CHEMISTRY LETTERS, pp. 559-562, 1981. 

# SYNTHETIC STUDIES ON IRIDOID TERPENES VIA REGIOSELECTIVE SULFENYLATION OF β-KETOESTERS AND OXIDATIVE CLEAVAGE OF β-THIOALCOHOLS -A NOVEL SYNTHETIC ROUTE TO (±)-LOGANIN-

Kunio HIROI,* Hideyuki MIURA, Kumiko KOTSUJI, and Shuko SATO
Synthetic Chemistry Division, Tohoku College of Pharmacy
Komatsushima, Sendai, Miyagi 983

Regioselective sulfenylation of ethyl 2-oxocyclopentanecarboxylate (3) and methyl 7,7-ethylenedioxy-3-oxobicyclo[3.3.0]octane-2-carboxylate (12), followed by $NaBH_4$ reduction and subsequent oxidative ring cleavage with lead(IV) acetate gave ethyl 2-acetoxy-6-phenylthio-2,3,5,6-tetrahydro-4H-pyran-3-carboxylate (7) and methyl 3-acetoxy-6,6-ethylenedioxy-1,3,4,4a,5,6,7,7a-octahydro-1-phenylthiocyclopenta[c]pyran-4-carboxylate (15). Hydrolysis of the thioacetals (7 and 15) led to the 5,6-dihydro-6-hydroxy-4H-pyran-3-carboxylic acid esters characteristic of iridoid terpenes.

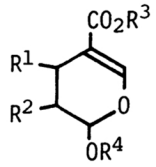
In a past decade there have been found from plant sources and characterized many kinds of natural products with dihydropyran ring systems, known as the iridoids.[1]

These iridoid terpenes possessing cyclopentanopyran frameworks have received much attention, since some of them have been found to show significant biological activity[2] and play an important role in biosynthesis of the other natural products.[3]

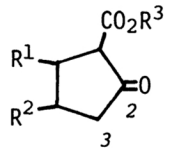
We wish to communicate herein a novel method for construction of the characteristic structural units of iridoids, 5,6-dihydro-4H-pyran-3-carboxylic acid derivatives (1), initiated by the regioselective sulfenylation of β-ketoesters and involving an oxidative cleavage of β-thioalcohols.

Our strategy is based on facile conversion of the readily available β-ketoesters 2 into 1 by regioselective cleavage of $C_2$-$C_3$ bond of 2 using modification with organo-sulfur functions.

To this end, we developed our original plan as outlined in scheme 1, using a simple five-membered ring system, which involves regioselective sulfenylation of the easily obtainable β-ketoester 3 followed by reduction of ketone 5 and subse-



1

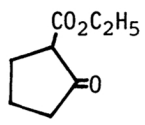


2

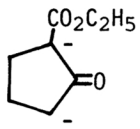
quent oxidative cleavage of β-thioalcohol 6.

The dianion 4, prepared from 3 with 1.5 equiv of sodium hydride and 1.2 equiv of butyllithium, underwent regioselective γ-sulfenylation,[4] upon treatment with 2.4 equiv of diphenyl disulfide in tetrahydrofuran initially at 0 °C for 1.5 h and subsequently at room temperature for 4 h, to give 5 in 85% yield.

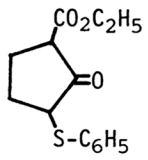
Reduction of 5 with $NaBH_4$ was performed in the normal way in ethanol at room temperature for 10 h, yielding 6 almost quantitatively. Oxidative cleavage of the resulting β-thioalcohol 6[5] was executed with 1.2 equiv of lead(IV) acetate in a 4 : 1 (v/v) mixture of anhydrous toluene and glacial acetic acid at 0 °C for 4 h to afford a cyclic hemithioacetal acetate 7 in 58% yield, which was smoothly converted into 8 by refluxing in benzene for 5 h in the presence of a catalytic amount of p-toluenesulfonic acid (83% yield). Treatment of 7 with 4 equiv of mercury(II) chloride in refluxing aqueous acetonitrile ($CH_3CN/H_2O$ 3 : 1) for 20 h led, via hydrolysis of the thioacetal group, to smooth conversion into a dihydropyran derivative 9. The structure is clearly supported by the ir absorptions ($\nu_{max}^{film}$ $cm^{-1}$: 3500 (OH), 1700 (C=C-$CO_2C_2H_5$), 1630 (C=C)) and the nmr spectrum (δ 7.20 (1H, s, O-CH=C)).



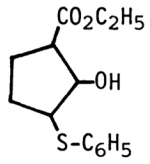
3



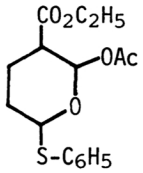
4



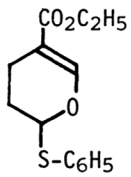
5



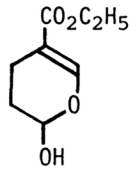
6



7



8

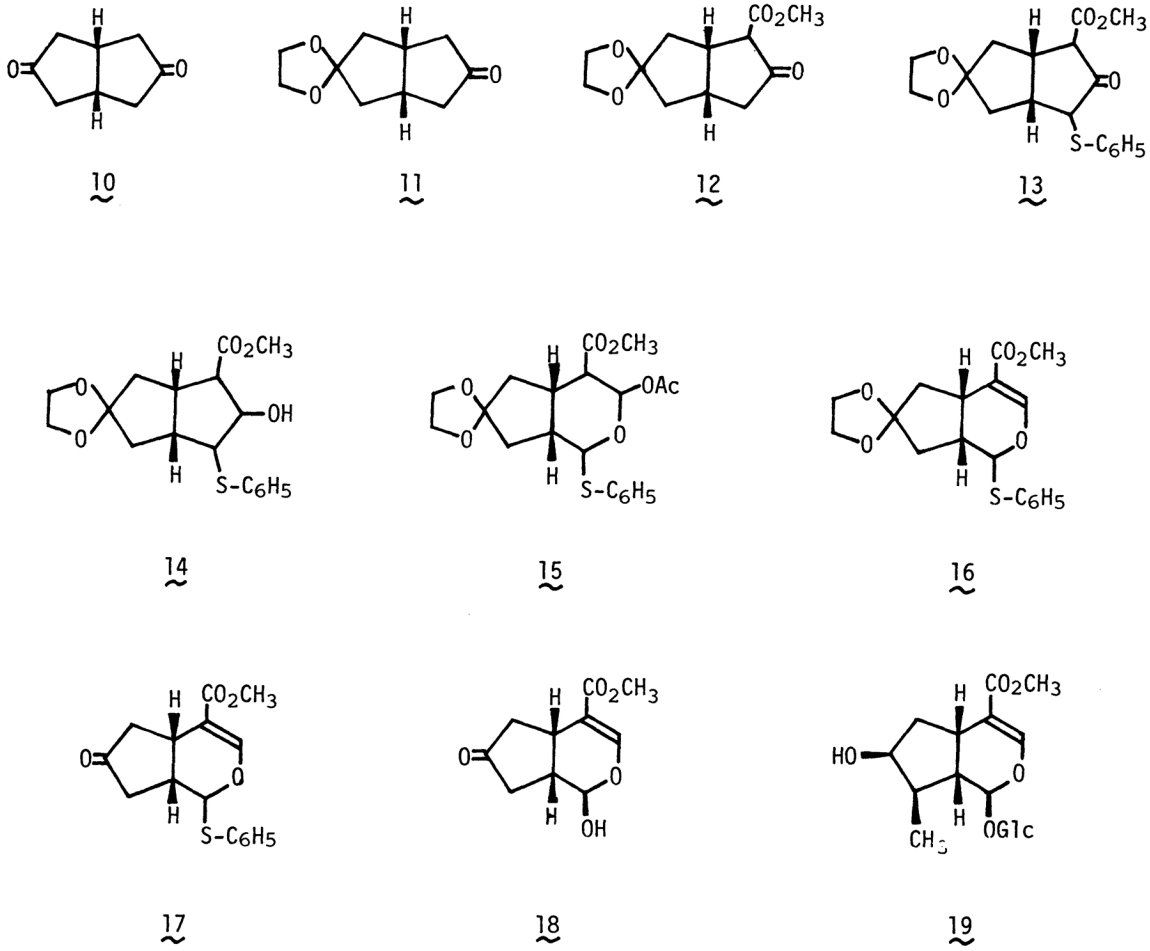


9

Scheme 1

Application of this method to a bicyclo[3.3.0]octane system provides its general availability for construction of the 1,4a,5,6,7,7a-hexahydrocyclopenta[c] pyran skeleton (1: $R^1$, $R^2$= $-(CH_2)_3-$).

Carbomethoxylation of 11, prepared by ketalization of 10[6] with ethylene glycol, was accomplished by refluxing in benzene for 7-8 h with a large excess of dimethyl



Scheme 2

carbonate in the presence of sodium hydride, giving 12 in 60% yield.

Regioselective sulfenylation of 12 via the dianion was carried out in the same way by reacting with 2.4 equiv of diphenyl disulfide in the presence of 2.4 equiv of lithium diisopropylamide in tetrahydrofuran at 0 °C for 1 h and at room temperature for 1 h to produce 13 in 69% yield.

Reduction of 13 with $NaBH_4$ followed by oxidative cleavage of 14 with 1.5 equiv of lead(IV) acetate (toluene-acetic acid 4 : 1, 0 °C 18 h) resulted in 47% yield of a cyclic hemithioacetal acetate 15. Upon treatment with a catalytic amount of p-toluenesulfonic acid in refluxing benzene, deacetoxylation of 15 and partial hydrolysis of the acetal function were underwent to give 16 and 17 in 36 and 35% yield, respectively. Both compounds showed the ir absorptions characteristic of α,β-unsaturated ester ($\nu_{max}^{CHCl_3}$ $cm^{-1}$: 1705 ($C=C-CO_2CH_3$), 1630 (C=C)).

Hydrolysis of the thioacetal group of 15 was achieved by treating with mercury

(II) chloride in refluxing aqueous acetonitrile ($CH_3CN/H_2O$ 3 : 1) to produce 18 (40% yield). The structure of 18 was unequivocally confirmed by the ir absorptions at 3500 $cm^{-1}$ (OH), at 1740 $cm^{-1}$ (ketone), at 1710 $cm^{-1}$ (α,β-unsaturated ester), and at 1630 $cm^{-1}$ (C=C) and by the nmr peak at δ 7.50 caused by the olefin proton of the α,β-unsaturated ester as a singlet. This has already been converted into (±)-loganin (19) by Büchi and co-workers.[7]

All new compounds exhibited appropriate ir, nmr, and mass spectral characteristics and gave acceptable elemental analyses or high resolution mass spectral analyses.

Thus, this novel method with regioselective sulfenylation of β-ketoesters and subsequent oxidative cleavage of β-thioalcohols would provide a facile entry to the iridoids possessing the 1,4a,5,6,7,7a-hexahydrocyclopenta[c]pyran skeletons.

## References

1. a) V. Plouvier and J. Favre-Bonvin, Phytochemistry, 10, 1697 (1971); b) E.C. Bate-Smith, Nature, 236, 353 (1972); c) O. Sticher and U. Junod-Busch, Pharm. Acta Helv., 50, 127 (1975).
2. a) R. Hegnauer, Pharm. Acta Helv., 41, 577 (1966); b) G. Büchi and J.A. Carlson, J. Am. Chem. Soc., 90, 5336 (1968); c) R.C. Kelly and I. Schletter, J. Am. Chem. Soc., 95, 7156 (1973) and references cited therein; d) S.K. Kupchan, A.L. Dessertine, B.T. Blaylock, and R.F. Bryan, J. Org. Chem., 39, 2477 (1974).
3. a) E. Leete, Acc. Chem. Res., 2, 59 (1969); b) D. Gross, Fortschr. Chem. Org. Naturst., 28, 140 (1970); c) A.I. Scott, Acc. Chem. Res., 3, 151 (1970); d) A.R. Battersby, "The Alkaloids," Vol. 1, ed. by J.E. Saxton, The Chemical Society, London, 1971, pp. 31-47; e) H. Inouye, S. Ueda, and Y. Takeda, Heterocycles, 4, 527 (1976).
4. K. Hiroi, Y. Matsuda, and S. Sato, Synthesis, 1979, 621; idem, Chem. Pharm. Bull., 27, 2338 (1979).
5. a) B.M. Trost and K. Hiroi, J. Am. Chem. Soc., 97, 6912 (1975); b) idem, ibid., 98, 4313 (1976); c) K. Hiroi, S. Sato, and K. Matsuo, Chem. Pharm. Bull., 28, 558 (1980); d) B.M. Trost, K. Hiroi, and L.N. Jungheim, J. Org. Chem., 45, 1839 (1980).
6. P. Vates, E.S. Hand, and G.B. French, J. Am. Chem. Soc., 82, 6347 (1960).
7. G. Büchi, J.A. Carlson, J.E. Powell, Jr., and L.-F. Tietze, J. Am. Chem. Soc., 92, 2165 (1970); idem, ibid., 95, 540 (1973).

(Received February 20, 1981)