Enantioselective Synthesis of the Gibbane Framework

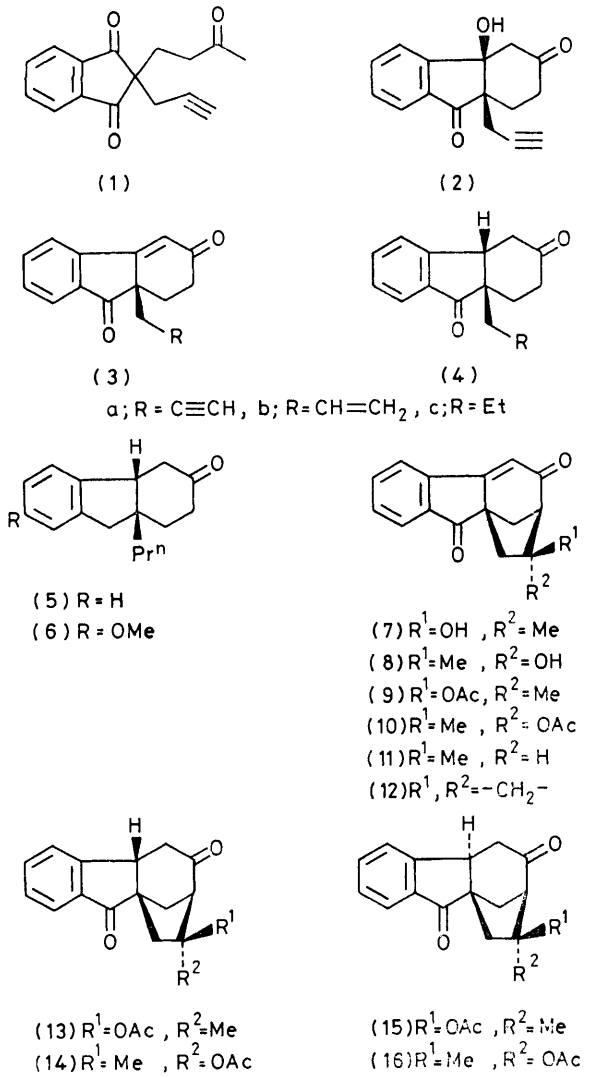
By SEIICHI TAKANO,* CHIYOSHI KASAHARA, and KUNIO OGASAWARA
(*Pharmaceutical Institute, Tohoku University, Aobayama, Sendai* 980, *Japan*)

Summary The triketone (**1**), possessing a mirror plane of symmetry, prepared from indane-1,3-dione, has been transformed into the gibbane framework enantioselectively by asymmetric aldolization catalysed by L-proline.

THE efficient asymmetric intramolecular aldolization of certain triketones with a reflective symmetry axis using chiral catalysts has been reported with a view to obtaining optically active steroids.[1—5] We sought to exploit this asymmetric aldolization for the synthesis of more functionalized chiral products possessing units suitable for the construction of certain tetracyclic triterpenes, such as gibberellins and kaurenes. We now describe an enantioselective synthesis of the tricyclic enone (**3**) from the symmetric triketone (**1**) and its conversion into the gibbane framework.[6]

The symmetric triketone (**1**), m.p. 71—73 °C, obtained from indane-1,3-dione (53% overall) by alkylation successively with prop-2-ynyl bromide and then methyl vinyl ketone,[7] was treated with L-proline (0·1 equiv.) in dimethyl formamide (DMF) (room temp.; 2 days)[2] to give the unstable ketol† (**2**) (89% yield), m.p. 132—133 °C, $[\alpha]_D$ + 2·9° (MeOH),‡ which furnished the chemically pure enone (**3a**) (92% yield), m.p. 149 °C, $[\alpha]_D$ + 168·3° (MeOH), on dehydration (*p*-$MeC_6H_4SO_3H$; benzene; reflux; 0·5 h).§ The enantiomerically pure enone (+)-(**3a**), $[\alpha]_D$ + 186·5° (MeOH), was obtained in 66% recovery after a single crystallization from methanol.

† All new compounds gave satisfactory spectral (i.r., n.m.r., m.s.) and analytical (combustion and high-resolution m.s.) data.
‡ Optical rotations were measured with a JASCO DIP-4B automatic polarimeter.
§ The enantiomeric enone (−)-(**3a**) {m.p. 147—148 °C; $[\alpha]_D$ −148·7 ° (MeOH)} was obtained in 68% yield from (**1**) using D-proline as catalyst.

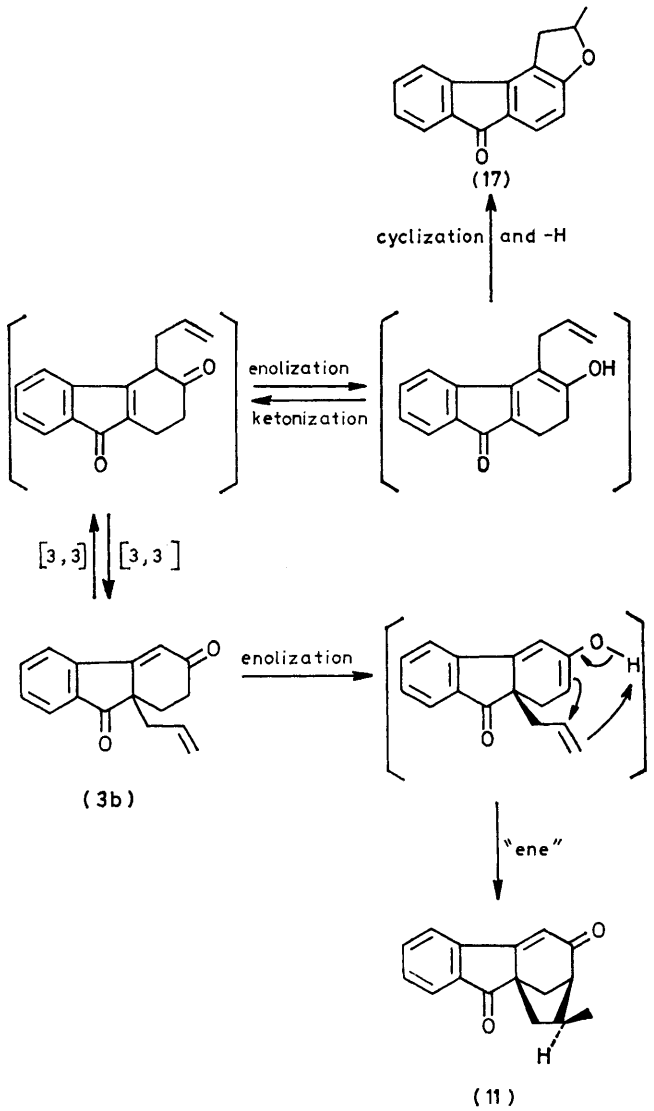


SCHEME 1

Conversion of the enone (+)-(**3a**) into the gibbane framework was carried out by two separate routes. First, attempted hydration of (+)-(**3a**) with mercury(II) oxide in dilute sulphuric acid (3·4%)–tetrahydrofuran (6·2:100) (60 °C; 18 h) initiated concomitant aldol cyclization to give the gibbanes (**7**) {38%; m.p. 236 °C, $[\alpha]_D$ + 2·0° ($CHCl_3$)} and (**8**) {32%; m.p. 218 °C, $[\alpha]_D$ + 107·5° ($CHCl_3$)}. Upon acetylation (Ac_2O–AcOH, BF_3–Et_2O, 0 °C to room temp.; 1·2 h) each gave the corresponding acetate (**9**) {m.p. 161—162 °C, $[\alpha]_D$ + 29·35° (MeOH)} and (**10**) {m.p. 155—156 °C, $[\alpha]_D$ + 72·81° (MeOH)}, which were transformed into the same unsaturated compound (**12**) {81·1% from (**9**) and 78·7% from (**10**); m.p. 172—173 °C, $[\alpha]_D$ − 103·9° ($CHCl_3$)}, respectively, by treatment with boron trifluoride in acetic acid (90 °C; 2 h). Similarly, the *cis* B/C compound (**4a**) {$[\alpha]_D$ + 118·25° (MeOH)} obtained from (+)-(**3a**) (*vide infra*) afforded the isomeric acetates (**13**) {24·4%; m.p. 173—174 °C; $[\alpha]_D$ − 20·36° (MeOH)} and (**14**) {22·0%; m.p. 190—191 °C; $[\alpha]_D$ − 57·07° (MeOH)}.

Secondly, the vinyl enone (**3b**) {m.p. 94—95 °C; $[\alpha]_D$ + 180·7° (MeOH)}, obtained by reduction of (+)-(**3a**) (H_2; Lindlar catalyst; AcOH), afforded the tetracyclic enone (**11**) {51·0%; m.p. 102—104 °C, $[\alpha]_D$ + 14·29° (MeOH)} accompanied by the fluorenone (**17**) (18·5%; oil) on ene reaction (benzene; sealed tube; 380 °C; 24 h). However, racemization, presumably through concurrent reversible [3,3] sigmatropic rearrangements, seemed to occur to a considerable extent since the same compound (**11**) obtained from the olefin (**12**) by hydrogenation [H_2, Pd–C (10%); AcOH–EtOH] possessed a much higher optical rotation {$[\alpha]_D$ + 65·0° (MeOH)} (Scheme 2).

Upon reduction with sodium hydrotelluride[8] the tricyclic products furnished saturated ketones with *cis* B/C ring junctions selectively. Thus the enones (**3a**—**c**) {(**3c**), oil, $[\alpha]_D$ + 15·2° ($CHCl_3$), was obtained by reduction (H_2; 5% Pd–C; EtOH–AcOH) of (**3a**)} gave the corresponding *cis* B/C ketones (**4a**) {oil, $[\alpha]_D$ + 171·08° (MeOH)}, (**4b**) {oil,



SCHEME 2

$[\alpha]_D$ + 185·8° ($CHCl_3$)}, and (**4c**) {oil, $[\alpha]_D$ + 140·1° ($CHCl_3$)}, respectively, in excellent yield. The *cis*-diketones (**4a**—**c**) could be converted into the monoketone (**5**) {oil, $[\alpha]_D$ + 15·2° ($CHCl_3$)} by catalytic hydrogenation [H_2 (3·5 kg/cm²); 10% Pd–C; AcOH]. The stereochemistry and chirality of the *cis* ketone (**5**) were confirmed by comparing its n.m.r. spectrum [δ 1·00 (3H, s), 1·20—2·61 (8H, m), 2·85 (4H, dd, *J* 6 and 10 Hz), 3·36 (1H, t, *J* 6 Hz), and 7·26 (4H, br.s)] and c.d. spectrum¶ ($\Delta\epsilon_{265}$ +0·18, $\Delta\epsilon_{286}$ −0·42, $\Delta\epsilon_{340}$ +0·05) with those of the methoxy-analogue (**6**) [δ 1·00 (3H, m), 1·20—2·61 (8H, m), 2·83 (4H, dd, *J* 6 and 10 Hz), 3·30 (1H, t, *J* 6 Hz), 3·80 (3H, s), 6·78 (1H, d, *J* 10 Hz), 6·83 (1H, s), and 7·12 (1H, d, *J* 10 Hz); $\Delta\epsilon_{274}$ +0·49, $\Delta\epsilon_{291}$ −3·11, $\Delta\epsilon_{356}$ +0·20] obtained from L-glutamic acid by a fundamentally different route.[9]

In the tetracyclic series sodium hydrotelluride reduction furnished the *cis* B/C derivatives while the following sequential procedure: (i), $NaBH_4$; (ii) Na, liq.NH_3–EtOH; (iii) Jones oxidation, furnished the *trans* B/C derivatives, both routes being highly stereoselective. Thus, the enones (**9**) and (**10**), on sodium hydrotelluride reduction, gave the *cis*-ketones (**13**) {78%; m.p. 177—178 °C, $[\alpha]_D$ − 28·95° (MeOH)} and (**14**) {69%; m.p. 190—191 °C, $[\alpha]_D$ − 90·14° (MeOH)}, respectively, while the enones (**7**) and (**8**), using the sequential procedure, gave the *trans*-ketones (**15**) {23%; m.p. 138 °C, $[\alpha]_D$ + 27·50° (MeOH)} and (**16**) {62%; oil, $[\alpha]_D$ + 93·04° (MeOH)}, respectively.

(*Received*, 24*th February* 1981; *Com.* 207.)

¶ C.d. measurements were made with a JASCO J-400X spectropolarimeter for chloroform solutions.

[1] U. Eder, G. Sauer, and R. Wiechert, *Angew. Chem., Internat. Ed. Engl.*, 1971, **10**, 496.
[2] Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1615.
[3] K. Nagasawa, H. Takahashi, K. Hiroi, and S. Yamada, *J. Pharm. Soc. Japan*, 1975, **95**, 33, 46.
[4] S. Danishefsky and P. Cain, *J. Am. Chem. Soc.*, 1975, **97**, 5282; 1976, **98**, 4975.
[5] For review see N. Cohen, *Accounts Chem. Res.*, 1976, **9**, 412.
[6] A part of the present work was presented at the 22nd Symposium on the Chemistry of Natural Products, Fukuoka, 1979, Symposium Papers, p. 118.
[7] Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, 1974, **39**, 1612.
[8] M. Yamashita, Y. Kato, and R. Suemitsu, *Chem. Lett.*, 1980, 847.
[9] S. Takano, C. Kasahara, and K. Ogasawara, *J. Chem. Soc., Chem. Commun.*, following communication.