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# SYNTHETIC STUDY ON BREYNIN A : SYNTHESIS OF BREYNOLIDE SULFONE

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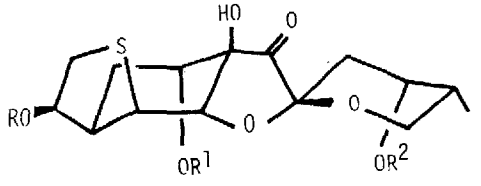
Summary: In connection with breynin A having a significant hypocholesterolemic activity in rats, an optically active perhydrobenzothiophene has been synthesized starting from L-carvone in 11% overall yield. Furthermore, this sulfur-containing bicyclic segment has been successfully converted into an oxygenated breynolide.

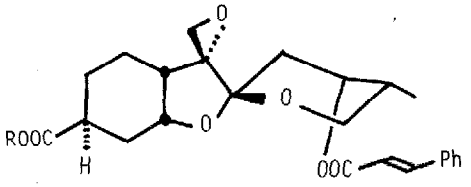
Breynin A (**1**), isolated from the plant Breynia officinalis H. growing in Taiwan, shows a remarkable hypocholesterolemic activity in rats.[1] On the basis of an X-ray crystallographic analysis of breynolide (**2**),[2] an acid-hydrolysis product of breynin A, it was determined that breynin A has a glycoside structure carrying breynogenin (**3**) as the aglycon which involves a novel perhydrobenzothiophene and spiroketal moieties. However, positions of sugars (D-glucose and L-rhamnose) in **1** remain undecided. From a structural point of view, breynin A is quite similar to phyllanthoside (**4**),[3] although its structure is more complex than that of **4**. We describe herein the first synthesis of an oxygenated breynolide (**5**) starting from L-carvone through a perhydrobenzothiophene (**6**) as a synthetic key-intermediate, from which breynin A (**1**) will be derived.



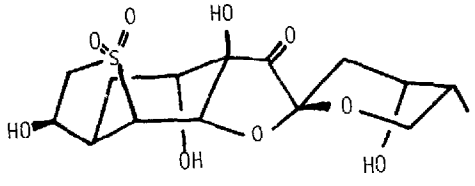

**1** : R, $R^1$ = Sugar (not decided)
$R^2$ = p-HO-$C_6H_4CO$

**2** : R = $R^1$ = $R^2$ = H

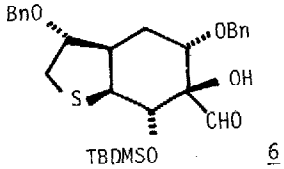
**3** : R = $R^1$ = H, $R^2$ = p-HO-$C_6H_4CO$




**4** : R = 3-O-Acetyl-2-O-(3-O-acetyl-β-D-chinovosyl)-β-D-chinovosyl

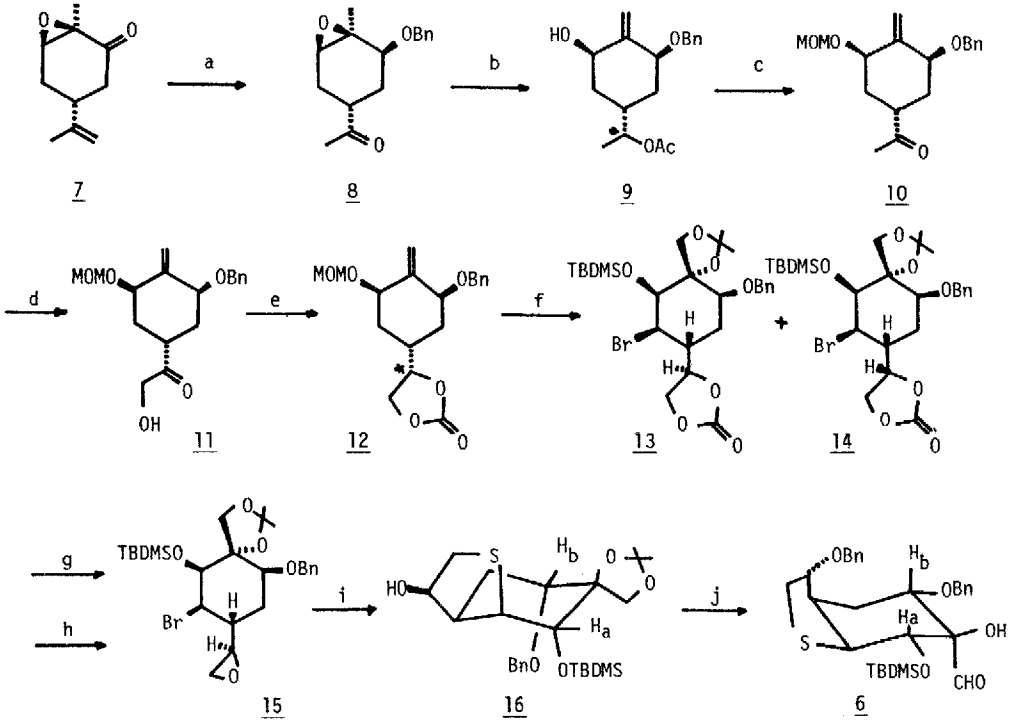



**5**




**6**

The known epoxide (**7**)[4] of L-carvone was readily converted into the corresponding ketone (**8**),[5] in 81% overall yield. This ketone was treated with $NaBH_4$ and then with $Ac_2O$-pyridine to afford two epimeric acetates which were converted into the corresponding allyl alcohols (**9**),[5] in 94% overall yield, according to Noyori's procedure.[6] The mixture of two epimers was further converted into the ketone (**10**)[5] as a sole product, in 87% overall yield, as shown in Scheme 1. where direct conversion of **8** to **10** has not given any good result. This ketone (**10**) so far obtained was subjected to oxidative hydroxylation using $MoO_5$-HMPA-pyridine complex to afford an α-hydroxy ketone (**11**),[5] in 71% yield, which was further treated with $NaBH_4$ and then carbonyl diimidazole to afford a mixture of two carbonates (**12**),[5] in 91% overall yield. As

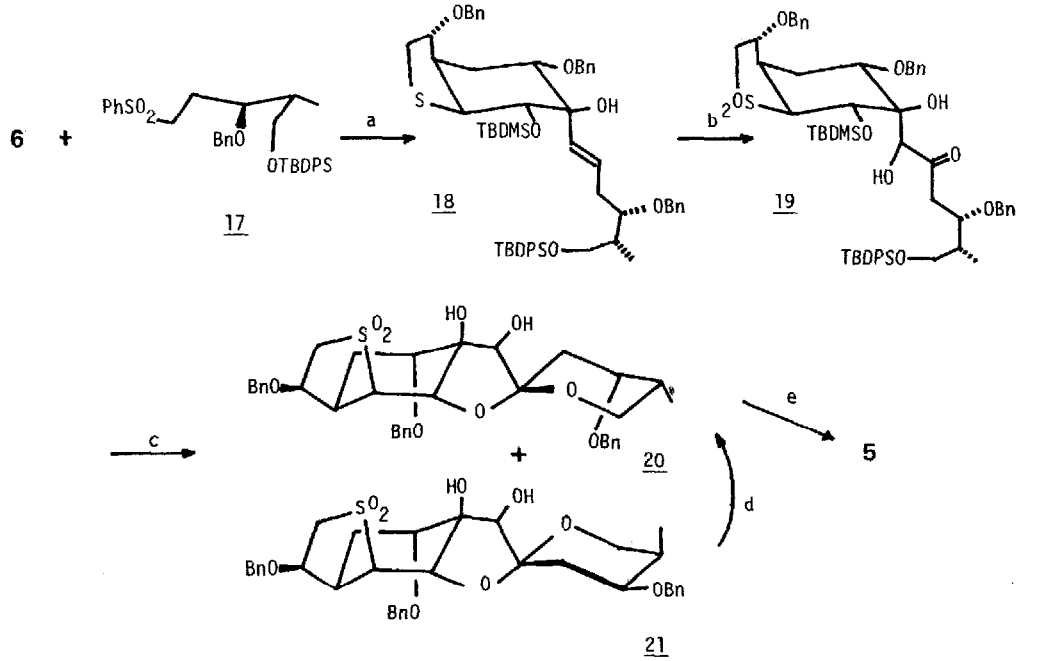



a)i.L-Selectride/THF (-78°C, 2h) (100%), ii.BnBr-NaH/THF (room temp., overnight) (100%), iii. $O_3$/MeOH (-78°C, 15min) and then $Me_2S$ (81%). b)i. $NaBH_4$/EtOH (0°C, 2h) (100%), ii.$Ac_2O$-pyridine (room temp., overnight) (100%), iii.TMSOTf-2,6-lutidine/$CH_2Cl_2$ under argon (-78°C, 4.5h), DBU (2 equiv.) (-78°C, 3h) and then $H^+$/MeOH (room temp., 1h) (94% overall yield). c)i. MOMCl-$^iPr_2NEt$/$(ClCH_2)_2$ (80°C, 4h) (87%), ii.$K_2CO_3$/MeOH (room temp., overnight) (100%), iii.PDC -Celite/$CH_2Cl_2$ (room temp., overnight) (100%). d)MoOPH (1.3 equiv.)-LiN$(TMS)_2$ (1.1 equiv.)/ THF under argon (-40°C, 2h) (71%). e)i. $NaBH_4$/EtOH (0°C, 0.5h) (91%), ii.$(Imd)_2CO$/ PhH (refluxing temp., overnight) (100%). f)i.$OsO_4$ (0.3 equiv.)-NMMO/$H_2O$-acetone-$^tBuOH$ (4:2:1) (room temp., 1 day) (100%), ii.acetone-TsOH under argon (refluxing temp., 3 days) (90%), iii. PDC/DMF (60°C, 3h) (93%), iv.pyr.$HBr_3$/THF (room temp., 3h), $NaBH_4$ (room temp., 30min) and then 2,2-dimethoxypropane-TsOH/acetone (room temp., 1h), (69% overall yield), v.$^tBuMe_2SiCl$-$Et_3N$/ $CH_2Cl_2$ (room temp., 7h) (100%). g)i.$K_2CO_3$/MeOH (room temp., 1h) (93%), ii.MsCl/pyridine (-25° - -10°C, 3h) (87%), iii.NaOMe/MeOH (0°C - room temp., 1h) (100%). h)i. $K_2CO_3$/MeOH (room temp., 1h) (93%), ii.BzCl-pyridine/$CHCl_3$ (0°C - room temp., 1 day) (100%), iii.MsCl-pyridine/ $CH_2Cl_2$ (room temp., overnight) (89%), iv.NaOMe/MeOH (room temp., overnight) (75%). i)$Na_2S$ (3 equiv.)/DMF under argon (room temp., 2h) (67%). j)i.BnBr-NaH/DMF (room temp., 1h) (95%), ii.$(HSCH_2)_2$ (10 equiv.)-TsOH/$CHCl_3$ (room temp., 7.5h) (100%), iii.Swern oxidation (-50°C, 45min) (100%).

Scheme 1. Synthesis of a perhydrobenzothiophene (**6**).

seen in Scheme 1., this mixture was stereoselectively converted into a separable mixture of two epimers (**13** and **14**; **13**/**14** ≃ 1)[5] in 7 steps (58% overall yield). The former (**13**) was hydrolyzed with $K_2CO_3$ to afford the corresponding diol, which was further subjected to selective mesylation followed by treatment with NaOMe to give rise to a desired epoxide (**15**),[5] in 81% overall yield. This epoxide was also obtained from **14** in 62% overall yield, wherein $S_N2$ inversion took place at the carbon atom bearing the sec. OH group on epoxidation. Thus, total yield of **15** from the mixture of **13** and **14** is 71%. Furthermore, the epoxide (**15**) was treated with $Na_2S$ in DMF to give a sulfur-containing bicyclic compound (**16**),[5] in 67% yield, which was readily converted into the desired perhydrobenzothiophene (**6**),[5] in almost quantitative yield. As judged from the $^1H$ NMR spectral data [δ 3.68(d, J= 10 Hz) (Ha) and 3.56 (dd, J= 5, 11 Hz) (Hb) in **6**; δ 3.88(d, J= 3 Hz) (Ha) and 3.53(t, J= 4 Hz) (Hb) in **16**], the conformation of **6** is different from that of breynolide (**2**), while **16** adopts the same conformation as that of **2**, suggesting that both two conformers seem to be reversible to each other.

In the next step, the perhydrobenzothiophene (**6**), synthesized from L-carvone in 11% overall yield, was converted into the oxygenated breynolide (**5**), as shown in Scheme 2.. When treated with the sulfone (**17**) derived from L-tartaric acid[7] in the presence of LDA as a base, the aldehyde (**6**) was converted into a hydroxy sulfone, in 62% yield, which was subjected to Na-Hg reduction to afford a trans olefin (**18**)[5] in 42% yield. Furthermore, this olefin (**18**) was treated with $OsO_4$ in pyridine and then subjected to Swern oxidation to give an




a)i.LDA/THF under argon (-78°C, 1.5h) (62%), ii.Na-Hg, $Na_2PO_4$/MeOH under argon (room temp., 1.5h) (42%). b)i.excess $OsO_4$/pyridine (room temp., overnight) and then $Na_2S_2O_4$ (room temp., 2h) (74%), ii.Swern oxidation (-50°C, 45min) (95%). c)i.$^nBu_4NF$ (0°C, 2h) (89%), ii.CSA/PhH (room temp., overnight) (100%: **20**/**21**= 2). d)CSA/PhH (refluxing temp.). e)i.Moffatt oxidation (0°C - room temp.) (100%), ii. $H_2$-Pd black/cyclohexene-MeOH (1:4) (room temp., 1 day) (100%).

Scheme 2. Synthesis of the oxygenated breynolide (**5**).

α-hydroxyketone (**19**),[5] in 70% overall yield, which was desilylated with $^{n}Bu_4NF$ and then treated with camphorsulfonic acid (room temp., overnight) to afford a mixture of two ketals (**20** and **21**)[5] in quantitative yield (**20**/**21** = 2). On repeated acid-catalyzed equilibrium using camphorsulfonic acid, the later was converted into the desired one (**20**), in more than 95% yield. The $^1H$ NMR spectrum of **20** has the methyl doublet at δ 0.90 (J= 7 Hz) similar to that of breynolide (**2**) [δ 0.82 (d, J= 6.9 Hz), while in **21** the corresponding signal is observed at δ 1.03 (d, J= 7 Hz)]. Finally, this ketal (**20**) was subjected to Moffatt oxidation followed by catalytic hydrogenation to give rise to the oxygenated breynolide (**5**)[5] in quantitative yield. This compound (**5**) was completely identical with the sulfone derivative of breynolide, which was obtained by mCPBA oxidation of **2**, in all respects of their spectral data. Further synthetic study on breynin A is in progress.

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## References

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5. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: **8**: $C_{16}H_{20}O_3$ [m/z260.1419($M^+$)]; IR (film) 1705 $cm^{-1}$; δ($CDCl_3$) 2.08(3H, s) and 3.07(1H, t, J= 2 Hz). **9**: $C_{18}H_{24}O_4$ [m/z304.1672($M^+$)]; δ($CDCl_3$) 4.96(1H, broad s) and 5.17(1H, broad s). **10**: $C_{17}H_{21}O_3$ [m/z273.1496($M^+$-OMe)]; IR (film) 1710 $cm^{-1}$; δ ($CDCl_3$) 2.16(3H, s), 3.35(3H, s), 5.13(1H, d, J= 2 Hz), and 5.20(1H, d, J= 2 Hz). **11**: $C_{11}H_{21}O_4$ [m/z289.1446($M^+$-OMe)]; IR (film) 3470 and 1715 $cm^{-1}$; δ($CDCl_3$) 3.37(3H, s), 4.02(1H, t, J= 3 Hz), and 4.36(2H, s). **12**: $C_{17}H_{19}O_5$ [m/z303.1235($M^+$-$CH_2OMe$)]; IR (film) 1800 $cm^{-1}$; δ($CDCl_3$) 3.33(3H, s), 5.16 (1H, d, J= 2 Hz), and 5.23(1H, d, J= 2 Hz). **13**: $C_{25}H_{36}O_7Si^{79}Br$ [m/z555($M^+$-Me)]; IR (film) 1800 $cm^{-1}$; δ($CDCl_3$) 0.86(9H, s), 3.57(1H, broad s), and 5.16(1H, m). **14**: $C_{25}H_{36}O_7Si^{79}Br$ [m/z555($M^+$-Me)]; IR (film) 1810 $cm^{-1}$; δ($CDCl_3$) 0.80 (9H, s), 3.55(1H, broad s), and 5.22(1H, m). **15**: $C_{24}H_{36}O_5Si^{81}Br$ [m/z513.1494($M^+$-Me)]; δ ($CDCl_3$) 2.65(1H, dd, J= 3, 5 Hz), 2.83(1H, m), 2.91(1H, dd, J= 4, 5 Hz), 3.50(1H, t, J= 1 Hz), and 3.92(1H, d, J= 2 Hz). **16**: $C_{25}H_{40}O_5SSi$ [m/z480.2367($M^+$)]; IR (film) 3470 $cm^{-1}$; δ ($CDCl_3$) 2.78(1H, dd, J= 2, 12 Hz), 3.20(1H, dd, J= 4, 12 Hz), 3.53(1H, t, J= 4 Hz), 3.66 (1H, dd, J= 3, 5 Hz), and 3.88(1H, d, J= 3 Hz). **6**: $C_{25}H_{31}O_5SSi$ [m/z471.1678($M^+$-$^tBu$)]; $[\alpha]_D^{25}$ +91.5° (c 0.96, $CHCl_3$); IR (film) 3510 and 1730 $cm^{-1}$; δ($CDCl_3$) 2.74(1H, dd, J= 9, 10 Hz), 3.12(1H, dd, J= 6, 10 Hz), 3.50(1H, dd, J= 8, 10 Hz), 3.56(1H, dd, J= 5, 11 Hz), 3.68 (1H, d, J= 10 Hz), and 9.88(1H, s). **18**: $[\alpha]_D^{26}$ +52.3° (c 1.1, $CHCl_3$); IR (film) 3580 $cm^{-1}$; δ($CDCl_3$) 0.91(3H, d, J= 8 Hz), 2.65(1H, dd, J= 9, 10 Hz), 3.08(1H, dd, J= 6, 10 Hz), 3.45 (1H, d, J= 10 Hz), and 5.73(1H, d, J= 15.5 Hz). **19**: IR (film) 3430, 1710, and 1300 $cm^{-1}$; δ($CDCl_3$) 2.32(1H, dd, J= 3, 15 Hz), 3.04(1H, m), 3.86(1H, dd, J= 1.5, 12 Hz), and 4.67(1H, d, J= 2 Hz). **20**: IR (film) 3480 and 1300 $cm^{-1}$; δ($CDCl_3$) 0.90 (3H, d, J= 7 Hz). **21**: IR (film) 3520 and 1300 $cm^{-1}$; δ($CDCl_3$) 1.03(3H, d, J= 7 Hz). **5**: mp 225°C (dec.); $[\alpha]_D^{31}$ +64.4° (c 0.16, MeOH); IR (KBr) 3450, 1785, and 1300 $cm^{-1}$; δ(DMSO-$d_6$+$D_2O$) 0.83(3H, d, J= 7 Hz), 1.6-1.8(4H, complex), 2.86(1H, m), 3.13(1H, dd, J= 3, 14 Hz), 3.67(1H, m), 3.88(1H, m), 4.22(1H, m), and 4.43(1H, broad s).
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7. Compound **17** was synthesized from the known triol[8] in 9 steps. The details will be published elsewhere.
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