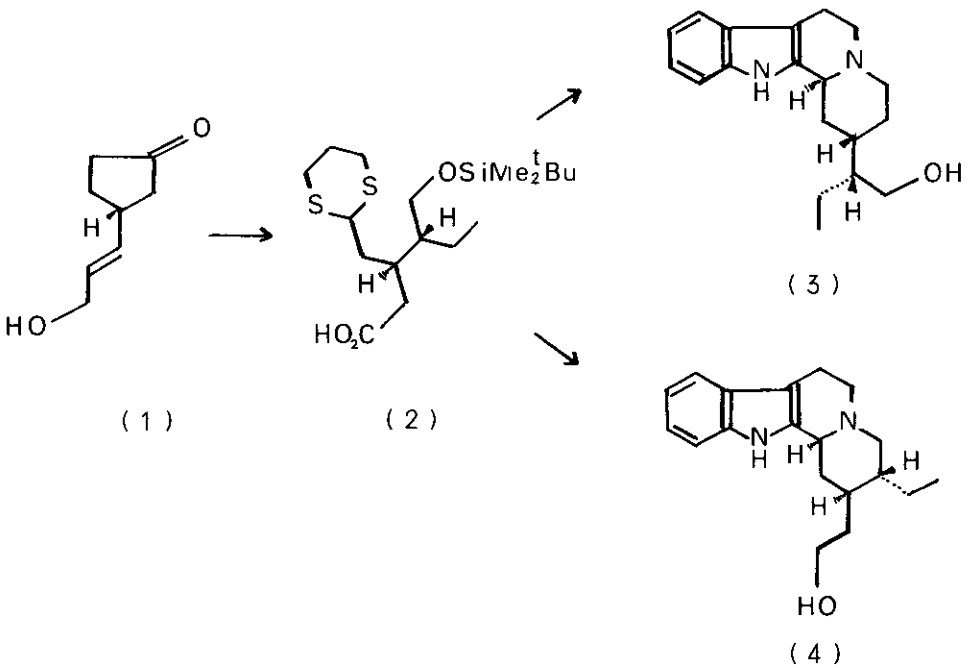
THE TOTAL SYNTHESIS OF (-)-DIHYDROCORYNANTHEOL

Toshio Suzuki*, Etsuko Sato, and Katsuo Unno
Department of Pharmacy, Akita University Hospital,
Hondo 1-1-1, Akita 010, Japan
Tetsuji Kametani*
Institute of Medicinal Chemistry, Hoshi University,
Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan

Abstract —— The total synthesis of (-)-dihydrocorynantheol (4) has been achieved using a potentially useful chiral synthon, thioketal carboxylic acid (2).

The synthesis of enantiomerically pure compounds has received increasing attention over the past years. One of the most direct approaches to their synthesis is the use of carbohydrates.

Recently we have disclosed an enantioselective synthesis of (+)-dihydroantirhine (3)[1] from a readily available chiral synthon, (3S)-[3-hydroxy-(E)-prop-1-enyl]-cyclopentanone (1)[2] obtained from (R)-1,2-isopropylideneglyceraldehyde via the thioketal carboxylic acid (2). Using the same chiral synthon (2), we have now



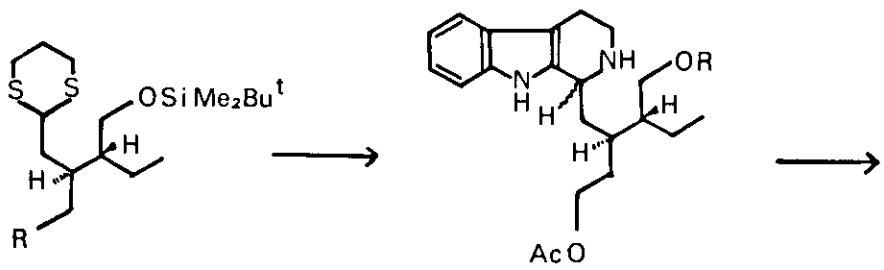
(1) (2) (3) (4)

succeeded the total synthesis of (-)-dihydrocorynantheol (4) of Corynanthe-type indole alkaloids, which was firstly isolated from Aspidosperma marcgravianum by B.Gilbert.[3] Although the total synthesis of racemic forms of (4)[4] was achieved, none of the enantioselective synthesis of (-)-(4) has been accomplished yet. Here we wish to report the first total synthesis of (-)-dihydrocorynantheol.

Esterification (CH_2N_2, r.t.) of the known carboxylic acid (2), prepared in 9 steps from (1)[1] gave the methyl ester (5) $\{[\alpha]_D$-0.6° (c=0.13, $CHCl_3)\}$. Reduction of (5) with diisobutylaluminum hydride in tetrahydrofuran (-70°C, 2.5h), followed by acetylation (acetic anhydride, pyridine, 1 h, r.t.) of the alcohol (6) provided the acetate (7) $\{[\alpha]_D$-2.6° (c=0.156, $CHCl_3)\}$ in 92.8 % overall yield from (5).

Hydrolysis[5] of the dithiane group in (7) (MeI, Na_2CO_3 in aq. CH_3CN, 14 h, r.t.) followed by condensation with tryptamine (1.1 equiv.) in acetic acid (1 h, r.t.) afforded secondary amine (8), which in turn was deprotected (nBu_4NF, THF, 1 h, r.t.) to the alcohol (9) in almost quantitative yield from (7). Treatment of (9) with methanesulfonyl chloride (1.5 equiv., pyridine, 2 h, r.t.) resulted in cyclisation to give a separable mixture of (10) and (11) in 29.5 and 26.1 % yield respectively. In order to certify the relationship between (10) and (11), a transformation of (11) to (10) was examined. Dehydrogenation (11) with mercuric acetate[5d,6] followed by reduction with $NaBH_4$[5d,6,7] proceeded smoothly to give (10) via the imunium base (12). These conversions indicated that these compounds were the C(3) epimers of each other.

Finally, deacetylation (K_2CO_3, MeOH, 3 h, r.t.) of (10) afforded (-)-dihydrocorynantheol (4) $\{[\alpha]_D$-20.0° (c=0.03, $CHCl_3)\}$ (lit.,[3] $[\alpha]_D$-19° (c=1.02, $CHCl_3$) in quantitative yield. This synthetic substance had identical t.l.c. behavior, i.r., ^1H n.m.r., and mass spectra with those of authentic dihydrocorynantheol.[4b] Thus, the transformation of (R)-1,2-isopropylideneglyceraldehyde via the thioketal carboxylic acid (2) into (-)-dihydrocorynantheol has been achieved.



(2) R = CO_2H

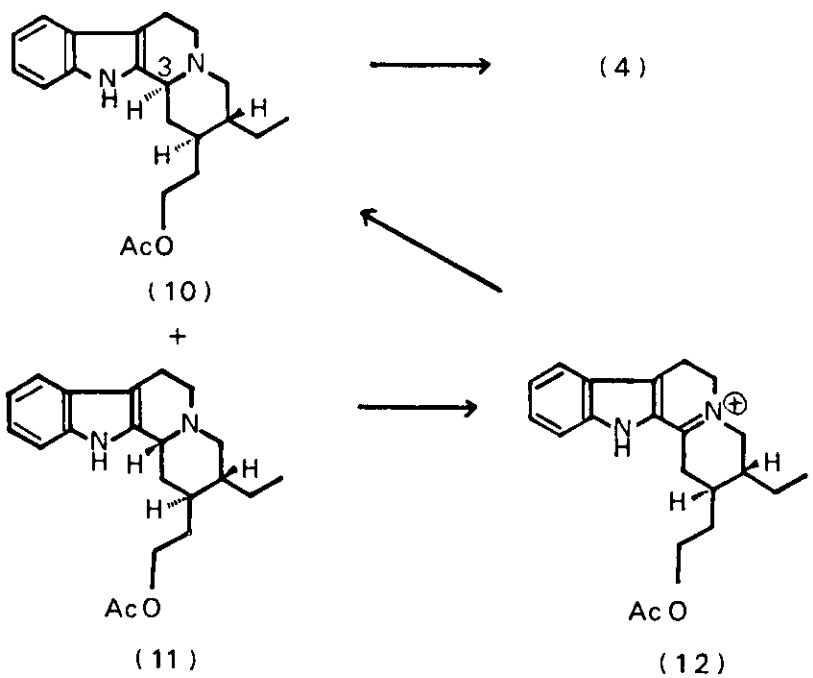
(5) R = CO_2Me

(6) R = CH_2OH

(7) R = CH_2OAc

(8) R = $SiMe_2Bu^t$

(9) R = H



REFERENCES

1. T.Kametani, T.Suzuki, E.Sato, M.Nishimura, and K.Unno, J. Chem. Soc., Chem. Commun., 1982, 1201.
2. T.Kametani, T.Suzuki, E.Sato, M.Nishimura, and K.Unno, J. Chem. Soc., Chem. Commun., 1982, 123.
3. B.Gilbert, L.D.Autonaccio, and C.Djerassi, J. Org. Chem., 1962, 27, 4702.
4. (a) C.Vamvacas, W.V.Philpsborn, E.Schlittler, H.Schmid, and P.Karrer, Helv. Chim. Acta, 1957, 40, 1793.
   (b) F.E.Ziegler and J.G.Sweeny, Tetrahedron Lett., 1969, 1097.
   (c) T.Kametani, N.Kanaya, H.Hino, S.Hung, and M.Ihara, Heterocycles, 1980, 14, 1771; T.Kametani, N.Kanaya, H.Hino, S.Hung, and M.Ihara, J. Chem. Soc., Perkin I, 1981, 3168.
   (d) S.Takano, K.Shibuya, M.Takahashi, S.Hatakeyama, and K.Ogasawara, Heterocycles, 1981, 16, 1125.
   (e) B.Danieli, G.Lesma, G.Palmisano, and S.Tollari, J. Chem. Soc., Perkin I, 1984, 1237.
5. (a) M.Petizon and M.Jurion, J. Chem. Soc., Chem. Commun., 1972, 382.
   (b) S.Takano, S.Hatakeyama, and K.Ogasawara, J. Am. Chem. Soc., 1976, 98, 3022; 1979, 101, 6414: (c) S.Takano, M.Takahashi, and K.Ogasawara, J. Am. Chem. Soc., 1980, 102, 4282.
   (d) S.Takano, K.Masuda, and K.Ogasawara, J. Chem. Soc., Chem. Commun., 1980, 887.
6. (a) N.J.Dastoor, A.A.Gorman, and J.Schmid, Helv. Chim. Acta, 1967, 50, 213: (b) H.T.Openshaw and N.Whittaker, J. Chem. Soc., 1963, 1461.
   (c) S.Takano, S.Hatakeyama, and K.Ogasawara, Tetrahedron Lett., 1978, 2519.
7. E.Wenkert, K.G.Dave, and F.Haglid, J. Am. Chem. Soc., 1965, 87, 5461.

Received, 23rd January, 1985