# A Novel Synthesis of Brassinolide and Related Compounds

**Zhou Wei-Shan,*[a] Biao Jiang,[b] and Xin-fu Pan[b]**

[a] *Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai, China*
[b] *Department of Chemistry, Lanzhou University, Lanzhou, China*

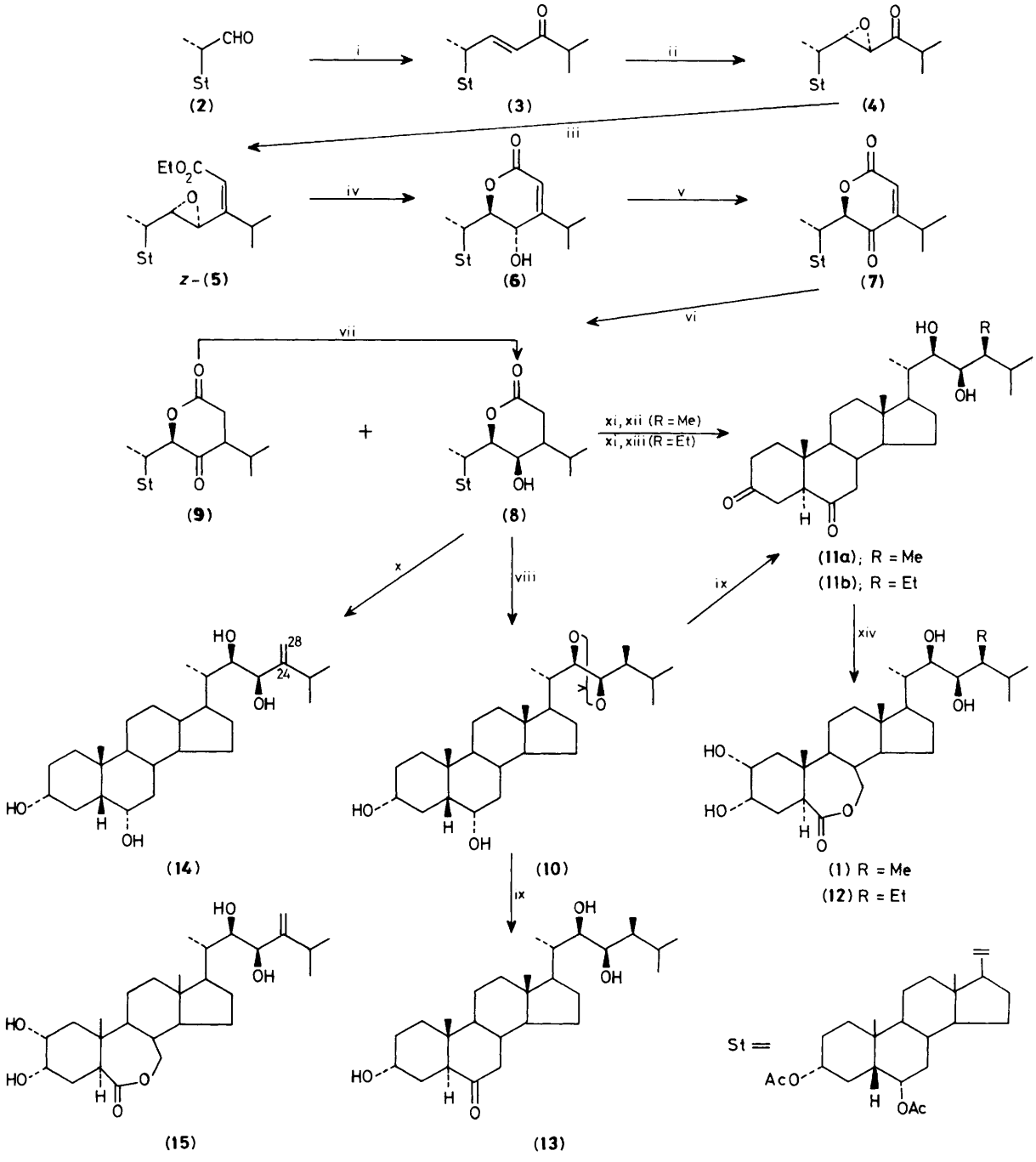
A stereoselective synthesis of the natural promoting steroids, brassinolide, homobrassinolide, and typhasterol is described, which involves construction of a side chain by lactonisation of *Z*-(**5**) under acidic conditions to give an α,β-unsaturated δ-lactone (**6**) with the inversion of the configuration at C-22 of the epoxy steroid in quantitative yield.

Brassinolide (**1**) is a growth promoting steroid.[1] Its remarkable biological activities and the novel chemical structure have led many laboratories to synthesise this natural product.[2] We report here a new method for constructing the brassinolide side chain, which is stereoselective and produces high yields.

The 22-aldehyde (**2**) obtained from hyodeoxycholic acid by the known procedure[3] was treated with isobutyl carbonyl arsonium ylide[4] to form α,β-unsaturated ketone (**3**) in 72% yield.† Epoxidation of (**3**) with $H_2O_2$–NaOH afforded the α,β-epoxyketone (**4**) in 86% yield. The Wittig–Horner reaction of methoxycarbonylmethyl phosphonic acid dimethyl ester with (**4**) furnished a mixture of *Z*- and *E*-α,β-unsaturated-γ,δ-α-epoxy acid ester *Z*-(**5**) and *E*-(**5**) in 72% yield in a ratio of 10:1. This key intermediate *Z*-(**5**) was lactonised under acidic conditions to give an α,β-unsaturated-δ-lactone (**6**) formed by the carboxylate-aided epoxide ring opening of *Z*-(**5**) with the inversion of the configuration at C-22 in quantitative yield. The 23*S*-configuration of (**6**) could be easily converted into a 23*R* configuration by successive oxidation and reduction. Thus, oxidation of (**6**) with pyridinium dichromate (PDC) followed by hydrogenation over $PtO_2$ gave a mixture of 22*R*,23*R*-γ-hydroxy-δ-lactone (**8**)‡ and 22*R*-γ-keto-lactone (**9**) in almost quantitative yield in a ratio of 88:12. Compound (**9**) could easily be converted into (**8**)[5] by $KBH_4$ in quantitative yield. Reduction of lactone (**8**) with di-isobutylaluminium hydride (DIBAH) afforded a hemiacetal and this compound was treated with 2,2-dimethoxypropane to form the 22,23-acetonide which was decarbonylated with tris-(triphenylphosphine) rhodium chloride to give the known 24*S*-methyl derivative (**10**).[2g] These three-step reactions were performed in 76% overall yield. The overall yield for the synthesis of the side chain, starting from (**2**), was 32%. This is one of the best methods for construction of the side chain of brassinolide and related compounds.[2d] Brassinolide was prepared from (**10**) in five sequential steps: oxidation of

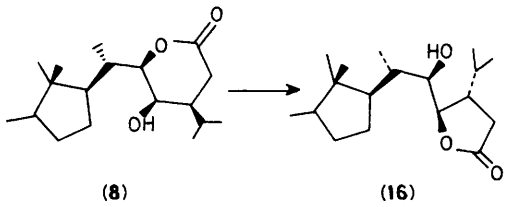
† All new compounds gave satisfactory analytical and $^1$H n.m.r. (200 MHz, $CDCl_3$), i.r. ($CHCl_3$) and mass spectra. *Selected data*: (**3**), δ 1.02 (3H, d, *J* 6.8 Hz 21-H), 1.12, 1.14 (6H, 2d, *J* 6.8 Hz, 26 and 27-H), 6.20 (1H, d, *J* 16 Hz 23-H), 6.71 (1H, dd, *J* 16 Hz, 8 Hz, 22-H); $\nu_{max}$: 1720, 1710, 1680, 1620 cm$^{-1}$; *m/z*: 500 ($M^+$), 440 ($M^+$ – $MeCO_2H$). (**4**), δ: 1.01 (3H, d, *J* 6.8 Hz, 21-H), 1.20 (6H, 2d, *J* 6.8 Hz, 26 and 27-H), 2.80 (1H m, 22-H), 3.20 (1H, m, 23-H); $\nu_{max}$ 1740, 1720 cm$^{-1}$; *m/z*: 517 ($M^+$ + 1), 475 ($M^+$ – MeCO). (**5**), δ: 1.02 (3H, d, *J* 6.4 Hz, 21-H), 1.13, 1.15 (6H, 2d, *J* 8 Hz, 26, 27-H), 2.60 (1H, m, 22-H), 4.25 (2 H, q, *J* 8 Hz, $MeCH_2O$), 4.41 (1H, m, 23-H), 5.83 (1H, s, 29-H), $\nu_{max}$ 1740, 1720, 1680 cm$^{-1}$; *m/z*: 587 ($M^+$ + 1), 569 ($M^+$ – $H_2O$), 527 ($M^+$ – $MeCO_2H$). (**6**), δ: 4.10 (1 H, d, *J* 12 Hz, 23-H), 4.28 (1H, d, *J* 12 Hz, 22-H), 5.84 (1H, s, 29-H); $\nu_{max}$: 3400, 1740, 1720, 1640 cm$^{-1}$; *m/z* 558 ($M^+$), 498 ($M^+$ – $MeCO_2H$). (**8**), δ: 4.04 (1H, s, 23-H), 4.21 (1H, s, 22-H); $\nu_{max}$: 3450, 1740, 1720 cm$^{-1}$; *m/z*: 561 ($M^+$ + 1). (**10**), δ: 0.70 (3H, s, 18-H), 0.80, 0.84 (6H, 2d, *J* 6 Hz, 26 and 27-H), 0.94 (3H, d, *J* 6.8 Hz, 28-H), 1.06 (3H, d, *J* 6.8 Hz, 21-H), 1.34, 1.36 (6H, 2s, acetonide), 3.68—3.88 (4H, m, 3, 6, 22 and 23-H); $\nu_{max}$: 3450 cm$^{-1}$; *m/z* 491 ($M^+$ + 1). (**11a**). δ: 3.72 (1H, d, *J* 9 Hz 22-H), 3.82 (1H, d, *J* 8 Hz, 23-H); $\nu_{max}$ 3450, 1720 cm$^{-1}$; *m/z*: 447 ($M^+$ + 1). (**11b**), δ: 3.70 (1H, d, *J* 9 Hz, 22-H), 3.82 (1H, d, *J* 9 Hz 23–H); $\nu_{max}$: 3450, 1720 cm$^{-1}$; *m/z*: 461 ($M^+$ + 1), 453 ($M^+$ – $H_2O$).

‡ Hydroxylactone (**8**) was partly isomerised to thermodynamically stable γ-lactone (**16**) as shown in Scheme 2. On treatment with 4% KOH in MeOH (**8**) was quantitatively isomerised to (**16**).[5]




**Scheme 1.** i, $Me_2CH_2COCH{=}AsPh_3$/tetrahydrofuran (THF), room temp., 24 h; ii, 1.30% $H_2O_2$-4M NaOH/$C_2H_5OH$, 35 °C, 4 h, 2. $Ac_2OPy$; iii, 1. $(MeO)_2POCH_2CO_2Et$/NaH/THF, room temp., 2 h, 2. $Ac_2O$-Py; iv, 30% $HClO_4$/MeOH, room temp., 10 min; v, PDC/ $CH_2Cl_2$, room temp., 5 h; vi, $H_2$-$PtO_2$/$MeCH_2OH$-$MeCO_2CH_2Me$ (1 : 1), room temp.; vii, $KBH_4$/MeOH-$CH_2Cl_2$ (1 : 1); viii, 1. DIBAH/Toluene, −78 °C, 1 h, 2. *p*-TsOH/$(MeO)_2CMe_2$, 3. $[(Ph)_3P]_3RhCl$/toluene reflux; ix, 1. PDC-$CH_2Cl_2$, 2. 5% HCl/MeOH; x, 1. (PPTS)/(DHP) $CH_2Cl_2$, room temp. 24 h, 2.4% KOH/MeOH, 3. $Ac_2O$-Py, 4. $PhI(OAc)_2$ (IDBA)/$Cu(OAc)_2$/Py/$C_6H_6$ reflux, 5.5% HCl, 6.4% KOH-MeOH; xi, 1. $LiAlH_4$/THF, room temp., 4 h, 2. *p*-TsOH/$(MeO)_2CMe_2$; xii, 1. $CrO_3$/Py, 2. $[(Ph)_3P]_3RhCl$/toluene, reflux, 3.5% HCl/MeOH; xiii, 1. $CH_3SO_2Cl/Et_3N$, 0 °C, 10 min, 2. $LiAlH_4$/THF, 3. $CrO_3$ Py, 4. 5% HCl/MeOH; xiv, 1. Zn(Hg)-TMSCl/THF, room temp., 12 h, 2. $OsO_4$-NMMO/THF/$H_2O$ Bu$^t$OH, 3. $CF_3CO_3H/CH_2Cl_2$.

(**10**) with PDC followed by acid treatment afforded (**11a**) (R = Me) in 91% yield. Compound (**11a**) (R = Me) was readily obtained from the γ-hydroxy lactone compound (**8**) by the sequence of 5 reactions: 1. $LiAlH_4$, 2. $(MeO)_2CMe_2$-*p*-TsOH (Ts = *p*-$MeC_6H_4SO_2$), 3. $CrO_3$–Py, 4. $[(Ph)_3P]_3RhCl$, and 5. 5% HCl in 57% overall yield. Compound (**11a**) (R = Me) was then subjected to a reductive elimination by treatment with chlorotrimethylsilane (TMSCl) and zinc amalgam to give $\Delta^2$-6-keto compound[6] which on osmylation with $OsO_4$–(NMMO) followed by Baeyer–Villiger oxidation afforded brassinolide m.p. 273—275 °C (lit.[2a] m.p. 273—274 °C) in 34% overall yield in three steps.




(8) (16)

Scheme 2

Conversion of (**10**) to typhasterol (**13**) m.p. 230—231 °C (lit.[7] m.p. 227—230 °C), was achieved in 56% yield in two steps by oxidation with $CrO_3$–Py and then acid treatment with simultaneous epimerisation of C-5.

The homobrassinolide (**12**) (R = $C_2H_5$) was prepared from (**8**) in nine sequential steps: reduction of (**8**) with $LiAlH_4$ followed by treatment with 2,2-dimethoxy propane gave 24-hydroxy-ethyl-22,23-acetonide, which was then mesylated with methanesulphonyl chloride followed by reduction with $LiAlH_4$ to give 24-ethyl-22,23-acetonide; this compound was oxidised with $CrO_3$–Py followed by treatment with acid to give (**11**) (R = $C_2H_5$) in 59% overall yield; (**11**) (R = $C_2H_5$) was converted into homobrassinolide (**12**) m.p. 269—271 °C (lit[8] m.p. 268—271 °C) by using a procedure similar to that described for brassinolide.

Compound (**8**) could be readily converted to $\Delta^{24,28}$-compound which makes available dolicholide (**15**)[9] as shown in Scheme 1. The key step is the oxidative decarboxylation effected with iodobenzenediacetate. Thus, treatment of (**8**) with 4% KOH MeOH followed by acetylation and decarboxylation with iodobenzenediacetate in the presence of $Cu(OAc)_2$ gave $\Delta^{24,28}$-compound in 80% yield.

The new key intermediate (**8**) could be used for synthesis of natural promoting steroids, brassinolide (**1**), homobrassinolide (**12**), typhasterol (**13**), and dolicholide (**15**).

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## References

1 M. D. Grove, G. F. Spencer, W. K. Rohwedder, N. Mandava, J. F. Worley, J. D. Warthen, Jr., G. L. Steffens, J. L. Flippen-Anderson, and J. C. Cook, Jr., *Nature (London)*, 1979, **281**, 216.
2 (a) S. Fung and J. B. Siddall, *J. Am. Chem. Soc.*, 1980, **102**, 6580; (b) S. Takatsuto and N. Ikekawa, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2133; (c) K. Mori, M. Sakakinara and K. Okada, *Tetrahedron*, 1984, **40**, 1767; (d) J. R. Donaubauer, A. M. Greaun, and T. C. McMorris, *J. Org. Chem.*, 1984, **49**, 2833; (e) M. Anastasia, P. Alleri, P. Ciuffreda, A. Fiecchi, and A. Scalca, *ibid.*, 1984, **49**, 4297; (f) T. Kametani, T. Katoh, M. Tsubuki, and T. Honda, *J. Am. Chem. Soc.*, 1986, **108**, 7055; (g) W. S. Zhou and W. S. Tian, *Tetrahedron*, 1987, **43**, 3705.
3 W. S. Zhou and W. S. Tian, *Acta Chemia Sinica*, 1984, **42**, 1173.
4 Y. Z. Huang, L. L. Shi, and S. W. Li, *Synthesis*, 1988, 975.
5 T. Kametani, M. Kigawa, M. Tsubuki, and T. Henda, *J. Chem. Soc., Perkin Trans. 1*, 1988, 1503.
6 W. B. Motherwell, *J. Chem. Soc., Chem. Commun.*, 1973, 935.
7 J. A. Schreider, K. Yoshihoro, K. Nakanishi, and N. Kato, *Tetrahedron Lett.*, 1983, **24**, 2859.
8 S. Takatsuto and N. Ikekawa, *Chem. Pharm. Bull.*, 1982, **30**, 4181.
9 T. Yokota, J. Baba, and N. Takahashi, *Tetrahedron Lett.*, 1982, **23**, 4965.