Lewis Acid Catalyzed, Selective Cyclopropane-Ring Opening in Ingol Diterpene Derivatives

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Lewis acid mediated skeletal rearrangement of the ingol diterpenoids **1** and **4** *via* regio- and stereospecific cyclopropane-ring opening afforded the four new compounds **2**, **3**, **5**, and **6**, named nivulianol A – D (*Scheme 1*). Their structures were established by means of IR, MS, and in-depth NMR spectroscopic analyses. The rearranged congeners were tested for lipopolysaccharide (LPS)-induced prostaglandin (PG) E_2 (cyclo-oxygenase-2) inhibition. Thereby, nivulianol B (=(1*S**,2*E*,4*R**,5*S**,7*Z*,9*S**,11*R*,13*S**,14*S**)-14-acetoxy-5-methoxy-3,9,13-trimethyl-6-(1-methylethenyl)-10-oxo-15-oxatricyclo[9.3.1.$0^{1,11}$]pentadeca-2,7-dien-4-yl (2*Z*)-2-methylbut-2-enoate; **3**) was found to be significantly active, with an IC_{50} value of 36.3 μg/ml.

Introduction. – The unique reactivity of cyclopropanes is due to their high level of ring strain, which offers considerable utility in organic synthesis [1 – 3]. Many potential applications of cyclopropanes as useful building blocks have been predicted based on regio- and stereo-controlled ring-opening reactions [4 – 6]. Typically, electrophilic ring opening has been achieved by transition metals (Pd, Pt, Rh, and Ir), halide ions, and *Lewis* acids [7 – 12]. Electron-donor-substituted cyclopropanes, particularly alkoxy, silyloxy, and arylsulfanyl compounds, have found increasing use, primarily due to facile and regio-controlled cyclopropane ring opening [13 – 18].

Results and Discussion. – 1. *Chemical Transformation and Structure Elucidation*. During our studies on the chemical modification of various secondary metabolites from plant sources [19] and marine organisms [20][21], we observed that $BF_3 \cdot OEt_2$ reacts with the diterpenoid **1** (= 3,12-di-*O*-acetyl-8-*O*-methyl-7-*O*-(2-methylbut-2-enoyl)ingol)[1]) [22] to yield the rearranged compounds nivulianol A (**2**) and B (**3**), whereas scandium triflate, $Sc(OTf)_3$[2]), gave only **3** (*Scheme 1*). In turn, the related compound **4** [23][24], lacking the angeloyl group[3]), reacted with $BF_3 \cdot OEt_2$ to afford both nivulianol C (**5**) and D (**6**), whereas, in the presence of $Sc(OTf)_3$, only **6** was obtained.

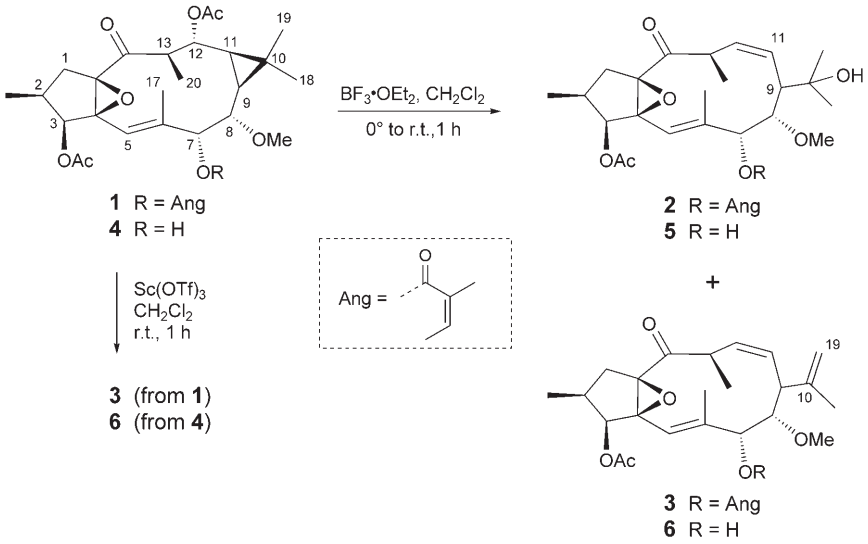
Compound **2** was obtained as a semisolid material ($[\alpha]_D = -102.6$ ($c = 0.15$, $CHCl_3$)), which analyzed for $C_{28}H_{40}O_8$ by HR-FAB-MS, as confirmed by the ion at *m/z* 505.2765 ($[M+1]^+$, calc. 505.2791). Its IR spectrum showed bands at 3423, 1740, 1720,

[1]) The systematic name of ingol is (1*R*,3*R*,4*R*,5*R*,7*S*,8*S*,9*R*,10*E*,12*S*,13*S*,14*S*)-4,8,9,13-tetrahydroxy-3,6,6,10,14-pentamethyl-16-oxatetracyclo[10.3.1.$0^{1,12}$.$0^{5,7}$]hexadec-10-en-2-one.

[2]) Triflate (Tf) = trifluoromethanesulfonate.

[3]) Angeloyl (Ang) = (*Z*)-2-methylbut-2-enoyl.

Scheme 1



and 1705 cm^{-1}, indicating OH, and keto and ester C=O groups. The ^{1}H-NMR spectrum of compound **2** (*Table*) showed an AcO group at δ(H) 2.10 (*s*, 3 H), a MeO group at 3.48 (*s*, 3 H), and an AngO group (δ(H) 6.15 (*m*, 1 H), 1.95 (*d*, $J = 1.4$ Hz, 3 H), 2.03 (dd, $J = 7.3$, 1.4 Hz, 3 H)). Also observed were three olefinic H-atoms at δ(H) 5.81 (*s*, H–C(5)), 4.99 (*dd*, $J = 14.9$, 9.8 Hz, H–C(12)), and 4.78 (*dd*, $J = 14.9$, 9.8 Hz, H–C(11)), a vinylic Me group at 1.90 (*s*, Me(17)), two Me groups connected to an oxygenated C-atom at δ(H) 1.15 and 0.99 (Me(18) and Me(19), resp.), two methine groups (geminal to ester functions) at δ(H) 5.02 (*d*, $J = 8.4$ Hz, H–C(3)), and 5.26 (br. *s*, H–C(7)), and a methine geminal to an ether linkage at δ(H) 2.77 (*dd*, $J = 12.0$, 2.8 Hz, H–C(8)). Finally, an exchangeable H-atom at δ(H) 4.58 (*s*, 10-OH) was detected.

Careful comparison of the ^{1}H- and ^{13}C-NMR (DEPT) spectra of compounds **1** and **2** (*Table*) revealed that the latter was devoid of signals due to the cyclopropane ring [δ(C) 27.31(C(9)), 19.28 (C(10)), 30.53 (C(11)) in **1**] and the methine connected to the Ac group (δ(C) 71.0 (C(12) in **1**). Instead, the presence of an (*E*)-configured C=C bond at δ(C) 132.31 (C(11)) and 129.8 (C(12)), and a quaternary C-atom connected to an O-atom at δ(C) 81.4 (C(10)) were noticed. Further, the ^{1}H,^{1}H-COSY spectrum of **2** established that H–C(12) at δ(H) 4.99 (*dd*) was correlated with H–C(13) at 3.68 (*dd*) and H–C(11) at 4.78 (*dd*). The latter, in turn, showed a correlation with H–C(9) at δ(H) 3.69 (dd), which was linearly correlated with H–C(8) at δ(H) 2.77 (*dd*).

The relative configurations at most of the stereogenic centers of **2** were established by NOESY experiments. The H–C(9) signal at δ(H) 3.69 was correlated with Me(18) at δ(H) 1.15 (*s*). H–C(7) at δ(H) 5.26 (*s*) showed correlations with H–C(8), H–C(13), and Me(17) at δ(H) 2.77 (*dd*), 3.68 (*dd*), and 1.90 (*s*), respectively. From all these data, the structure of nivulianol A (**2**) was established as (1*S**,2*E*,4*R**,5*S**,7*Z*,9*S**,11*R**,13*S**,14*S**)-14-acetoxy-6-(1-hydroxy-1-methylethyl)-

Table. *NMR Data of Compounds* **2**, **3**, **5**, and **6**. At 200 MHz in $CDCl_3$; δ in ppm, J in Hz.

Position	**2**		**3**		**5**		**6**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1α	1.74 (*d*, *J* = 14.6)	33.5	1.73 (*d*, *J* = 14.8)	33.82	1.73 (*d*, *J* = 14.5)	33.61	1.73 (*d*, *J* = 14.5)	33.86
1β	2.74 (*dd*, *J* = 14.6, 9.1)	–	2.73 (*dd*, *J* = 14.8, 9.0)	–	2.80 (*dd*, *J* = 14.5, 9.0)	–	2.76 (*dd*, *J* = 14.5, 9.2)	–
2	2.50–2.62 (*m*)	29.7	2.50–2.62 (*m*)	29.79	2.50–2.62 (*m*)	29.69	2.50–2.62 (*m*)	29.69
3	5.02 (*d*, *J* = 8.4)	77.7	5.02 (*d*, *J* = 8.4)	79.34	5.10 (*d*, *J* = 8.4)	77.96	5.09 (*d*, *J* = 8.4)	78.10
4	–	73.7	–	73.72	–	73.73	–	73.72
5	5.81 (*s*)	116.6	5.81 (*s*)	116.78	5.63 (*s*)	117.01	5.62 (*s*)	116.90
6	–	141.4	–	141.62	–	142.51	–	142.53
7	5.26 (*s*)	72.19	5.27 (*s*)	72.60	4.40 (*s*)	72.35	4.41 (*s*)	73.14
8	2.77 (*dd*, *J* = 11.9, 2.8)	72.39	3.52 (*d*, *J* = 10.4)	77.8	3.58 (*dd*, *J* = 10.3, 1.6)	72.73	3.40 (*dd*, *J* = 10.6, 2.0)	73.13
9	3.69 (*dd*, *J* = 16.6, 6.8)	54.05	3.15 (br. *t*, *J* = 10.1)	52.77	2.74–2.80 (*m*)	52.33	3.13 (*t*, *J* = 10.3)	51.19
10	–	81.4	–	145.5	–	83.01	–	145.98
11	4.78 (*dd*, *J* = 14.9, 9.8)	132.31	5.30 (*dd*, *J* = 18.1,13.7)	132.35	4.91 (*dd*, *J* = 15.1, 10.0)	132.25	5.21 (*dd*, *J* = 15.0, 10.3)	132.08
12	4.99 (*dd*, *J* = 14.9, 10.4)	129.8	4.70 (*dd*, *J* = 18.1, 5.5)	128.43	4.78 (*dd*, *J* = 15.0, 9.5)	129.36	4.67 (*dd*, *J* = 15.0, 10.0)	128.18
13	3.68 (*dd*, *J* = 10.4, 1.7)	45.8	3.62–3.7 (*m*)	45.89	3.58–3.62 (*m*)	45.68	3.60–3.68 (*m*)	45.72
14	–	207.1	–	206.99	–	206.66	–	206.61
15	–	72.68	–	72.51	–	73.21	–	73.72
16	0.89 (*d*, *J* = 7.6)	16.9	0.89 (*d*, *J* = 7.2)	16.89	0.91 (*d*, *J* = 7.4)	17.09	0.91 (*d*, *J* = 7.3)	17.05
17	1.90 (*s*)	17.3	1.93 (*s*)	17.44	1.82 (*s*)	17.09	1.85 (*s*)	17.04
18	1.15 (*s*)	29.7	1.68 (*s*)	20.65	1.06 (*s*)	29.69	1.69 (*s*)	29.69
19	0.99 (*s*)	24.9	4.69, 4.74 (2*s*)	110.79	1.15 (*s*)	25.33	4.70, 4.74 (2*s*)	110.57
20	1.08 (*d*, *J* = 7.6)	17.3	1.08 (*s*)	17.03	1.07 (*d*, *J* = 7.4)	17.08	1.06 (*d*, *J* = 7.3)	20.64
3-AcO	2.10 (*s*)	20.7	2.10 (*s*)	20.65	2.08 (*s*)	20.64	2.07 (*s*)	20.80
		170.2		170.09		170.00		170.12
8-MeO	3.48 (*s*)	56.55	3.36 (*s*)	57.48	3.50 (*s*)	56.44	3.38 (*s*)	57.71
10-OH	4.58 (*s*)	–	–	–	4.50 (*s*)	–	–	–
7-AngO	6.15 (*m*)	166.3	6.1–6.15 (*m*)	166.20	–	–	–	–
	1.95 (*d*, *J* = 1.4)	127.2	1.94 (*d*, *J* = 1.5)	127.45				
	2.03 (*dd*, *J* = 7.3, 1.4)	139.8	2.02 (*dd*, *J* = 7.2, 1.5)	139.48				
		15.9		16.03				
		20.6		20.65				

5-methoxy-3,9,13-trimethyl-10-oxo-15-oxatricyclo[9.3.1.0^{1,11}]pentadeca-2,7-dien-4-yl (2*Z*)-2-methylbut-2-enoate.

Compound **3** was obtained as a semisolid, with $[\alpha]_D = -18.0$ ($c = 0.25$, $CHCl_3$), and analyzed for $C_{28}H_{38}O_7$ by HR-FAB-MS [*m*/*z* 487.2690 ($[M+1]^+$, calc. 487.2712)]. IR bands at 1739, 1720, and 1705 cm^{-1} indicated keto and ester C=O groups. The ^{1}H- and ^{13}C-NMR spectra (*Table*) were similar to those of compound **2**, except for the presence of an isopropylidene group instead of an isopropyl alcohol, as evident from the signals at δ(H) 4.69/4.74 (2*s*, CH_2(19)) and 1.68 (s, Me(18)). From these data, the structure of nivulianol B (**3**) was established as (1*S**,2*E*,4*R**,5*S**,7*Z*,9*S**,11*R*,13*S**,14*S**)-14-acetoxy-5-methoxy-3,9,13-trimethyl-6-(1-methylethenyl)-10-oxo-15-oxatricyclo[9.3.1.0^{1,11}]pentadeca-2,7-dien-4-yl (2*Z*)-2-methylbut-2-enoate.

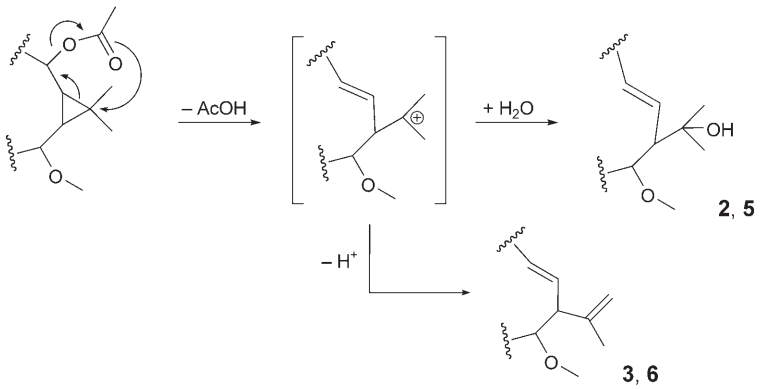
Similarly, the structures of compounds **5** and **6** were derived by analyses of their MS and NMR (^{1}H, ^{13}C, COSY, NOESY) data (*Table*). Nivulianol C (**5**) was obtained as a semisolid, $[\alpha]_D = +5.83$ ($c = 0.3$, $CHCl_3$), which analyzed for $C_{23}H_{34}O_7$ by HR-FAB-MS

[*m*/*z* 423.2375 ([*M* + 1]$^+$, calc. 423.2394)], and was identified as (1*R**,3*S**,4*Z*,7*S**,8*R**,9*E*,11*S**,12*S**,13*S**)-8-hydroxy-6-(1-hydroxy-1-methylethyl)-7-methoxy-3,9,13-trimethyl-2-oxo-15-oxatricyclo[9.3.1.0^{1,11}]pentadeca-4,9-dien-12-yl acetate.

Nivulianol D (**6**), a semisolid with $[\alpha]_D = -42.85$ ($c = 0.35$, $CHCl_3$), analyzed for $C_{23}H_{32}O_6$ by HR-FAB-MS (*m*/*z* 405.2286 ([*M* + 1]$^+$, calc. 405.2269)), and was found to correspond to (1*R**,3*S**,4*Z*,7*S**,8*R**,9*E*,11*S**,12*S**,13*S**)-8-hydroxy-7-methoxy-3,9,13-trimethyl-6-(1-methylethenyl)-2-oxo-15-oxatricyclo[9.3.1.0^{1,11}]pentadeca-4,9-dien-12-yl acetate.

From a mechanistic point of view, the rearrangement of compounds **1** and **4** probably involves an intermediary carbocation formed *via* acetoxy-promoted ring opening followed by loss of AcOH, as proposed in *Scheme 2*.

Scheme 2



2. *Biological Activity.* In earlier work [23], we had tested the prostaglandin (PG) E_2 inhibition properties of several ingol diterpenoids, and found that 12-*O*-acetyl-8-*O*-methyl-7-*O*-(2-methylbut-2-enoyl)ingol exhibits strong *in vitro* anti-inflammatory activity, with an IC_{50} value of 0.003 μM, which lies one order of magnitude below that of celecoxib (*Celebrex*^{TM}; 0.050 μM) [23].

The role of cyclooxygenase-2 (COX-2) induction in the pathogenesis of colorectal and breast cancer is well reported [25][26]. Hence, compounds **3**–**6** were tested for COX-2 inhibition in an *in vitro* enzyme immuno-assay, which involves lipopolysaccharide (LPS)-induced PG E_2 inhibition. Of all the compounds tested, nivulianol B (**3**) showed 40% inhibitory activity at a concentration of 10 μg/ml. The other compounds did not show significant activity up to 50 μg/ml concentration, nivulianol A (**2**) giving rise to only 10% activity. Hence, nivulianol B (**3**) was chosen for the determination of IC_{50}. For a concentration range of 10–50 μg/ml, we determined an IC_{50} value of 36.3 μg/ml for **3**.

Experimental Part

Boron Trifluoride Catalyzed Rearrangement. To a stirred soln. of **1** (25 mg) in anh. CH_2Cl_2 (5 ml) under Ar atmosphere, $BF_3 \cdot OEt_2$ (46%; 80 μl, 0.56 mmol) was added at 0°. The mixture was allowed to warm to r.t. over

1 h. Then, the mixture was diluted with AcOEt, and extracted with sat. aq. $NaHCO_3$ soln. The org. layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by column chromatography (SiO_2; hexane/AcOEt 8:2) to afford compounds **2** (13.2 mg) and **3** (8.2 mg).

Similarly, with **4** as the starting material, compounds **5** (11.3 mg) and **6** (5.2 mg) were obtained.

Scandium Triflate Catalyzed Rearrangement. To a stirred soln. of **1** (25 mg) in anh. CH_2Cl_2 (5 ml) under Ar atmosphere, $Sc\cdot(OTf)_3$ (5 mg, 0.01 mmol) was added at r.t., and the mixture was stirred for 1 h. Then, the mixture was diluted with AcOEt, and extracted with sat. aq. $NaHCO_3$ soln. The org. layer was washed with H_2O and brine, dried (Na_2SO_4), and evaporated. Purification by CC (as above) furnished compound **3** (16.5 mg).

Similarly, with **4** as the starting material, compound **6** (13.2 mg) was obtained.

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