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STEREOISOMERS OF COLEONOL (FORSKOLIN) AND RELATED DITERPENOIDS

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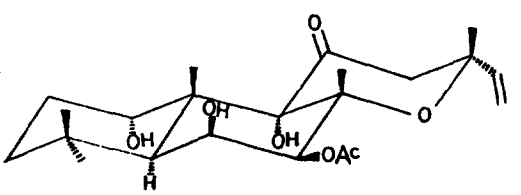
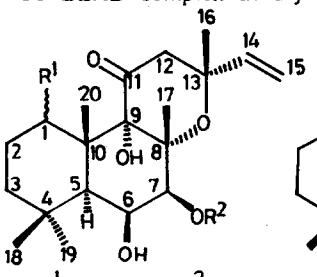
Abstract: Regioselective Mitsunobu inversion of the hydroxyl groups of coleonol (forskolin) led to new, unnatural epimers as potential adenylate cyclase stimulant and pharmacodynamic agents.

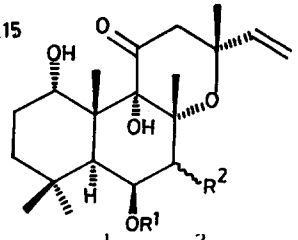
Coleonol (Forskolin, 1α, 6β, 9α-trihydroxy-7β-acetoxy-8, 13-epoxy-labd-14-en-11-one, **1**), a labdane diterpenoid isolated[1] from the Indian medicinal plant Coleus forskohlii and a potential drug for glaucoma, congestive heart-failure and bronchial asthma, activates adenylate cyclase in unique manner by direct and reversible action on catalytic subunit of the enzyme in absence of guanine nucleotide stimulating protein[2]. Forskolin, owing to its highly oxygenated structure and novel pharmacodynamic action, has emerged as a highly attractive target for synthetic investigations[2].

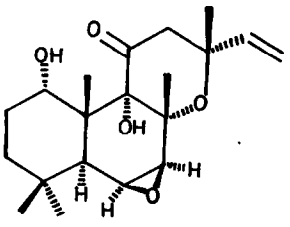
During our studies on the physiological effects of Coleonol (Forskolin) and its analogues, we decided to prepare new and unnatural stereoisomers (epimers) of **1** to correlate biological activity with the stereochemical orientation of various hydroxyl groups. Herein we report the synthesis of various 1-epi- and 7-epi coleonols (forskolins) and 6,7-epoxy-6,7-dideoxycoleonol using versatile Mitsunobu reaction[3] which has become a useful tool in organic synthesis with stereochemical outcome being almost invariably a clean inversion of configuration of secondary hydroxyl centres. The reaction of **1** (1 mmol) with triphenylphosphine (TPP, 3 mmol), diethyl-azodiacarboxylate (DEAD, 3 mmol) and benzoic acid (1.1 mmol) in dry THF at room temperature for 36 h gave compound **2** after chromatography and characterized as 1β-benzoyloxy-1-deoxy-coleonol (yield 45%). The PMR spectra of **2** showed[4] dd at δ 5.75 ($J_{ax/ax}$ = 10 Hz, $J_{ax/eq}$ = 2Hz) assigned to 1-α-axial proton coupled with two neighbouring C-2ax and C-2eq protons. Debenzoylation of **2** with methanolic NaOMe at r.t. yielded 1-epi-7-deacetylcoleonol (**3**) which on selective acetylation (Ac_2O, Py, 0-5°) gave 1-epi coleonol (**4**). The stereochemistry of C_1-OH of **4** was assigned as β-equatorial by PMR[5] which showed dd at 3.95 ($J_{ax/ax}$ = 9.5 & $J_{ax/eq}$ = 2.0 Hz). A recently modified Mitsunobu procedure[6] to obtain equatorial vs axial-hydroxyl selectivity using trifluoroacetic acid (TFA) as nucleophile and sodium benzoate as catalyst was used to synthesize 7α-axial epimer of **1**. The 7-deacetylcoleonol (**5**) prepared by deacetylation of **1**, on Mitsunobu reaction using TFA (1.1 mole equivalent) and NaOBz afforded 7-deacetyl-7-epi-trifluoro-acetylcoleonol (**6**) in 60% yield. The PMR of **6** showed[7] d at 5.50 (J = 2 Hz) for 7-β-equatorial CH proton. The hydrolysis of **6** by refluxing in MeOH led to 7-deacetyl-7-epi-coleonol (**7**). The reaction of coleonol-B (6-acetyl-7-deacetylcoleonol, **8**) with TPP-DEAD complex using TFA and NaOBz gave 6-acetyl-7-deacetyl-7-epi-trifluoroacetylcoleonol (**9**) which on selective hydrolysis (reflux in MeOH) gave



7-epi coleonol-B (**10**). Further hydrolysis (NaOMe in MeOH at r.t.) **9** gave **7**. An interesting product, 6,7-epoxy-6,7-dideoxycoleonol (**11**) was formed when 7-deacetylcoleonol (**5**) was reacted with TPP-DEAD complex in dry THF in absence of acidic component. The result indicated







1, R^1 = α-OH, R^2 = Ac
2, R^1 = β-OBz, R^2 = Ac
3, R^1 = β-OH, R^2 = H
4, R^1 = β-OH, R^2 = Ac

5, R^1 = H, R^2 = β-OH
6, R^1 = H, R^2 = α-$OCOCF_3$
7, R^1 = H, R^2 = α-OH
8, R^1 = Ac, R^2 = β-OH
9, R^1 = Ac, R^2 = α-$OCOCF_3$
10, R^1 = Ac, R^2 = α-OH

11

the inversion at C-7 being successful but followed by an intramolecular nucleophilic displacement by free hydroxyl at C-6. The stereochemistry of epoxide ring was ascertained[8] to be 6β-7β-oriented as determined by PMR spectrum of **11**.

Conclusively, it is possible to regioselectively invert the configuration of 1- and 7-OH of forskolin using Mitsunobu reaction to prepare new and unnatural epimeric compounds as potential pharmacodynamic agents. The 6- and 9-hydroxyl groups being much more hindered did not react. The biological activity of the epimeric forskolins will be published separately.

References and Notes

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4. PMR data of **2**. 7.50 (m, 5H, COPh), 6.00 (dd, 1H, H-14, J = 10 & 17), 5.75 (dd, 1H, H-1ax, J = 10 & 2), 5.50 (d, 1H, H-7, J = 4), 5.24 (dd, 1H, H-15, J = 17 & 1.5), 4.48 (m, 1H, H-6), 4.93 (dd, 1H, H-15', J = 10 & 1.5), 3.18 (d, 1H, H-12, J = 17), 2.50 (d, 1H, H-12, J = 17), 2.15 (s, 3H, $COCH_3$), 1.00, 1.10, 1.27, 1.30, 1.60 (all s, 5 x CH_3).
5. PMR data of **4**. 6.13 (dd, 1H, H-14, J = 10 & 17)), 5.21 (dd, 1H, H-15, J = 17 & 1.5), 4.99 (dd, 1H, H-15, J = 10 & 1.5), 3.95 (dd, 1H, H-1ax, J = 9.5 & 2), 4.40 (m, 1H, H-6), 5.50 (d, 1H, H-7, J = 4), 3.18 (d, 1H, H-12, J = 17), 2.50 (d, 1H, H-12, J = 17), 2.10 (d, 1H, H-5, J = 3), 2.15 (s, 3H, $COCH_3$), 1.0, 1.05, 1.25, 1.40, 1.60 (all s, 5 x CH_3).
6. M. Varasi, K.A.M. Walker and M.L. Maddox, J. Org. Chem., **52**, 4235 (1987).
7. PMR data of **6**. 6.00 (dd, 1H, H-14, J = 10 & 17), 5.21 (dd, 1H, H-15, J = 17 & 1.5), 4.99 (dd, 1H, H-15, J = 10 & 1.5), 5.50 (d, 1H, H-7, J = 2), 4.55 (m, 1H, H-1), 4.48 (m, 1H, H-6), 3.15 (d, 1H, H-12, J = 17), 2.50 (d, 1H, H-12, J = 17), 2.30 (d, 1H, H-5), 0.95, 1.05, 1.25, 1.30, 1.55 (all s, 5 x CH_3).
8. PMR data of **11**. 6.00 (dd, 1H, H-14, J = 10 & 17), 5.15 (dd, 1H, H-15, J = 17 & 1.5), 5.00 (dd, 1H, H-15, J = 10), 4.20 (m, 1H, H-1), 3.30 (d, 1H, H-12, J = 15), 2.40 (d, 1H, H-12', J = 15), 2.55 (d, 1H, H-7, J = 3.5), 2.15 (dd, 1H, H-6, J = 3.5 & 1.9), 2.05 (d, 1H, H-5, J = 1.9), 1.20, 1.21, 1.40, 1.50, 1.60 (all s, 5 x CH_3).

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