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STUDY ON THE SYNTHESIS OF BRASSINOLIDE AND RELATED COMPOUNDS III
STEREOSELECTIVE SYNTHESIS OF TYPHASTEROL FROM HYODEOXYCHOLIC ACID

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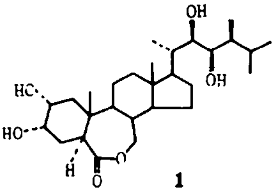
Abstract----Typhasterol **2** was synthesized stereoselectively from hyodeoxycholic acid **3**. The aldehyde **5** derived from **3** was reacted with the anion of 3-methylbutenolide under kinetic condition to afford (22R,23R)-**7** as the major product. Hydrogenation of **7** and its 22-acetate **14** over PtO_2-Pt/C yielded the expected compound **8** and **15**, respectively, in very good yield. Typhasterol was obtained from **8** and **15** through the following sequence of reaction **8**→**9**→**10**→**12**→**13**→**2** and **15**→**16**→**17**→**13**→**2**.

Since the discovery of novel plant-growth hormone brassinolide 1 in 1979[1], a number of new brassinosteroids in other higher plant have been isolated and identified[2]. A simple analogue of brassinolide isolated from cat-tail pollen (Typha latifolia L.) represents the first example of 2-deoxy-brassinosteroid plant-growth hormone[3]. Although synthesis of brassinolide and its analogues has been achieved by several research groups from stigmasterol or ergosterol as starting material[4], the synthesis of them starting from hyodeoxycholic acid 3 has not yet been reported. In our previous work, we have finished the conversion of A,B ring of hyodeoxycholic acid into the A,B ring of brassinolide[5] and the synthesis of a stereoisomer of typhasterol 2, (22S,23S)-**4** from 3[6]. We now wish to report here the synthesis of natural typhasterol 2 also starting from 3.



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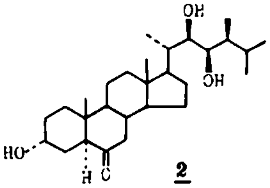

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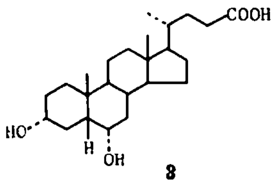

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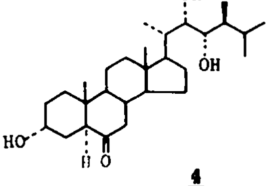

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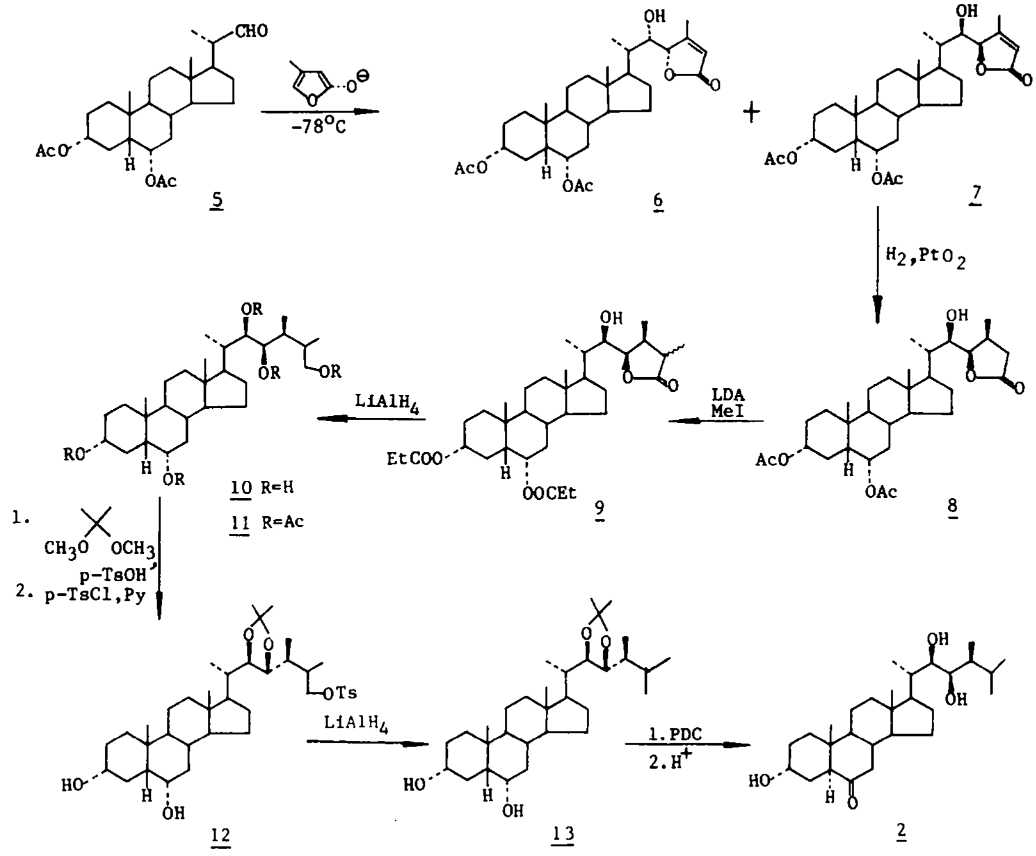
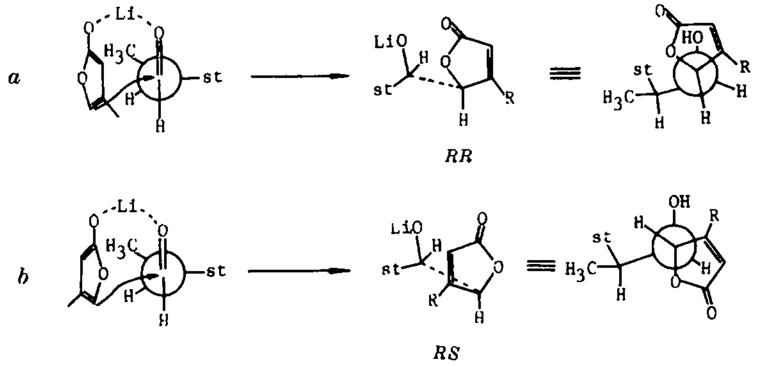


Scheme 1

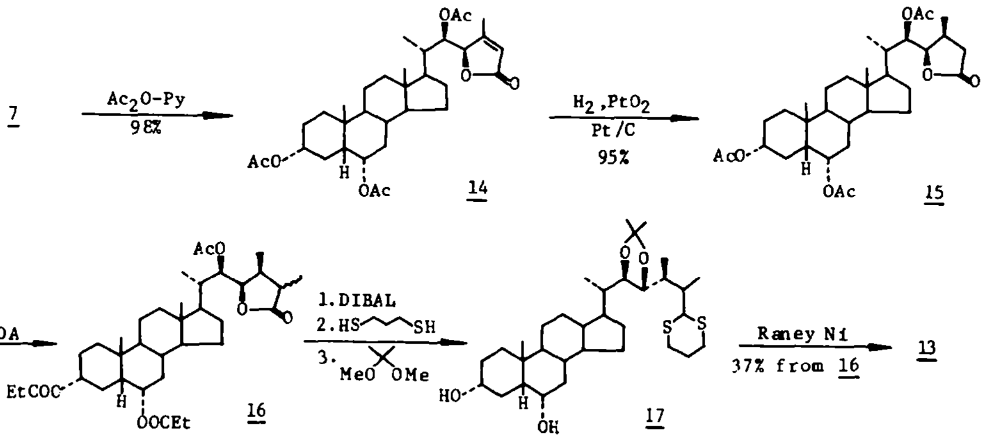


Scheme 2

The aldol reaction of the aldehyde **5** derived from **3** with the anion of 3-methylbutenolide generated in THF from butenolide and lithium diisopropylamide under kinetic condition yielded a mixture of the Cram **7** and anti-Cram **6** isomers in a ratio of 64:36(Scheme 1)[7]. The coupling constant for H-20 to H-22 in major Cram isomer **7**($J_{H(20)(22)}$=0Hz) was much smaller than that of H-20 to H-22 in the minor anti-Cram isomer **6**($J_{H(20)(22)}$=4.4Hz) and the configuration at C-22 in **7** was therefore assigned as R[8]. The stereochemistry at C-23 seems to be determined by the approach of the anion as shown in scheme 2[4d]. It is obvious that path a involves less steric interaction and is thus favored over path b, which results in the predominance of the 23 R stereochemistry. The configuration of C-23 was further confirmed by the CD curves(**7**:λmax 217nm,$\Delta\varepsilon$=11.9; **6**:λmax 227nm,$\Delta\varepsilon$=-3.7), which is in accord with that reported in literature[9]. Hydrogenation of **7** over PtO_2 yield **8** in 62% yield. The coupling constant for H-23 to H-24 in ^{1}H-NMR spectra of **8** is larger than 6Hz, and appears to be cis relationship for H-23 to H-24. Thus the configuration of C-24 was assigned as S[10].

Methylation of **8** with CH_3I in the presence of LDA occurred not only at C-25 but also at the α-carbon of two acetoxyl groups of C-3 and C-6 to give **9** in 89% yield. Reduction of **9** with $LiAlH_4$ in THF afforded pentahydroxy compound **10**. Acetonation of 10 with 2,2-dimethoxypropane followed by selective tosylation with p-toluenesulfonyl chloride and reduction with $LiAlH_4$ afforded **13**. Conversion of 13 to typhasterol **2** was achieved in 40% yield utilizing procedure similar to those reported by us[5,6]. The spectral data of **2** were identical with those reportd in litereture[3].

An improved route for the synthesis of **13** was achieved from **7** through the following sequence of reaction: **7→14→15→16→17→13** in 30% overall yield from **7** which is much better than that obtained from the above route: **7→8→9→10→12→13** in 7% overall yield from **7**.



Scheme 3

EXPERIMENTAL

The silica gel used for the chromatography was 100-200 or 200-300 mesh in size and GF_{254}, silica gel H,respectively. Iodine vapour and vanillin were used for colour developing.The m.p.s were uncorrected. The optical rotation was measured on Autopol III polarimeter. IR spectra were recorded as KCl disks on Zeiss-75 model spectrometer. ^{1}H-NMR spectra were recorded on Varian XL-200 (200MHz)spectrometers using TMS as an internal standard. The unit of δ was ppm. Mass spectra were run on JMS-01U and MAT 711 instruments. Elemental analyses were performed by Analytical Department of this Institute.

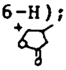
Condensation of 3α,6α-diacetoxyl 22,23-bisnor-cholanyl aldehyde 5 with 3-methylbut-2-enolide 5→6+7:

To a solution of 3.5ml of diisopropylamine and trace of α,α'-bipyridine in 30ml of dry THF was added 5ml of n-BuLi (1.8M/hexane) at -30°C under N_2 with stirring. A deep red solution was formed immediately. The reaction temperature was kept at -30°C for 30min and then allowed to warm to R.T. for further 30min. This LDA solution was cooled to -78°C, and a solution of 3-methylbut-2-enolide (1.6g) in 20ml of dry THF was added dropwise. After the red color was disappeared, a solution of aldehyde **5** (1g) in dry THF (50ml) was then added dropwise and the mixture was stirred for 7 h, and quenched with 10% HCl at -78°C. After extraction with CH_2Cl_2, the combined organic extracts were washed with brine, dried over Na_2SO_4. Removal of the solvent in vacuo followed by chromatography on silica gel(eluted solvent: benzene:acetone=9:1 or petroleum ether:ethyl acetate =4:1) gave 680mg of **7** in 55% yield and 280mg of **6** in 31% yield.

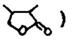
(22R,23R)-**7**: m.p. 194-195°C; $[\alpha]_D^{25}$+47.2°(c 0.14, $CHCl_3$); CD: λ_{max} (CH_3OH) 217nm($\Delta\varepsilon$=11.87); IR(KCl): 3400(OH), 1760, 1640(α,β-unsaturated lactone), 1730, 1240(acetate) cm^{-1}; ^{1}H-NMR(200MHz $CDCl_3$): 0.44(1H, s, OH), 0.69(3H, s, 18-H), 0.98(3H, s, 19-H), 1.11(3H, d, J=6.6Hz, 21-H), 2.02, 2.05(6H, 2s,2xCH_3CO), 2.11 (3H, s, 28-H), 3.86(1H, s, 22-H), 4.71(1H, m, 3-H), 4.77(1H, s, 23-H), 5.15(1H, m, 6-H), 5.88(1H, s, 25-H); MS m/z 531(M^++1), 471(M^+-CH_3CO_2), 410(M^+-2xCH_3CO_2H), 312(M^+-98-2xCH_3CO_2H), 98(); Found: C, 70.37, H,8.80; Calcd. for $C_{31}H_{46}O_7$: C, 70.19, H, 8.75.

(22S,23S)-**6**: m.p. 219-221°C; $[\alpha]_D^{28}$+55.1°(c 0.96, CH_3Cl); CD: λ_{max}(CH_3OH) 227nm($\Delta\varepsilon$=-3.68); IR(KCl): 3400(OH), 1760,1640(α,β-unsaturated lactone), 1730, 1240(acetate) cm^{-1}; ^{1}H-NMR(200MHz $CDCl_3$): 0.70(3H, s, 18-H), 0.99(3H, s, 19-H), 1.08(3H, d, J=7Hz, 21-H), 2.02, 2.05(6H, 2s, 2xCH_3CO), 2.10(3H, s, 28-H), 3.89 (1H, d, J=4.4Hz, 22-H), 4.71(1H, m, 3-H), 4.90(1H, s, 23-H), 5.16(1H, m, 6-H), 5.88(1H, m, 25-H); MS m/z: 531(M^++1), 470(M^+-CH_3CO_2H), 410(M^+-2xCH_3CO_2H), 312 (M^+-98-2xCH_3CO_2H),98(); Found: C, 70.66, H, 8.88; Calcd. for $C_{31}H_{46}O_7$: C, 70.19, H, 8.75.

Hydrogenation of (22R, 23R)-7 with Adams' catalyst 7→8:

7(100mg) dissolved in glacial acetic acid (6ml) was hydrogenated over PtO_2 (5mg) at room temp. for 10h. The catalyst was filtered off and the filtrate was poured into cold water (10ml). The precipitate was purified by flash column chromatography on silica gel to give **8** (62mg) in 62% yield. m.p. 120-124°C $[\alpha]_D^{17}$-12.2°(c 0.49, $CHCl_3$); IR(KCl): 3450(OH), 1764(lactone),1720,1240(acetate) cm^{-1}; ^1H-NMR(200MHz $CDCl_3$): 0.67(3H, s, 18-H), 0.91(3H, d, J=6Hz, 21-H), 0.96 (3H, s, 19-H), 1.09(3H, d, J=7Hz, 28-H), 2.01, 2.04(6H, 2s, $2xCH_3CO$), 3.97 (1H, d, J=6Hz, 22-H), 4.41(1H, dd, J=6Hz, 6Hz, 23-H), 4.70(1H, m, 3-H), 5.41(1H, m, 6-H); MS m/z: 472(M^+-CH_3CO_2H), 412(M^+-$2xCH_3CO_2H$), 313(M^+-CH_3CO_2H-CH_3CO_2-99), 99().

Methylation of 8 with LDA and methyl iodide 8→9:

To a solution of diisopropylamine (1.2ml) and trace of 2,2'-dipyridine in 5ml of dry THF was added dropwise n-BuLi (2.4ml, 1.6M/ether) at -30°C under N_2. It was stirred at -30°C for 30 min and at room temperature for further 30 min. A deep red solution of LDA was formed. It was cooled to -78°C and a solution of **8**(260mg) in THF(16ml) was added. The mixture was stirred for 30min. When the red color of solution was discharged, 0.6ml of methyl iodide was added slowly. The reaction was kept at -78°C for 2h and quenched by addition of 10% HCl. The mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluted solvent: petroleum ether: ethyl acetate= 5:1) to give **9**(250mg) in 83% yield. m.p. 236-237°C; $[\alpha]_D^{25}$-18.4°(c 0.64, $CHCl_3$); IR(KCl): 3400(OH), 1720(lactone) cm^{-1}; ^1H-NMR(200MHz $CDCl_3$): 0.68(3H, s, 18-H), 0.99(3H, s, 19-H), 1.13(3H, d, J=4.6Hz, 21-H), 1.15(3H, d, J=4.8Hz, 28-H), 1.25(3H, d, J=7.2Hz, 26-H), 3.88(1H, d, J=4.4Hz, 22-H), 4.41(1H, dd, J=4.4Hz, 6.6Hz, 23-H), 4.70(1H, m, 3-H), 5.18(1H, m, 6-H); MS m/z: 576(M^+), 501(M^+-$C_3H_6O_2$), 313(M^+-114 -$2xC_3H_6O_2$), 114(), 57(CH_3CH_2CO); Found: C, 70.90, H, 9.54; Calcd. for $C_{34}H_{56}O_7$ C, 70.83, H, 9.72.

Reduction of 9 with lithium aluminum hydride 9→10→11:

$LiAlH_4$(120mg) was added to the solution of **9** (120mg) in dry THF (10ml). The mixture was refluxed for 3.5 h. After cooling to room temperature the excess of $LiAlH_4$ was destroyed by addition of ethyl acetate, and then the mixture was extracted with CH_2Cl_2. The extract was worked up as usual to give 98mg of **10**. MS m/z: 476(M^++1), 449(M^+-H_2O), 431(M^+-$2xH_2O$).

30mg of **10** in pyridine(1ml) was treated with acetic anhydride(1ml) at room temp. to afford **11**(33mg) in 75.8% yield. m.p. 155-157°C; ^1H-NMR(200MHz CD_3COCD_3): 0.74(3H, s, 18-H), 0.94(3H, d, J=6.8Hz, 21-H), 0.98(3H, d, J=7Hz, 28-H), 0.99(3H, s, 19-H), 1.04(3H, d, J=6.6Hz, 26-H), 1.97, 1.98, 1.99, 2.01 (15H, 4s, $5xCH_3CO$), 4.01(2H, d, J=6Hz, 27-H), 4.32(1H, m, 3-H), 5.09(1H, m,6-H), 5.18(1H, d, J=9Hz, 22-H), 5.28(1H, d, J=9Hz, 23-H); MS m/z: 617(M^+-CH_3CO_2); 557 (M^+-CH_3CO_2-CH_3CO_2H),497(M^+-$2xCH_3CO_2H$-CH_3CO_2).

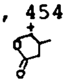
Conversion of 10 into 13:

To a solution of **10**(100mg) in CH_2Cl_2(1ml) was added 2,2'-dimethoxylpropane (1ml) and p-TsOH(10mg). The solution was stirred at room temp. for 2h and then concentrated in vacuo to remove the excess of 2,2'- dimethoxylpropane. To the crude acetonide dissolved in pyridine(1ml) was added p-toluenesulfonyl chloride (50mg) at 0°C, standing 1h. After stirring at room temp. for 3h the solution was poured onto cooled water, and the precipitate was reduced with $LiAlH_4$ in ether(6ml) at room temp. for 10h. Work up as usual, the crude product was purified by chromatography on silica gel to afford **13**(15mg) in 14% overall yield from **10**. m.p. 166-168°C; ^1H-NMR(200MHz $CDCl_3$): 0.64(3H, s, 18-H), 0.86(3H, d, J=7Hz, 26-H), 0.87(3H, d,J=8.2Hz, 28-H), 0.91(3H, s, 19-H), 0.94(3H, d, J=6.8Hz, 27-H), 0.97(3H, d, J=5.4Hz, 21-H), 1.34, 1.37(6H, 2s, $(CH_3)_2C$); MS m/z: 489 (M^+-1), 475(M^+-CH_3), 419(M^+-171), 171().

Acetylation of 7 with acetic anhydride and pyridine 7→14:

A solution of **7**(217mg) in acetic anhydride(4ml) and pyridine(4ml) was allowed to stand at room temp. for 24h and then it was poured onto 30ml of cooled water. The precipitate was recrystallized from acetone-isopropyl ether to give 230mg of **14** in 98% yield. m.p. 209-211°C; $[\alpha]_D^{21}$+62.4°(c 0.1, CH_3OH); IR(KCl): 3015(=CH), 1700, 1650(α,β-unsaturated lactone), 1740, 1240(acetate) cm^{-1}; ^1H-NMR(200MHz $CDCl_3$): 0.69(3H, s, 18-H), 0.97(3H, s, 19-H), 1.16(3H, d, J=6.8Hz, 21-H), 2.02, 2.04(9H, 2s, $3xCH_3CO$), 2.10(3H, d, J=7Hz, 28-H), 4.63(1H, s, 23-H), 5.05(1H, s, 22-H), 5.57(1H, brs, 25-H), MS m/z: 573(M^++1), 513(M^+-CH_3CO_2), 453(M^+-CH_3CO_2H-CH_3CO_2), 393(M^+-$2xCH_3CO_2H$-CH_3CO_2), 313(M^+-$2xCH_3CO_2H$-CH_3CO_2-98), 98().

Hydrogenation of 14 over Pt/C-PtO_2 14→15:

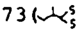
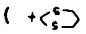
To a suspension of PtO_2(10mg) and 10%Pt/C in 2ml of glacial acetic acid was added a solution of dioxane (4ml) containing **8** (126mg) at room temp. under H_2. The mixture was continually stirred for 20h, and the catalyst was filtered off and the solvent was concentrated under reduced pressure. The residue was recrystallized from diisopropyl ether to give **15**(120mg) in 95% yield. m.p.211-213°C; $[\alpha]_D^{21}$-11.87°(c 0.23, CH_3OH); IR(KCl): 1790(lactone), 1740, 1240(acetate) cm^{-1}; ^1H-NMR(200MHz $CDCl_3$): 0.68(3H, s, 18-H), 0.97(3H, s, 19-H), 1.03(3H, d, J=6.8Hz , 21-H), 1.11(3H, d, J=6.8Hz, 28-H), 4.50(1H, dd, J=8.4Hz, 6Hz, 23-H), 5.24(1H, d, J=8.4Hz 22-H); MS m/z: 575(M^++1), 515(M^+-CH_3CO_2), 454(M^+-$2xCH_3CO_2H$), 395(M^+-$2xCH_3CO_2H$-CH_3CO_2), 313(M^+-$2xCH_3CO_2H$-CH_3CO_2-99), 99().

Methylation of 15 15→16:

Methylation of **15** was the same as that of **8** in yield of 89%. m.p. 94-98°C; ^1H-NMR(200MHz $CDCl_3$): 0.66(3H, s, 18-H), 0.97(1H, s, 19-H); MS m/z: 557(M^+-$CH_3CH_2CO_2$), 482(M^+-$CH_3CH_2CO_2H$-$CH_3CH_2CO_2$), 409(M^+-$CH_3CH_2CO_2H$-$2xCH_3CH_2CO_2$).

Conversion of 16 into 17:

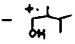
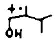
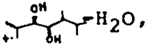
To a solution of **16** (74mg) in toluene (2ml) was added dropwise 0.4ml of the diisobutyl aluminum hydride (DIBAL, 1M/toluene) at- 78°C under N_2. The solution was kept at -78°C for 5h. The solution was allowed to come to room temp., and poured onto the saturated NH_4Cl and extracted with CH_2Cl_2. The extract was worked as usual manner to give **64**mg of product. IR(KCl): 3400(OH) cm^{-1}.

The product dissolved in 4ml of CH_2Cl_2 was treated with $TiCl_4$ (0.4ml) and propane 1,3-dithiol. The mixture was stirred at room temp. for 27h and extracted with CH_2Cl_2. The extract was washed with 5% NaOH, brine and dried over Na_2SO_4. After removal of the solvent, the residue was treated with 4ml of 2,2'-dimethoxy propane in the presence of p-TsOH(10mg) at room temp. for 8h. Work up gave 80mg of **17** which could be used directly for next step without further purification. ^1H-NMR(200MHz $CDCl_3$): 0.64(3H, s, 18-H), 0.91(3H, s, 19-H), 0.93(3H, d, J=7.4Hz, 21-H), 0.97(3H, d, J=7.4Hz, 28-H), 1.09(3H, d, J=6.8Hz, 26-H), 1.35, 1.38(6H,2s, $(CH_3)_2C$), 2.88(4H, m, $-SCH_2CH_2CH_2S-$), 4.11(1H, d, J=6Hz, -SCHS-); MS m/z: 594 (M^+), 579(M^+-CH_3), 173(), 146(), 119().

Hydrogenolysis of 17 over Raney Ni 17→13:

To a suspension of Raney Ni (10mg) in 10ml of absolute ethanol was added a solution of **17** (80mg) in ethanol under H_2. The mixture was refluxed for 9h and the catalyst was filtered and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel to give **13** (21mg) in 37% overall yield from **16**. m.p. 166-168°C. The m.p. of this compound was not depressed on mixing with that obtained in the previous experiment. ^1H-NMR(200MHz $CDCl_3$): 0.64(3H. s, 18-H), 0.86(3H,d, J=7Hz, 26-H), 0.87(3H, d, J=8.2Hz, 28-H), 0.91 (3H, s, 19-H), 0.94(3H, d, J=6.8Hz, 27-H), 0.97(3H, d, J=5.4Hz, 21-H), 1.34, 1.37(6H, 2s, $(CH_3)_2C$); MS m/z: 489(M^+-1), 475(M^+-CH_3), 419(M^+-171), 171().

Typhasterol 2:

To a solution of 13(18mg) in CH_2Cl_2(2.5ml) was added PDC(20mg). After the solution was stirred at room temp. for 2.5h, acetone(5ml) was added and filtered. The filtrate was concentrated under reduced pressure to give the residue which was dissolved in 5% HCl-MeOH (5ml) and allowed to stand overnight followed by chromatography on silica gel to afford **2** (3mg). m.p. 225-228°C(CH_3OH-H_2O)(Lit[3] m.p. 227-230°C); ^1H-NMR(400MHz,$CDCl_3$): 0.68(3H, s, 18-H), 0.72(3H, s, 19-H), 0.74(3H, d, J=7Hz, 28-H), 0.80(3H, d, J=6.9Hz, 21-H), 0.93(3H,d,J=6.9Hz, 26-H), 1.03(3H, d,J=6.9Hz, 27-H), 1.74(2H, dd, J=8.3Hz, 2.5Hz, 4-H),2.30(1H, dd,J=13Hz, 4.5Hz,7β-H), 2.61(1H, t, J=8Hz,5α-H), 3.44(1H, d, J=9.3Hz, 22-H), 3.68(1H,d, J=4.1Hz, 23-H), 4.15(1H, $W_{1/2}$=6.5Hz, 3-H); HRMS m/z: 449.3589(M^++1, requires 449.3631, $C_{28}H_{49}O_4$), 348.2609(M^+-  , requires 348. 2665 $C_{22}H_{26}O_3$), 329.2460 (M^+-  $-H_2O$, requires 329.2482, $C_{22}H_{33}O_2$), 271.2039(M^+-H_2O, requires 271.2062, $C_{19}H_{27}O$).

References and Notes

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