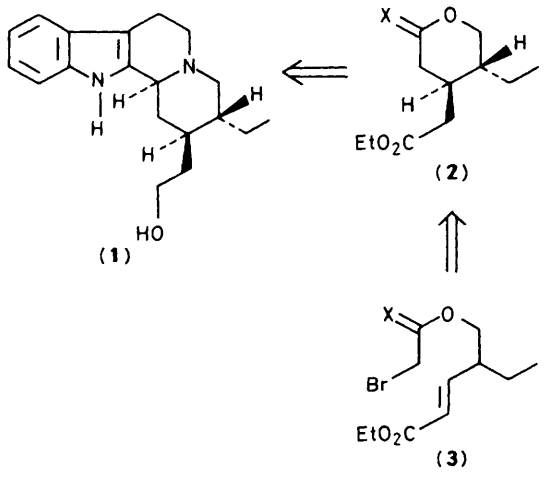
A Stereoselective Total Synthesis of (±)-Dihydrocorynantheol *via* Radical Cyclisation

Masataka Ihara,[a] Nobuaki Taniguchi,[a] Keiichiro Fukumoto,*[a] and Tetsuji Kametani[b]

[a] *Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan*
[b] *Institute of Medicinal Chemistry, Hoshi University, Ebara 2-4-41, Shinagawa-ku, Tokyo 142, Japan*

Stereoselective total synthesis of (±)-dihydrocorynantheol (**1**) has been accomplished *via* radical cyclisation of a bromoacetal (**9**) of a homoallylic alcohol.

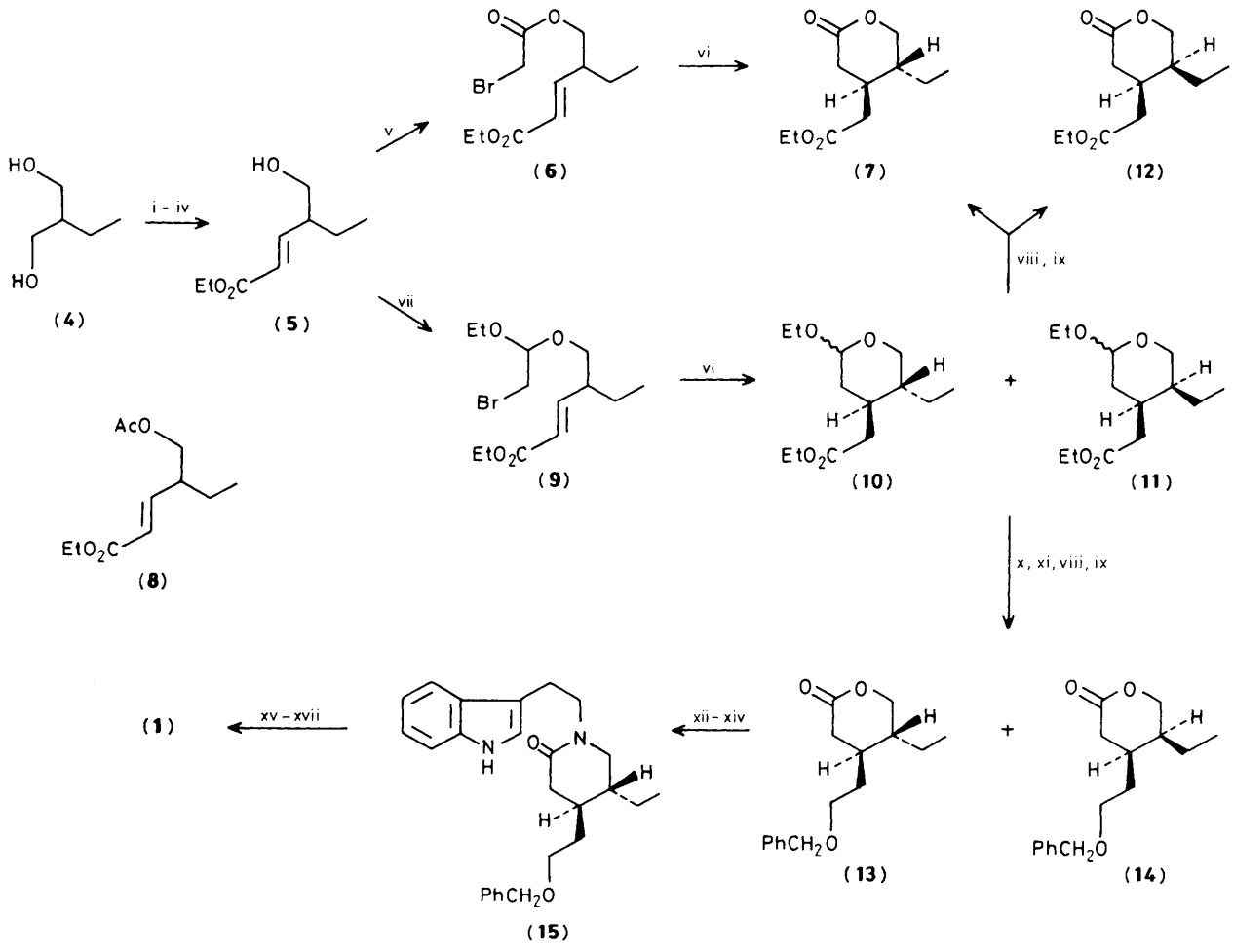
Within the last decade, a new approach to bond formation, through free-radical-mediated cyclisation, has emerged as a highly versatile and often indispensable method.[1] Although five-membered ring formation reactions have been utilized in the syntheses of a number of natural products, relatively few studies have been done on the construction of six-membered ring systems.[2] We have examined 1,2-asymmetric induction in the assembly of six-membered rings by radical cyclisation, and here report a stereoselective total synthesis of (±)-dihydrocorynantheol (**1**) according to the synthetic plan shown in Scheme 1.



Scheme 1

Monoprotection of 2-ethylpropane-1,3-diol[3] with a t-butyldimethylsilyl group, followed by Swern oxidation, then Wittig reaction and deprotection, gave the homoallylic alcohol (**5**) in 72% overall yield. Acylation using bromoacetic acid, dicyclohexylcarbodi-imide (DCC), and dimethylaminopyridine (DMAP) gave the bromoacetate (**6**) in 93% yield; this was subjected to radical cyclisation by heating with Bu^n_3SnH in the presence of azoisobutyronitrile (AIBN) in refluxing benzene. The lactone (**7**)† was obtained as a single stereoisomer in 35%

† I.r. ($CHCl_3$) and n.m.r. ($CDCl_3$) data: (**7**) i.r. 1733 cm^{-1} (C=O); 500 MHz n.m.r. δ 0.96 (3H, t, *J* 7.8 Hz, CH_2*Me*), 1.27 (3H, t, *J* 6.8 Hz, OCH_2*Me*), 4.01 (1H, dd, *J* 8.0 and 12.0 Hz, 6-H), 4.16 (2H, q, *J* 6.8 Hz, OCH_2Me), and 4.34 (1H, dd, *J* 4.0 and 12.0 Hz, 6-H); (**9**) i.r. 1708 cm^{-1} (C=O); 90 MHz n.m.r. δ 0.96 (3H, t, *J* 7.5 Hz, CH_2*Me*), 1.22 (3H, t, *J* 6.6 Hz, OCH_2*Me*), 1.30 (3H, t, *J* 7.4 Hz, OCH_2*Me*), 4.19 (2H, q, *J* 7.4 Hz, OCH_2Me), 3.34 (2H, t, *J* 5.7 Hz, CH_2Br), 5.86 (1H, dd, *J* 0.9 and 15.3 Hz, =$CHCO_2$), and 6.83 (1H, dd, *J* 9.1 and 15.3 Hz, C*H*=$CHCO_2$); (**13**) i.r. 1735 cm^{-1} (C=O); 90 MHz n.m.r. δ 0.96 (3H, br. t, *J* 7.5 Hz, CH_2*Me*), 3.53 (2H, t, *J* 7.5 Hz, CH_2OCH_2Ph), and 4.50 (2H, s, OCH_2Ph); (**15**) i.r. 3480 (NH) and 1625 cm^{-1} (C=O); 90 MHz n.m.r. δ 0.78 (3H, br. t, *J* 7.5 Hz, CH_2*Me*), 4.49 (2H, s, OCH_2Ph), and 8.10 (1H, br. s, NH).



Scheme 2. *Reagents:* i, Bu^tMe_2SiCl, Et_3N, DMAP; ii, Me_2SO, $(COCl)_2$, Et_3N; iii, $Ph_3P{=}CHCO_2Et$; iv, Bu^n_4NF; v, $BrCH_2CO_2H$, DCC, DMAP; vi, Bu^n_3SnH, AIBN, heat; vii, $CH_2{=}CHOEt$, NBS; viii, dil. HCl, tetrahydrofuran (THF); ix, CrO_3, dil. H_2SO_4, acetone; x, $LiAlH_4$; xi, $PhCH_2Br$, KH, 18-crown-6; xii, tryptamine, heat; xiii, $MeSO_2Cl$, Et_3N; xiv, KH, 18-crown-6; xv, $POCl_3$, MeCN; xvi, $NaBH_4$; xvii, H_2, $PdCl_2$, $CHCl_3$, MeOH.

yield together with the corresponding reduced product (**8**) (65% yield).

Radical cyclisation of the bromoacetal (**9**),† prepared from (**5**) by Ueno's method[4] in 86% yield, produced in 96% yield a mixture of the four possible cyclic compounds (**10**) and (**11**), which was transformed by the usual procedure into two lactones (**7**) and (**12**) in the ratio of about 4:1. The major product (**7**) was identical with that already obtained (see above) and its stereochemistry was determined by chemical correlation (see later). The mixture of cyclic compounds (**10**) and (**11**) was reduced with $LiAlH_4$ and then protected by benzyl ether formation, in 79% overall yield for the two steps. Deacetalisation (92% yield) followed by Jones oxidation (91% yield) afforded two lactones (**13**) and (**14**) in the ratio of about 4:1. Condensation of the major product (**13**),† isolated by h.p.l.c., with tryptamine, followed by mesylation of the resulting hydroxy amide, then ring closure using KH and 18-crown-6 in 1,2-dimethoxyethane (DME) at 0—18 °C, led to the lactam (**15**)† in 70% overall yield. This was then stereoselectively converted in 74% overall yield into (±)-dihydrocorynantheol (**1**), m.p. 179.0—179.5 °C (lit.,[5] 178.5—180 °C), identical with the authentic compound in all respects. Thus a stereoselective total synthesis of the racemic alkaloid was achieved.

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