Zinc(II)-promoted Stereospecific Rearrangement of 17-Hydroxy-20-oxopregnane Derivatives

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A new and highly efficient method for D-homo-rearrangements in the steroid field is described. The transformation is induced by the action of zinc(II) on different 17-hydroxy-20-oxopregnanes. With 17α-hydroxy-20-oxopregnanes the reaction afforded 17aα-hydroxy-17aβ-methyl-D-homo-derivatives while under the same conditions 17β-hydroxy-20-oxopregnanes gave the corresponding 17a-epimeric-D-homo-steroids. In both cases the rearrangement was stereospecif giving the corresponding products in almost quantitative yields.

Continuing our studies on the Reformatsky reaction in the steroid field[1] we carried out the reaction on 3β-acetoxy-17-hydroxypregn-5-en-20-one (**1a**) using ethyl bromoacetate, zinc, and a few crystals of iodine. Instead of the expected product, we obtained exclusively and in quantitative yield 3β-acetoxy-17aα-hydroxy-17aβ-methyl-D-homoandrost-5-en-17-one (**2a**) indicating that a D-homo-rearrangement had occurred. A more detailed analysis of the species participating in the reaction showed that the rearrangement had been induced solely by the action of zinc(II) on the steroid. This resulted in a new and efficient method for D-homo-rearrangements in the steroid field.

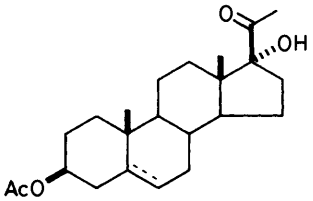
The rearrangement of 17-hydroxy-20-oxopregnanes to D-homo-derivatives was first observed by Ruzicka *et al.*[2] Since then, the stereospecificity of the rearrangement with various bases and Lewis acids and their influence on the production of both C-17-epimers has been studied by several groups.[3–6] The characteristic feature of the reaction, the formation of D-homo-derivatives, in several cases remains unaccounted for, and the yields are quite low. No method seems to afford any of the possible D-homoisomers with 100% stereochemical purity.

Turner[3] treated 3β-acetoxy-17α-hydroxy-5α-pregnan-20-one (**1b**) with bases and Lewis acids. Using boron trifluoride in acetic anhydride–acetic acid the starting material was transformed into the proposed homo-derivative (**2b**) in very low yield, while treatment of the 17-epimer (**3b**) with alumina afforded the D-homo-derivative (**4b**), the 17a-epimer of compound (**2b**). D-Homo-rearrangement was not observed[3] with magnesium bromide, aluminium chloride, zinc chloride, or tin(IV) chloride as catalysts.

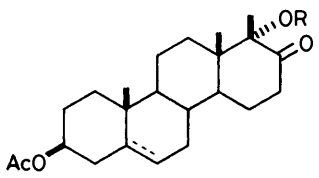
Contrasting with Turner results, Fukushima *et al.*[4] reported that treatment of the 17α-hydroxy-20-oxopregnane (**1b**) with boron trifluoride in acetic anhydride afforded a mixture of two products; the D-homo-derivative (**2b**) obtained by Turner was a minor component and the 17a-ketone (**5a**) was the major product, with a total yield of 60%.

Fukushima claimed that Turner's compound (**2b**) and his compound (**5a**) were the same derivative. He postulated that in this case the rearrangement involved the migration of the C-16–C-17 bond instead of the C-13–C-17 bond as Turner had stated.

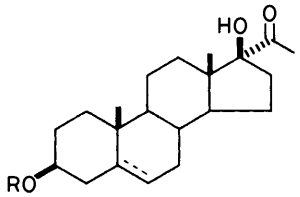
Kirk and Mudd[5] obtained a mixture of D-homo-derivatives (**2c**) and (**5b**) by treatment of the 17α-hydroxypregnane (**1b**) with boron trifluoride, in accordance with Fukushima's results.



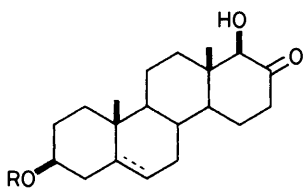
(1) **a**; Δ^5
b; no Δ^5,5α-H



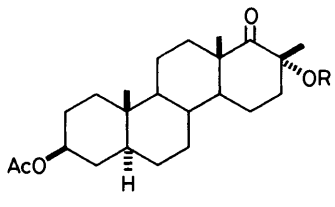
(2) **a**; Δ^5, R = H
b; no Δ^5, 5α-H, R = Ac
c; no Δ^5, 5α-H, R = H



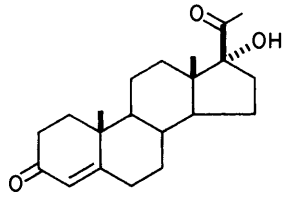
(3) **a**; Δ^5, R = H
b; no Δ^5, 5α-H, R = Ac



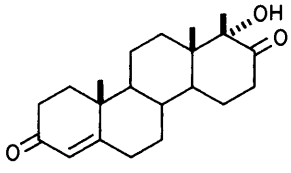
(4) **a**; Δ^5, R = H
b; no Δ^5, 5α-H, R = Ac



(5) **a**; R = Ac
b; R = H



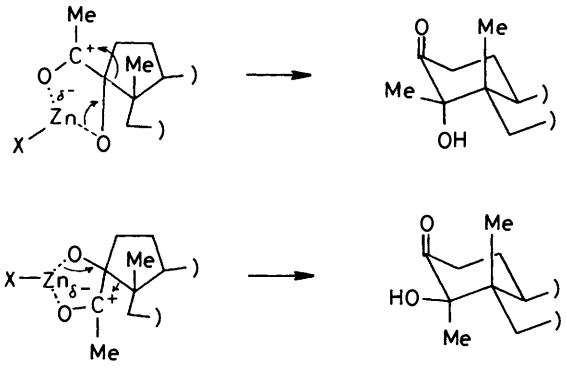
(6)



(7)

Results and Discussion

The reactions were carried out by treatment of the steroid in



Scheme 1.

ether–benzene, benzene, chloroform, or dichloromethane solution with zinc powder in the presence of a few crystals of iodine. The mixture was heated under reflux and after *ca.* 4 h (monitored by t.l.c.) one single product was quantitatively obtained in each case.

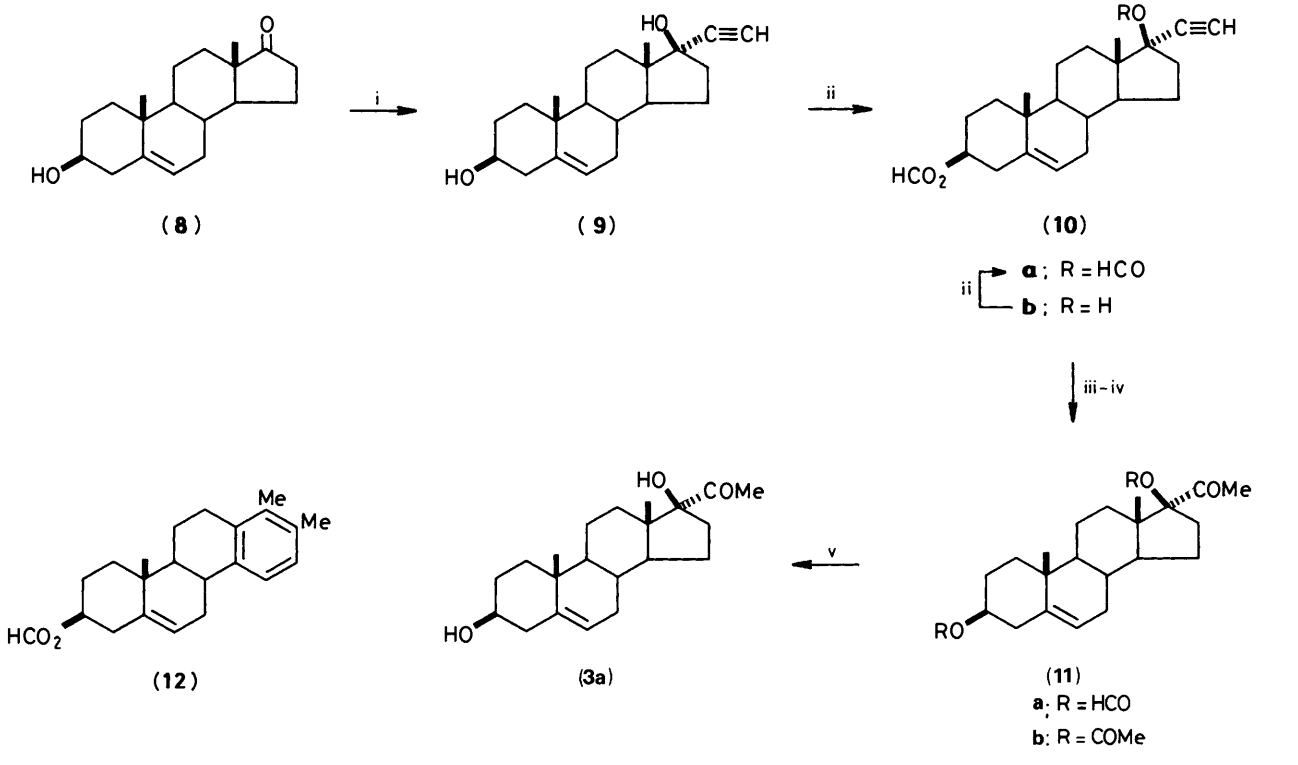
Under these conditions compound (**1a**) afforded, stereospecifically and in quantitative yield, the D-homo-derivative (**2a**). On the other hand, the 17-epimer (**3a**) of compound (**1a**) under the same conditions also reacted stereospecifically, affording quantitatively the D-homo-derivative (**4a**), the 17a-epimer of compound (**2a**). With 17α-hydroxypregn-4-ene-3,20-dione (**6**) as the starting material, the reaction produced in 90% yield the expected D-homo-derivative (7).

We found that the rearrangement could also be carried out using zinc bromide as catalyst, with the same results.

Comparison of our results with those obtained by other authors indicates good agreement in the case of the 17β-hydroxy-20-oxopregnane (**3a**) with the results obtained by Turner[3] using alumina as catalyst, but under our conditions the reaction led to quantitative yields. In the case of the 17α-hydroxy-20-oxopregnanes (**1a**) and (**6**) we obtained single products, (**2a**) and (7) respectively, in agreement with Turner's results[3] using boron trifluoride as catalyst but contrasting with the mixtures obtained by Kirk[5] and by Fukushima,[4] both of whom used the same catalyst as Turner.

The stereochemistry of the products obtained by these zinc(II)-promoted rearrangements in both steroidal series is fully explained in terms of the formation of a cyclic complex (Scheme 1), with specific migration in both cases of the C-13–C-17 bond. These intermediaries are similar to those proposed by Turner[3] for the boron trifluoride-promoted rearrangement.

The reaction sequence for preparation of the starting material 3β,17β-dihydroxypregn-5-en-20-one (**3a**) from 3β-hydroxy-androst-5-en-17-one (**8**) is in Scheme 2. Treatment of the ketone (**8**) with lithium acetylide–ethylenediamine in tetrahydrofuran under acetylene afforded the ethynyl derivative (**9**) in 62% yield. Conversion of (**9**) into the 17β-hydroxy-20-oxopregnane (**3a**) was accomplished as described elsewhere[6] but with protection of the hydroxy groups of the diol (**9**) as formyl rather than acetyl derivatives, since, following acetylation, removal of the 17-acetate from the derivative (**11b**) required strongly basic conditions (refluxing methanolic potassium or sodium hydroxide) under which a D-homo-rearrangement took place directly and the 3β-hydroxy analogue of (**2a**) was obtained instead of the desired 17α-pregnane (**3a**).[7] Formylation of (**9**) with formic acid and toluene-*p*-sulphonic acid as catalyst[8] afforded a mixture of compounds (**10a**) and (**10b**) in 53 and 42% yield respectively. The mixture could be separated by flash column chromatography and the monoformate (**10b**) converted into the diformate (**10a**) by formylation in 80% yield, leading to a total yield of (**10a**) from (**9**) of 87%. Longer reaction times or refluxing of the mixture for the formylation of (**9**) caused almost total conversion into the D-aromatic derivative (**12**).[9] The methyl ketone (**11a**) was obtained in 80% yield from (**10a**) by



Scheme 2. *Reagents:* i, HC≡CLi, ethylenediamine, tetrahydrofuran; ii, HCO_2H, *p*-$MeC_6H_4SO_3H$; iii, *N*-bromoacetamide, AcOH, AcONa; iv, Zn; v, $KHCO_3$, MeOH.

treatment with *N*-bromoacetamide in buffered aqueous acetic acid, followed by debromination with zinc dust in the same medium.[6] The protecting groups were easily removed from (**11a**) in 98% yield by stirring a solution of (**11a**) with methanolic potassium hydrogencarbonate at room termperature, avoiding any D-homo-rearrangement. The desired pregnane (**3a**) was obtained by this sequence in 42% overall yield from the starting material (**8**).

Experimental

M.p.s (uncorrected) were determined on a Fisher–Johns apparatus. ^1H and ^{13}C N.m.r. spectra (Fourier transform) were determined at 100.1 and 25.2 MHz respectively in deuteriochloroform, unless otherwise indicated. Chemical shifts are expressed in p.p.m. downfield from internal tetramethylsilane. Extractive work-up included exhaustive extraction with the solvent indicated, washing with water, drying with anhydrous sodium sulphate, and evaporation under reduced pressure and *ca.* 40—60 °C. The homogeneity of all compounds was confirmed by t.l.c.

3β-*Acetoxy*-17aα-*hydroxy*-17aβ-*methyl*-D-*homoandrost*-5-*en*-17-*one* (**2a**) *from* (**1a**).—*Using zinc powder and iodine.* To a stirred and heated solution of compound (**1a**) (100 mg) in benzene (2.5 ml) and ether (2.5 ml) was added zinc powder (80 mg) and a few crystals of iodine. After 4 h under reflux, the green solution was cooled and filtered, and the filtrate was concentrated to dryness affording the D-homosteroid (**2a**) (100 mg), m.p. 273—274 °C (from methanol) (lit.,[7] 277—279 °C); δ_H 0.71 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 1.19 (3 H, s, 17aβ-Me), 2.03 (3 H, s, Ac), 2.95 (1 H, m, 16α-H), 4.62 (1 H, m, 3-H), and 5.35 (1 H, m, 6-H); δ_H (C_5D_5N) 0.76 (3 H, s, 18-H), 0.97 (3 H, s, 19-H), 1.48 (3 H, s, 17aβ-Me), 2.06 (3 H, s, Ac), 3.33 (1 H, m, 16α-H), 4.78 (1 H, m, 3-H), and 5.38 (1 H, m, 6-H); δ_C ($CDCl_3$–CD_3OD, 98:2) 15.0 (C-18), 17.0 (Me-17a), 19.1 (C-19), 20.1 (C-11), 21.4 (CH_3CO), 25.8 (C-15), 27.6 (C-2), 30.5 (C-12), 31.9 (C-7), 32.3 (C-8), 36.6 (C-10 and C-16), 36.8 (C-1), 37.8 (C-4), 42.6 (C-14), 43.2 (C-13), 48.8 (C-9), 73.7 (C-3), 80.1 (C-17a), 122.1 (C-6), 139.0 (C-5), 170.3 (CH_3CO), and 212.8 (C-17).

Using zinc bromide. To a stirred and heated solution of compound (**1a**) (30 mg) in benzene (2.5 ml), zinc bromide (15 mg) was added. After 3.5 h under reflux the solution was cooled and evaporated to dryness. The residue obtained was purified by flash column chromatography (silica gel, dichloromethane) affording (**2a**) (28 mg).

3β,17aβ-*Dihydroxy*-17aα-*methyl*-D-*homoandrost*-5-*en*-17-*one* (**4a**) *from* (**3a**).—The reaction was performed with (**3a**) (100 mg) under the same foregoing conditions as for (**2a**) using zinc and a few crystals of iodine, with dichloromethane as solvent. Purification by flash column chromatography on silica-gel with dichloromethane as eluant afforded the D-homo-derivative (**4a**) (90 mg), m.p. 175—176 °C (from light petroleum–acetone, 1:1) (lit.,[10] 177—178 °C); δ_H 0.75 (3 H, s, 18-H), 0.99 (3 H, s, 19-H), 1.35 (3 H, s, 17aα-Me), 3.48 (1 H, m, 3-H), and 5.35 (1 H, m, 6-H); δ_C 13.8 (C-18), 19.0 (C-19), 19.7 (C-11), 20.7 (Me-17a), 26.0 (C-15), 29.5 (C-2), 30.6 (C-12), 31.0 (C-16), 32.0 (C-7, C-8), 36.1 (C-10), 36.9 (C-1), 41.4 (C-4), 49.0 (C-14*), 49.2 (C-9*), 71.2 (C-3), 80.7 (C-17a), 120.6 (C-6), 140.4 (C-5), and 215.3 (C-17).

17aα-*Hydroxy*-17aβ-*methyl*-D-*homoandrost*-4-*ene*-3,17-*dione* (**7**) *from* (**6**).—The reaction was performed starting from (**7**) (100 mg) following the procedure described for (**2a**) using benzene as solvent, affording the D-homo-steroid (7) (90 mg), m.p. 282—284 °C (from methanol) (lit.,[11] 288—289 °C); δ_H 0.75 (3 H, s, 18-H), 1.17 (3 H, s, 19-H), 1.20 (3 H, s, 17aβ-Me), 2.93 (1 H, m, 16α-H), and 5.74 (1 H, br s, 4-H); δ_C 14.7 (C-18), 16.2 (Me-17a), 17.3 (C-19), 20.2 (C-11), 25.6 (C-15), 30.7 (C-12), 31.2 (C-6), 32.7 (C-7), 33.6 (C-2), 35.2 (C-1), 36.1 (C-8), 36.4 (C-16), 38.5 (C-10), 41.5 (C-14), 43.2 (C-13), 52.6 (C-9), 79.3 (C-17a), 122.9 (C-4), 172.0 (C-5), 200.1 (C-3), and 214.2 (C-17).

3β,17β-*Dihydroxypregn*-5-*en*-20-*yne* (**9**) *from* (**8**).—To a stirred solution of compound (**8**) (1.09 g) in anhydrous tetrahydrofuran (10 ml) was quickly added lithium acetylide–ethylenediamine (3.4 g) under acetylene. The mixture was kept for 24 h at 25 °C and water was then carefully added dropwise, until no more evolution of acetylene was observed. Flash column chromatography on silica gel using tetrahydrofuran as solvent led to a brown–orange solid. Neutralization of the basic solution with dilute HCl and extractive work-up with dichloromethane afforded a crude mixture (1.05 g). Silica gel column chromatography with dichloromethane and dichloromethane–methanol (99.5:0.5) as eluants afforded compound (**9**) together with small amounts of starting material (**8**). Recrystallization from methanol–water (95:5) afforded pure compound (**9**) (730 mg), m.p. 239—240 °C (lit.,[12] m.p. 240—242 °C); δ_H ($CDCl_3$–CD_3OD, 98:2) 0.87 (3 H, s, 18-H), 1.04 (3 H, s, 19-H), 2.58 (1 H, s, 21-H), 3.48 (1 H, m, 3-H), and 5.35 (1 H, m, 6-H); δ_C ($CDCl_3$–CD_3OD, 90:10) 12.4 (C-18), 19.2 (C-19), 20.6 (C-11), 23.0 (C-15), 31.1 (C-16), 31.3 (C-2), 32.4 (C-7, C-8), 36.4 (C-10), 37.1 (C-1), 38.6 (C-12), 41.7 (C-4), 46.4 (C-13), 49.7 (C-9*), 50.5 (C-14*), 71.1 (C-3), 73.2 (C-21), 78.2 (C-17), 87.6 (C-20), 120.9 (C-6), and 140.7 (C-5).

3β,17β-*Diformyloxypregn*-5-*en*-20-*yne* (**10a**) *from* (**9**).—A solution of (**9**) (370 mg) and toluene-*p*-sulphonic acid (20 mg) in formic acid (50 ml) was stirred at room temperature for 18 h and the mixture was poured into water. Extractive work-up with dichloromethane afforded a crude mixture which was chromatographed on a silica gel column using light petroleum–dichloromethane (1:1) as eluant. Two major fractions were collected. The first provided the pure *diformate derivative* (**10a**) (230 mg), m.p. 160—161 °C (from methanol) (Found: C, 74.3; H, 8.1. $C_{23}H_{30}O_4$ requires C, 74.6; H, 8.1%); δ_H 0.91 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 2.71 (1 H, s, 21-H), 4.72 (1 H, m, 3-H), 5.42 (1 H, m, 6-H), 8.03 (1 H, d, *J* 0.9 Hz, 3-HCO), and 8.17 (1 H, s, 17-HCO); δ_C 13.2 (C-18), 19.3 (C-19), 20.5 (C-11), 23.6 (C-15), 27.7 (C-2), 31.4 (C-16), 32.2 (C-7), 32.8 (C-8), 36.5 (C-10), 36.9 (C-1), 37.6 (C-12), 37.9 (C-4), 47.4 (C-13), 49.2 (C-14*), 49.4 (C-9*), 73.7 (C-3), 76.5 (C-21), 82.5 (C-17), 85.1 (C-20), 122.2 (C-6), 139.2 (C-5), 160.0 (HCO-17), and 160.4 (HCO-3).

The second fraction gave the *monoformate* (**10b**) (170 mg), m.p. 181—182 °C (from methanol) (Found: C, 77.0; H, 8.71. $C_{22}H_{30}O_3$ requires C, 77.2; H, 8.8%); δ_H 0.87 (3 H, s, 18-H), 1.05 (3 H, s, 19-H), 2.57 (3 H, s, 21-H), 4.72 (1 H, m, 3-H), 5.42 (1 H, m, 6-H), and 8.03 (1 H, d, *J* 0.9 Hz, HCO); δ_C 12.6 (C-18), 19.3 (C-19), 20.7 (C-11), 23.1 (C-15), 27.7 (C-2), 31.3 (C-16), 32.5 (C-7, C-8), 36.5 (C-10), 36.9 (C-1), 38.0 (C-4), 38.9 (C-12), 46.6 (C-13), 49.6 (C-9*), 50.6 (C-14*), 73.8 (C-3, C-21), 79.7 (C-17), 87.4 (C-20), 122.4 (C-6), 139.2 (C-5), and 160.4 (HCO). Compound (**10b**) was converted into compound (**10a**) by formylation as described above in 80% yield.

3β,17β-*Diformyloxypregn*-5-*en*-20-*one* (**11a**) *from* (**10a**).—A solution of (**10a**) (58 mg), sodium acetate (140 mg), and *N*-bromoacetamide (160 mg) in glacial acetic acid (12 ml) and water (1.2 ml) was stirred at room temperature for 40 min. Zinc powder (170 mg) was added and the mixture was heated under reflux for 40 min until the yellow–orange solution became colourless (40 min). Dilution with water (15 ml) and extractive work-up with dichloromethane afforded a yellow oil (49 mg)

* Assignments may be interchanged.

which on crystallization from light petroleum rendered the pure *diformyloxypregnene* (**11a**), m.p. 178—179 °C (from methanol) (Found: C, 71.0; H, 8.2. $C_{23}H_{32}O_5$ requires C, 71.1; H, 8.25%); δ_H 1.03 (6 H, s, 18-H, 19-H), 2.10 (3 H, s, 21-H), 4.72 (1 H, m, 3-H), 5.42 (1 H, m, 6-H), 8.03 (1 H, d, *J* 0.9 Hz, 3-HCO), and 8.10 (1 H, s, 17-HCO); δ_C 14.9 (C-18), 19.2 (C-19), 20.6 (C-11), 24.7 (C-15), 27.2 (C-21), 27.7 (C-2), 29.7 (C-12), 31.3 (C-16), 31.9 (C-8), 32.9 (C-7), 33.7 (C-10), 36.9 (C-1), 37.9 (C-4), 47.1 (C-13), 47.6 (C-14*), 49.2 (C-9*), 73.7 (C-3), 96.7 (C-17), 122.5 (C-6), 138.9 (C-5), 160.3 (HCO-3), 160.7 (HCO-17), and 207.0 (C-20).

3β,17β-*Dihydroxypregn-5-en-20-one* (**3a**) *from* (**11a**).—A solution of (**11a**) (50 mg) and sodium hydrogen carbonate (50 mg) in methanol (10 ml) was stirred at room temperature for 30 min. The solution was diluted with water and neutralized with aqueous HCl. Extractive work-up afforded compound (**3a**) (42 mg), m.p. 270—272 °C (from methanol–water, 80:20) (lit.,[13] 271—273 °C); δ_H 0.94 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 2.26 (3 H, s, 21-H), 3.48 (1 H, m, 3-H), and 5.35 (1 H, m, 6-H); δ_C 13.9 (C-18), 19.1 (C-19), 20.5 (C-11), 24.1 (C-15), 28.0 (C-21), 29.4 (C-2), 31.3 (C-7, C-8), 32.2 (C-12), 32.9 (C-16), 34.7 (C-10), 37.0 (C-1), 41.9 (C-4), 47.3 (C-13), 49.4 (C-9*), 49.8 (C-14*), 71.3 (C-3), 90.7 (C-17), 120.9 (C-6), 140.3 (C-5), and 213.6 (C-20).

* Assignments may be interchanged.

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