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SHORT COMMUNICATION

A FORMAL SYNTHESIS OF (±)-CALODENDROLIDE

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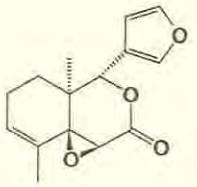
ABSTRACT. The synthesis of (±)-calodendrolide (**1**) from (±)-pyroangolensolide (**3**) has been achieved. Compound (**1**) represents a unique naturally occurring highly degraded limonoid with a structural feature common in several bioactive tetranortriterpenes.

INTRODUCTION

Calodendrolide (**1**) is a naturally occurring C_{15} highly degraded limonoid [1], isolated from *Calodendrum capensi* Thunb (Rutaceae) [2]. The structure of (**1**) is remarkable in that it retains the C/D ring segment of limonin and is a representative of a unique and abundant class of tetranortriterpenes [3]. Despite the wide spectrum of bioactivities displayed by the limonoids, to date, very few approaches have been reported on their synthesis [4-7]. Recently, we have been engaged in the synthesis of such compounds (7-10) and have reported the synthesis of (±)-dihydro-calodendrolide (**2**) [7]. We describe here a formal synthesis of (±)-calodendrolide (**1**) starting from (±)-pyroangolensolide (**3**).

RESULTS AND DISCUSSION

Tokoroyama *et al.* [11], recently reported the first total synthesis of **1**, their approach was, however, long and the yields very low. This, together with our continuing efforts to develop **1** as a general synthon for the synthesis of limonoids bearing ring C/D of limonin, prompted us to report herein our more efficient approach for the synthesis of **1**. Our strategy is based on the sequential two-step regio- and stereoselective epoxidation of (±)-pyroangolensolide (**3**) to give an α,β,γ,δ-diepoxide compound **5** followed by selective removal of the γ,δ-epoxide function to yield the target molecule (**1**). The starting derivative (**3**) was prepared as described previously [7]. We started by protecting the γ,δ-double bond in compound **3** as an epoxide group prior to the requisite stereoselective introduction of an epoxide function at the α,β-position. The oxidation of the diene (**3**) with mCPBA in CH_2Cl_2 produced the γ,δ-monoepoxide (**4**) in 95% yield. The configuration of the epoxy ring in **4** was tentatively assigned to be β from mechanistic considerations: attack of the reagent from the α-side would be hindered by the angular methyl group at C-8a. For the introduction of the second α,β-epoxy group to give the diepoxy derivative (**5**), the path *via* epoxidation by hydrogen



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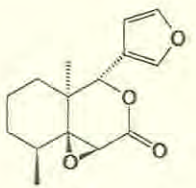

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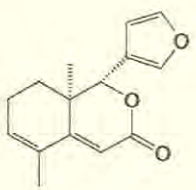

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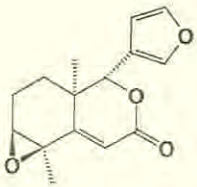

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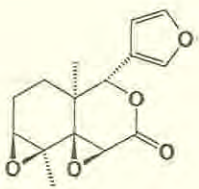

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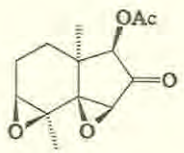

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peroxide in base was employed. Careful epoxidation of **4** with H_2O_2 in NaOH gave the α,β,γ,δ-diepoxide (**5**) as the only product in 90% yield. The configuration of the α,β-epoxide was similarly assigned to be β also from mechanistic consideration: attack of the reagent from the α-side would be hindered by the angular methyl group at C-8a. Also the chemical shift in the ^{1}H NMR of H-4 at δ3.95 is close to that of limonoids having a β-epoxide. This assignment was further supported by molecular mechanics (MM2, QCPE No. 396) calculations which were performed on the proposed compound (**5**) with the α,β-epoxide β and the other epoxide α. The compound with a β-oriented αβ-epoxide was more stable than the α isomer by 1.064 kcal. Assuming that the epoxidation reaction *via* H_2O_2/NaOH proceeds under product development control, where the product is similar to the transition state, we can argue that the transition state will have unfavourable interactions similar to those observed in the product. It thus follows that the formation of the compound with a β-oriented epoxide (**5**) will be energetically more favoured. Having the requisite diepoxide (**5**) in hand, attention was then directed to the selective conversion of the γ,δ-epoxide into a double bond. Tokoroyama *et al.* [11] in their synthesis of **1** failed to selectively deoxygenate a closely related compound (**6**). Interestingly, selective deoxygenation of the γ,δ-epoxy ring in our case was achieved with ease. Compound **5** was treated with *p*-TsOH/NaI/CH_3CN to give **1**, identical to a standard sample of the natural product, in 90% yield. In summary, since the synthesis of (±)-pyroangolensolide (**3**) has been achieved before [7,12], this accomplishes a formal synthesis of (±)-calodendrolide (**1**).

EXPERIMENTAL

^{1}H NMR spectra were obtained with a JEOL-90 MHz system at Addis Ababa University and a Varian XL-200 system at the University of Maine. Medium resolution mass

spectra was measured with VG GC-MS system at the International Center of Insect Physiology and Ecology, Nairobi. IR spectra were determined with a Shimadzu Infrared Spectrophotometer.

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

Compound 4. To a solution of (±)-pyroangolensolide (**3**) (200 mg, 0.820 mmol) in dichloromethane (25 ml) was added mCPBA in portion over 48 hr (50-60%, 344 mg, 2 mmol) and the mixture was stirred for a further 6 hr at RT. Dichloromethane (10 ml) was added and the solution washed successively with aq. $NaHCO_3$ and brine. The solution was then concentrated under vacuum and the residue (196 mg) purified by flash column chromatography (silica gel, acetone/hexane) to yield a colourless compound which was recrystallised from acetone to give 170 mg of pure **4** as needles m.p. 175-179°; IR (KBr) cm^{-1}: 2950, 1730, 1500, 1280, 1025, 880; ^1H NMR ($CDCl_3$): δ1.02 (3H, *s*, Me) 1.54 (3H, *s*, $CH_2CHOCMe$), 3.28 (1H, *m*, CH_2CHO), 5.12 (1H, *s*, CHOC), 6.29 (1H, *s*, =CHCOO), 6.41 (1H, *d*, furan), 7.41 (1H, *m*, furan), 7.46 (1H, *s*, furan); MS *m/z* (rel. int.): 260 [M^+] (2.83), 164 (85), 149 (11), 136 (100), 121 (35), 108 (25), 93 (22), 77 (1).

Compound 5. To 150 mg of *4* (0.577 mmol) in 5 ml of MeOH were added 1 ml of 30% H_2O_2 at 0 °. 6 N NaOH (0.5 ml) was then added dropwise over 10 min. and stirring continued at RT for five days. The mixture was then poured into water and extracted with chloroform. The combined extracts were dried over Na_2SO_4 and concentrated under vacuum to yield a crude product as a pale yellow solid which was recrystallised from acetone/hexane to give **5** (127 mg, 80%) as white needles m.p. 169-173 °; IR (KBr) cm^{-1}: 2950, 1730, 1500, 1280, 1025, 875; ^1H NMR (200 MHz, $CDCl_3$): δ0.98 (3H, *s*, Me), 1.31 (3H, *s*, Me), 3.24 (1H, *m*, CH_2CH-O), 3.95 (1H, *s*, COCHCO), 5.40 (1H, *s*, CHOCO), 6.34 (1H, *m*, furan), 7.40 (2H, *m*, furan); MS *m/z* (rel. int.): 276 [M^+] (55), 219 (6), 201 (9), 191 (16), 137 (38), 124 (55), 95 (100), 91 (30), 80 (27), 77 (29).

(±)-Calodendrolide (1): To **5** (50 mg, 0.181 mmol) in 5 ml of CH_3CN were added NaI (54 mg, 0.360 mmol) and *p*-toluenesulphonic acid (34 mg, 0.18 mmol) and the mixture stirred at RT for 2 hr. The crude product was recrystallised from acetone/hexane to give **1** (42 mg, 90%) as white needles m.p. 146-148 °; IR (KBr) cm^{-1}: 2950, 1730, 1500, 1280, 1025, 875; ^1H NMR (200 MHz, $CDCl_3$): δ0.99 (3H, *s*, Me), 1.60 (3H, *m*, CH_2CH=CMe), 2.20 (2H, *m*, furan) and 7.41 (2H, *m*, furan); MS, *m/z* (rel. int.): 260 [M^+] (2), 232 [M^+ - CO] (31.5), 217 [M^+ - $COCH_3$] (??), 203 (11), 189 (9), 107 (45), 137 (100). The IR and ^1H NMR spectra were superimposable with those of the natural product under the same conditions and with the same instruments.

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