in turn would be derived from ketal **3** *via* addition of 3-furyllithium. The ketal **3** would be obtained after transposition of carbonyl group of the decalone (–)-**4** whose absolute stereochemistry has been established as (5*R*,9*R*,10*R*) already.[6a]

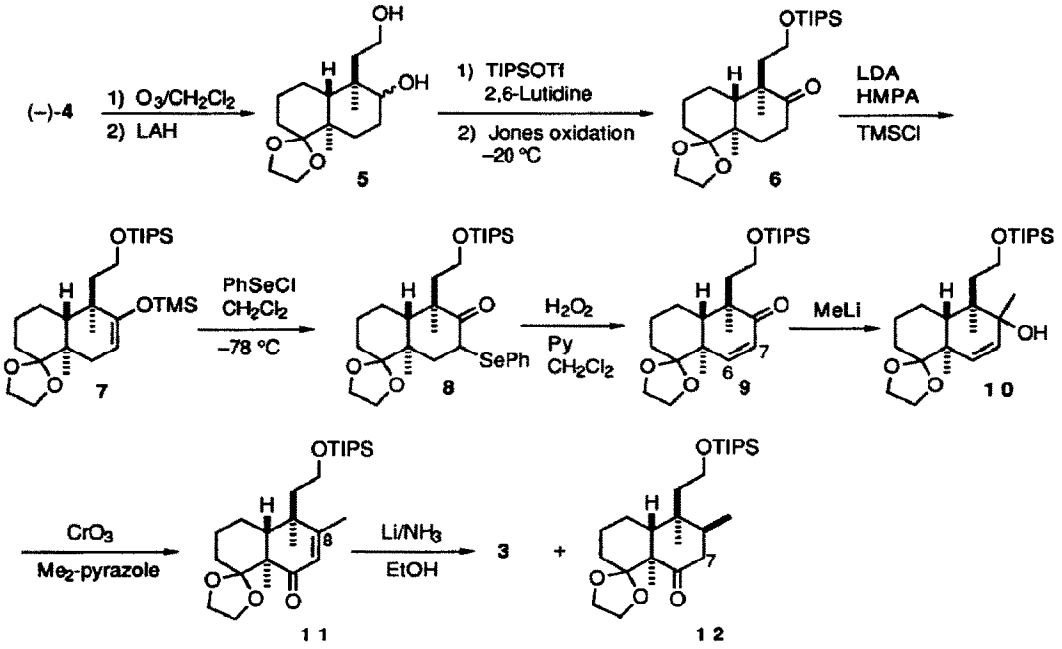
Scheme 1



The decalone (–)-**4** (99%ee) has already three asymmetric centers among requisite four contiguous asymmetric centers of **1**. Remaining asymmetric center at C-8 was installed by Li/liq.NH_3 reduction after

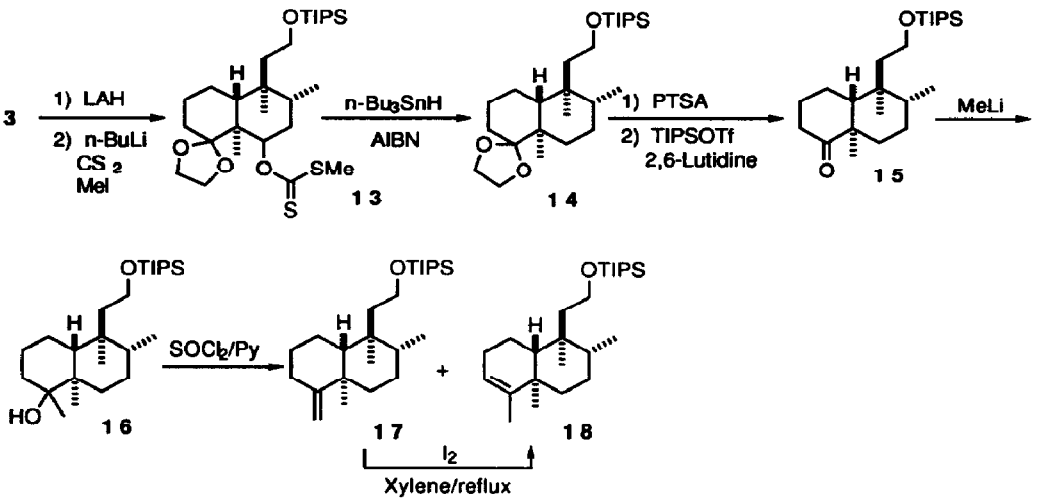
enone transposition (Scheme 2). Ozonolysis of **4** followed by LAH reduction of the resulting stable ozonide provided diol **5** in 88% yield. Among protecting reagents examined, selective protection of primary alcohol of the diol **5** was successful only by TIPSOTf in 85% yield and subsequent Jones oxidation at –20 °C gave ketone **6** in 94% yield. The ketone **6** was transformed to trimethylsilyl enol ether **7** which gave phenylselenide **8** in 80% overall yield. Introduction of $\Delta^{6,7}$-double bond was accomplished to give enone **9** by oxidative elimination of **8** in 67% yield. Addition of MeLi to the enone **9** gave an epimeric mixture (10:1) of allyl alcohol **10** (96% yield) whose oxidative rearrangement furnished $\Delta^{7,8}$-enone **11** in 62% yield by employing large excess of chromium oxide and 3,5-dimethylpyrazole. Dissolving metal reduction of the $\Delta^{7,8}$-enone **11** with Li in liq. NH_3 gave desired α-methyl decalone **3** and β-methyl decalone **12** in 65% yield (9 : 1)[8] along with recovered enone **11** (29%). The relative stereochemistry of α-methyl group at C-8 of **3** was determined by the coupling constants of 7β-H (δ 2.28, dd, *J* 14.4 and 2.8 Hz) and 7α-H (δ 2.46, dd, *J* 14.4 and 12 Hz) in NMR spectrum.

Scheme 2



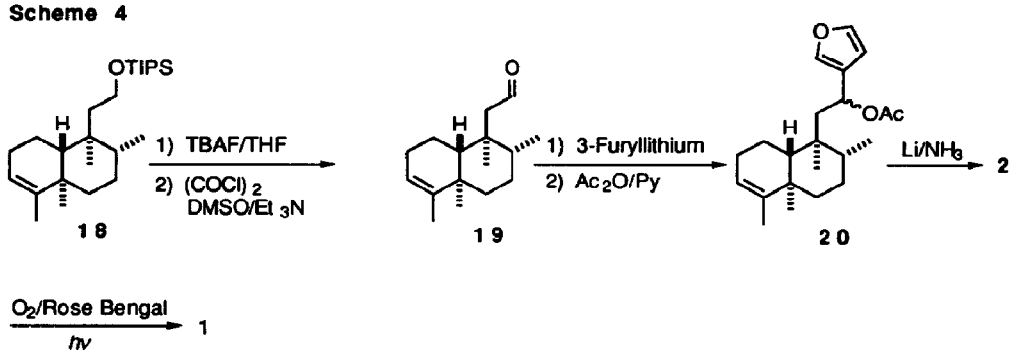
After reduction of carbonyl group at C-6 of **3** (93%), the resulting hydroxy group was protected as *S*-methyldithiocarbonate to give xanthate **13** and removed by Barton procedure[8] to afford ketal **14** in 89% overall yield (Scheme 3). Hydrolysis of the ketal **14** followed by re-protection of primary alcohol provided ketone **15** in 91% overall yield. Addition of MeLi gave alcohol **16** (97%) which was dehydrated with thionylchloride to give an inseparable mixture of *exo*-olefin **17** and *endo*-olefin **18** (1 : 2) in 74% yield. Refluxing a solution of a mixture of the *exo*-olefin **17** and the *endo*-olefin **18** with a catalytic amount of iodine in xylene completed isomerization of the *exo*-olefin **17** into the *endo*-olefin **18** in 91% yield.

Scheme 3



Requisite γ-hydroxybutenolide moiety of **1** was elaborated by singlet oxygen oxidation of the furan **2** (Scheme 4). To this end, deprotection of TIPS ether followed by Swern oxidation provided aldehyde **19** quantitatively. Addition of 3-furyllithium to the aldehyde **19** proceeded to give an epimeric mixture (1:1) of alcohol in 97% yield. Acetylation (92%) followed by reductive elimination of the acetate **20** with lithium in liq. NH_3 afforded the furan **2** in 89% yield. Finally, photosensitized oxidation of the furan moiety and regioselective opening of resulting dioxetane precursor in the presence of Hunig base[9] accomplished in 63% yield a total synthesis of the title compound **1** whose spectral data were in good agreement with those of natural **1** including optical rotational value{$[\alpha]_D$ –43 (*c* 0.21, $CHCl_3$), lit.,[3] $[\alpha]_D$ –42 (*c* 0.42, $CHCl_3$)}. Thus, the absolute stereochemistry of **1** was established to be 5*R*,8*R*,9*R*,10*R* as depicted in the Scheme.

Scheme 4



Acknowledgements: We thank Prof. Y. Fujimoto, Tokyo Institute of Technology, for providing spectral data of natural **1**. Thanks are also due to Prof. T. Tokoroyama, Osaka City University, for helpful discussions.

References

1. Tokoroyama, T. *J. Synth. Org. Chem., Jpn*, **1993**, *51*, 1164.
2. Iio, H.; Monden, M.; Okada, K.; Tokoroyama, T. *J. Chem. Soc., Chem. Commun.*, 358 (1987); Piers, E.; Roberge, J. Y. *Tetrahedron Lett.*, **1992**, *33*, 6923.
3. Bohlman, F.; Ahmed, M.; Jakupovic, J.; King, R. M.; Robinson. H. *Rev. Latinoamer. Quim.*, **1984**, *15*, 16.
4. (a) Phandnis, A. P.; Patwardhan, S. A.; Dhaneshwar, N. N.; Tavale, S. S.; Tayur, N. *Phytochemistry*, **1988**, *27*, 2899 (b) Kijjoa, A.; Pinto, M. M. M.; Hertz, W. *Planta Med.*, **1989**, *55*, 205 (c) Gupta, Y. K.; Hara, N.; Fujimoto, Y.; Sahai, M. *Abstracts of Papers of Annual Meeting of Chemical Society of Japan*, **1993**, II, 498.
5. Habtemariam, S.; Gray, A. I.; Waterman, P. G. *Planta Med.*, **1992**, *58*, 109.
6. (a) Hagiwara, H.; Uda, H. *J. Org. Chem.*, **1988**, *53*, 2308 (b) *idem*, *Bull. Chem. Soc.Jpn*, **1989**, *62*, 624 (c) *idem*, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1803.
7. Lutein, J. M.; de Groot, A. *J. Org. Chem.*, **1981**, *46*, 3448.
8. Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1*, **1975**, 1574; Barton, D. H. R.; Motherwell, W. B. *Pure Appl. Chem.*, **1981**, *53*, 15.
9. Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.*, **1988**, *53*, 2773.

(*Received in Japan* 16 *May* 1994; *accepted* 25 *July* 1994)