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SYNTHESIS OF (±)-DIHYDROCALODENDROLIDE

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Abstract. The synthesis of racemic dihydrocalodendrolide (1α-(3'furyl)-4ß-4aß-epoxy-5ß,8aα-dimethyl-3-oxo-octahydro-1H-2-benzopyran) (**3**) has been achieved. This represents a ubiquitous structural feature of several bioactive limonoids.

INTRODUCTION

The limonoids exhibit a variety of biological activities. Some act as antiinflammatory, antineoplastic, ascaricidal and more commonly as insect antifeedants and growth regulators [1]. Most limonoids contain the substructure unit (**1**) shown below, exemplified by the naturally occurring limonin, gedunin and calodendrolide amongst others.

Despite the wide spectrum of bioactivities displayed by the limonoids, to date very few approaches have been reported on their synthesis [2,3]. Recently, Mateos *et al.* [4] reported the synthesis of the partial structure (**2**) as an entry in to the synthesis of rings C and D of limonin, gedunin and related limonoids. This prompted us to report herein details of our results on the synthesis of the unnatural racemic dihydrocalodendrolide (1 α-(3'-furyl)-4ß-4aß-epoxy-5ß, 8aα-dimethyl-1-3-oxo-octahydro-1H-2-benzopyran) (**3**) representing the ubiquitous substructure unit (**1**). We had the occasion to synthesize this structure during our studies on the structure antifeedant activity of limonin and its derivatives [5,6].

RESULTS AND DISCUSSION

Our target compound (**3**), had the advantage of the excellent earlier synthetic work of Fukuyama and Tokoroyama [7] leading to the synthesis of the lactol precursor (**4**). The epimeric mixture of lactols (**4**) was prepared in six steps from 2,6-dimethylcyclohexanone in 46% overall yield. Reaction of (**4**) with 3-furyl lithium at -78 °C led to a 1:1 mixture of (**5a**) and (**5b**) which was readily separated by crystallisation. The sterochemistries of (**5a**) and (**5b**) were confirmed by conversion to the known (±)-pyroangolensolide (**6**) and (±)-epipyriangolensilide (**7**), respectively. Epoxidation of (**5a**) with 50% H_2O_2 in base led to the diastereofacially selective formation of the target compound (**3**) as the only product and, in a similar manner, epoxide (**8**) was prepared from (**5b**). The sterochemistries of (**3**) and (**8**) were differentiated by examination of the NOESY ^{1}H NMR spectrum of (**8**), which exhibited correlations of H-1α with H-10, H-10 with H-5α, H-5α, with H-9 and H-9 with H-4.

This remarkable diastereofacial selectivity observed in the epoxidation of (**5a**) and (**5b**) prompted us to carry out computational investigations in order to

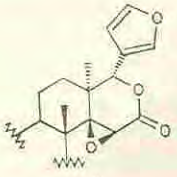
provide an insight into the reasons for the observed selectivity. Molecular Mechanics (MM2, QCPE No. 395) calculations were thus performed on all the expected products (**3**), (**8**), (**9**) and (**10**) resulting from the epoxidation of (**5a**) and (**5b**). For both epoxidations, the observed products (**3**) and (**8**) were found to be energetically more favoured than (**9**) and (**10**), respectively. Compound (**3**) is more stable than (**9**) by 0.7 kcal while (**8**) is more stable than (**10**) by 1.6 kcal. In both cases, the principal contribution of the unfavourable energy appears to arise from the lone pair-lone pair repulsion between the epoxide and the lactone oxygen in (**9**) and (**10**), respectively. Examination of molecular models indicate that steric effects play a minor role in the observed selectivity. Assuming the reaction proceeds under product development control, where the product is similar to the transitions state, we can argue that the transition state will have unfavourable interactions similar to those observed in the product. It thus follows that the diastereofacial preference might arise from electrostatic repulsion between the lactone oxygen lone pairs and the approaching electron rich peroxide reagent. This effect will necessarily disfavour the formation of (**9**) and (**10**) in accordance with our experimental results.

EXPERIMENTAL

NMR spectra were obtained with a Varian XL-200 system. The ^{1}H NMR NOESY spectrum was obtained on a 500 MHz GE NMR spectrometer at the University of Texas by Dr. Ben Shoulders. Medium resolution mass spectra were measured with a HP-5985-B GC-MS system and high resolution mass spectra with a VG-70-E by Dr. George Goodloe at Auburn University. Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected.

Molecular mechanics. Molecular mechanics calculation were performed with the Serena Software (POB 3076, Bloomington, IN 47402) version of MM2, QCPE No. 395.

Compounds (5a) and (5b). To a solution of 34.1 mmol of 3-lithiofuran in THF at -78° [prepared form 3-bromofuran (5 g, 34.1 mmol) in heptane] was added a solution of (**4**) (3.35 g, 17.05 mmol) [7] over 15 min. After stirring at this temperature for 15 min. and at RT for an additional 48 hr., water was added and the resulting mixture was extracted with 3 x 100 ml of $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield a 1:1 mixture (^{1}H NMR) of epimers (**5a**) and (**5b**). Pure (**5a**) was obtained after four successive recrystallizations from acetone hexane. Pure (**5b**) was obtained by concentration of the combined mother liquors and silica gel CC eluted with 20% acetone-hexane. (**5a**) was obtained as white needles (MP 130-132°) from acetone-hexane. ^{1}H NMR (200 MHz, $CDCl_3$, TMS): δ1.07(3H,s,18Me), 1.17 (3H,J=3.7,30Me), 1.20-2.00(6H,m,H-9,H-11,H-12), 2.40(1H,m,H-8), 5.05(1H,s,H-17), 5.86(1H,m,H-15), 6.44(1H,m,H-22), 7.42(1H,m,H-23), 7.46(1H,m,H-21);



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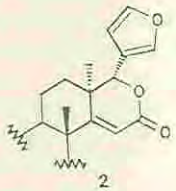

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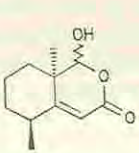
3



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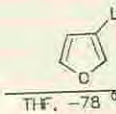
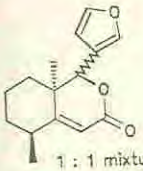
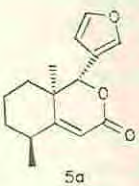
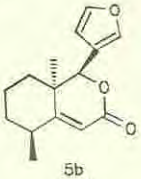




1 : 1 mixture of epimers



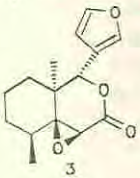
5a



5b

50% H_2O_2
MeOH/NaOH
0 → 25 °C
48 hrs, 80%

50% H_2O_2
MeOH/NaOH
0 → 25 °C
24 hrs, 80%



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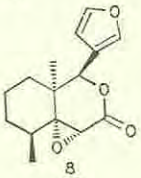

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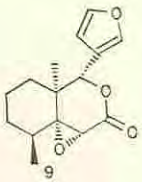

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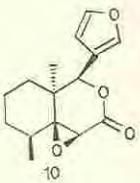

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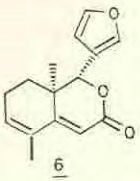

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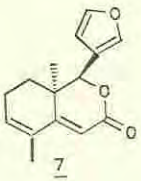

7

^{13}C NMR (50.3MHz, $CDCl_3$,TMS) δ17.72 (C-18, C-30), 20.84, 34.50, 35.63 (C-9,C-11,C-12), 33.56(C-13), 81.42(C-17), 110.02(C-22), 112.21(C-15), 120.19(C-20), 140.89(C-23), 142.66(C-21), 165.28(C-14), 171.05(C-16). Epimer (**5b**) was also obtained as white needles (mp 100-102°) from acetone-hexane. ^1H NMR ($CDCl_3$): δ1.17(3H,d,J=6.4,30Me), 1.32(3H,s,18-Me), 1.40-2.00(6H,m,H-9,H-11,H-12), 2.55(1H,m,H-8), 5.08(1H,s,H-17), 5.88(1H,m,H-15), 6.36(1H,m,H-22), 7.37(1H,m,H-23), 7.42(1H,m,H-21). ^{13}C NMR($CDCl_3$): δ17.39, 23.56(C-18,C-30), 20.92, 33.84, 36.31(C-9,C-11,C-12), 33.84(C-8), 39.92(C-13), 80.68(C-17), 109.86(C-22), 111.51(C-15), 121.56(C-20), 141.46(C-23), 143.00(C-21), 164.50(C-14), 170.36(C-16). HRMS Calc. for $C_{15}H_{18}O_3$:246.1251; Found: 246.1257.

Compounds (3) and (8). To 500 mg of **5a** in 20 ml of MeOH were added 2 ml of 50% H_2O_2 at 0°C. One ml 6N NaOH was then added dropwise over 10 min. and stirring continued at RT for 48 hr. The mixture was then poured into water and extd. with 3x50 ml portions of $CHCl_3$. The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield (**3**) (0.43 g, 80%) as a pale yellow solid which was recrystallized from acetone-hexane to give colourless needles (mp 141-143°). ^1H NMR ($CDCl_3$): δ0.78(3H,d,J=6.7,30-Me), 1.03 (3H,s,18-Me), 1.20-1.80 (6H,m,H-9,H-11,H-12), 2.30(1H,m,H-8), 3.66(1H,s,H-15), 5.46(1H,s,H-17), 6.36(1H,m,H-22), 7.39(2H,m,H-23,H-21); ^{13}C NMR δ13.58, 14.42(C-18,C-30), 20.73(C-11), 29.42(C-8), 32.61(C-9,C-12), 38.63(C-13), 52.92(C-15), 68.10(C-14), 77.82(C-17), 110.03(C-22), 120.26(C-20), 140.98(C-23), 142.90(C-21), 167.98(C-16); HRMS Calculated for $C_{15}H_{18}O_4$: 262.1200 Found : 262.1206.

In a similar manner, (**8**) was prepared from (**5b**) in 80% yield as colourless needles (mp 114-115°). ^1H NMR ($CDCl_3$): δ0.78(3H,d,J=6.7,30Me), 1.12(3H,s,18-Me), 1.40-2.00(6H,m,H-9,H-11,H-12), 2.40(1H,m,H-8), 3.59(1H,s,H-23,H-21); ^{13}C NMR ($CDCl_3$): δ13.40, 17.29(C-18,C-30), 20.46(C-12), 29.17,34.70(C-9,C-11), 30.09(C-8), 39.29(C-13), 50.94(C-15), 69.43(C-14), 76.63(C-17), 110.10(C-22), 120.14(C-20), 141.05(C-23), 142.76(C-21), 167.82(C-16); HRMS Calc. for $C_{15}H_{18}O_4$: 262.1200; Found: 262.1204.

(±)-Pyroangolensolide (6). 100 mg of (**5a**) and 80 mg of NBS were refluxed for 45 min in 20 ml of CCl_4. Water was added and the mixture was extd. several times with $CHCl_3$. The combined extracts were evaporated and the residue treated with excess K_2CO_3 in MeOH to yield (**6**), mp 144-146° (Lit.[8] 146.2-146.8°). ^1H NMR ($CDCl_3$): δ1.04(3H,s), 1.88(3H,d,J=2), 2.28(2H,m), 5.14(1H,s), 5.88(1H,m), 6.20(1H,m), 6.50(1H,m), 7.52(2H,m). The spectrum agreed closely with that reported [8].

±-Epipyroangolensolide (7). (**7**) (mp 138-140°), Lit.[8] 140-141.3°) was prepared from (**5b**) using the same procedure as described above for (**6**). ^1H NMR ($CDCl_3$): δ1.38(3H,s), 1.90(3H,d,J=2), 2.30(2H,m), 5.14(1H,s), 5.94(1H,s), 6.18(1H,m), 6.32(1H,m), 7.35(2H,d,J=2), 7.44(2H,m). This spectrum agreed closely with that reported in the literature [8].

REFERENCES

1. V.K. Kapoor and A.S. Chawla, *J. Scient. Ind. Res.*, **42**, 503 (1986).
2. E.J. Corey, J.G. Reid, A.G. Myers and R.W. Hahl, *J. Am. Chem. Soc.*, **109**, 918 (1987).
3. W. Lottenbach and W. Graf, *Helv. Chim. Acta.*, **61**, 3087 (1978).
4. A.F. Mateos and J.A. de la Fuente Blanco, *J. Org. Chem.*, **56**, 7084 (1991).
5. M.D. Bentley, M.S. Rajab, A.R, Alford and M.J. *Mendel, Entomol. Exp. Appl.*, **49**, 189 (1988).
6. M.D. Bentley, M.S. Rajab, M.J. Mendel and A.R. Alford, *J. Agric. Food Chem.*, **38**, 1400 (1990).
7. Y. Fukuyama and T. Tokorayama, *Terahedron Letters*, 4869 (1973).
8. T. Tokoroyama, Y. Fukuyama, Y. Kotsuji, *J. Chem. Soc. Perkin. Trans.*, 445 (1988).