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A new strategy for the synthesis of (+)-vernolepin related compounds: an unusual sulfene elimination leads to the 2-oxa-*cis*-decalin skeleton

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Abstract

A new strategy for the synthesis of (+)-vernolepin (**1**), (+)-vernodalin (**2**), and (+)-8-deoxyvernolepin (**3**), from the accessible germacrolides (+)-salonitenolide (**4**) and (+)-costunolide (**5**), has been developed. The key steps in the synthesis are a Cope rearrangement from the germacradiene to the elemadiene skeleton, the cyclization of a *trans*-fused δ-lactone from an epoxy ester, and an unusual sulfene elimination, which promotes a reaction cascade leading to the 2-oxa-*cis*-decalin skeleton.

Keywords: antibiotics; antitumour compounds; lactones; terpenoids; sulfonyl compounds.

(+)-Vernolepin (**1**) and (+)-vernodalin (**2**), from the Ethiopian plants *Vernonia hymenolepis*[1] and *V. amygdalina*,[2] respectively, and the synthetic derivative 8-deoxyvernolepin[3] (**3**), form a small group of sesquiterpene dilactones with a 10-vinyl-2-oxa-*cis*-decalin skeleton. They have interesting biological properties, such as antitumour capacity both in vitro and in vivo,[3–7] and anti-aggregating,[8] de-aggregating,[8] spasmolytic,[8] antiparasitic[9] and potent antibiotic[10] activities. These properties together with their unique chemical structure have attracted the attention of chemists. Thus, the groups of Grieco,[3,11] Danishefsky,[12] and others[13,14] have reported the total synthesis of **1** and/or **3**, but these syntheses all require numerous steps and generally provide low overall yields of racemic products. Vernodalin (**2**) has not been synthesised yet.

Semisynthesis constitutes a valuable alternative for the enantiospecific preparation of bioactive substances. In this way, some procedures for the synthesis of (+)-8-deoxyvernolepin from (−)-α-santonin have been reported.[7,15–17] Nevertheless, these procedures have not been extended to the synthesis of **1** and **2**, probably due to the lack of an adequate functional group at C-8 in α-santonin. We recently developed a new strategy for the synthesis of 8-*epi*-vernolepin derivatives.[18,19] With some modifications, this procedure can be adapted to the enantiospecific synthesis of **1**–**3** from the accessible germacrolides (+)-salonitenolide (**4**) and (+)-costunolide (**5**) (Scheme 1). (+)-Salonitenolide is abundant in several species of the widespread genus

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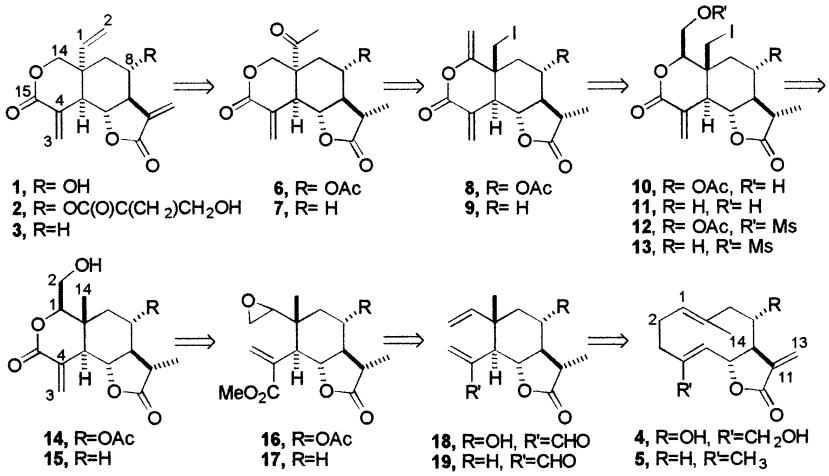
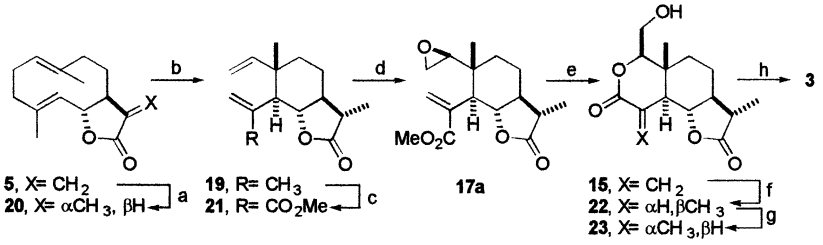
Centaurea,[19,20], whilst (+)-costunolide can be isolated in (multi)gram quantities from the commercially available extract Costus Resinoid.[21,22]



Scheme 1. Retrosynthesis from **1**–**3** to the germacrolides **4** and **5**

Taking the first step of Scheme 1 (from **6** and **7** to **1**–**3**) to be feasible using conventional methodology, the second step was planned on the basis of our experience gained from previous work.[18,19] Thus, **6** and **7** could be obtained from **8** and **9**, respectively, via an intramolecular substitution of the corresponding iodine atom by the carboxylate ion derived from selective saponification of the enol lactone group. The synthesis of dienes **8** and **9**, by means of β-elimination reactions from mesylates **12** and **13**, must be quite straightforward. Halohydrins **10** and **11** could be prepared from alcohols **14** and **15** by remote functionalization at C-14, taking advantage of the adequate spatial arrangement of the OH groups. Electrophilic opening of the epoxides **16** and **17** could lead to ring closure of the δ-lactones **14** and **15**, probably leaving their hydroxymethyl groups in the expected equatorial position. Finally, the methodology for the Cope rearrangements from germacrolides (**4** and **5**) to elemanolides (**18** and **19**) would be that previously proven in our laboratory.[19,21]

Following Scheme 1, we started the synthesis of **3** (Scheme 2) with the chemoselective reduction of α-methylen-γ-lactone **5**, in order to avoid subsequent complications with this reactive Michael acceptor group. Thus, mild hydrogenation of **5** took place stereoselectively by the β face of the conjugated double bond.



Scheme 2. Reagents, conditions and yields. (a) H_2 atmospheric pressure, Pd/C 10%, MeOH, mild stirring, 2 h, 93%. (b) Sealed tube, 205°C, 5 min, 88%. (c) i. SeO_2, *t*-BuOOH, CH_2Cl_2; ii. PDC; iii. $NaClO_2$, 2-methyl-2-butene *t*-BuOH, H_2O; iv. CH_2N_2, 72% from **19**. (d) Dimethyldioxirane, Me_2CO, 77%. (e) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 93%. (f) H_2/Pd, MeOH, 81%. (g) DBU, toluene, 100°C, 80%. (h) Ref. 17

Thermal Cope rearrangement conditions produced an equilibrium mixture of the germacrolide **20** itself and the elemanolide **19** at a 1/2 (**20**/**19**) ratio. The remaining germacrolide was recovered from the mixture and re-used, giving 88% yield of **19** after three turnovers. Ester **21**, obtained from **19**, reacted with dimethyldioxirane[23] to give a mixture of **17a** (77%) and its 1*R*-epimer **17b** (11%). As we had expected, electrophilic opening of the oxirane **17a** provided dilactone **15**† in high yield. The 1*R* configuration of **15** was indicated by the chemical shift of C-14 and was confirmed by NOE experiments. Under the same conditions **17b** gave a mixture of **15** and its 1*S*-epimer (C-14 at 20.2 ppm). Catalytic hydrogenation of **15** led to **22**, which isomerized to the more stable epimer **23** under basic treatment. The chemical transformation of **23** into (+)-8-deoxyvernolepin (**3**) has been recently reported[17] and thus the preparation of **23** (Scheme 2) constitutes a formal synthesis of **3** from **5**.

Two reports, however, deal with the difficulties involved in building the Δ^3 exocyclic double bond of **3**, avoiding mixtures with an endocyclic regioisomer and the corresponding yield fall.[7,15] Therefore, we decided to preserve the exocyclic double bond of **15** and develop a new procedure to accomplish the last steps in the synthesis of 8-deoxyvernolepin (Scheme 3). In this way, transformation of **15** into **11** was attempted using different reagents.[24] Under the conditions indicated in Scheme 3, a 30% yield of **11** was obtained, but 60% of **15** could be recovered and re-used, increasing the iodohydrin yield to almost 50%. Unexpectedly, base treatment of the mesylate **13**, obtained from **11**, directly gave the *cis*-fused δ-lactone **24**‡ (in its ^{1}H NMR spectrum, the signals from the C-3 and C-14 methylenes show chemical shifts, multiplicities and *J* values in agreement with those of the *cis*-fused α-methylen-δ-lactone unit of vernolepin).[25] Compound **9** (see Scheme 1) was not detected. Under the same conditions, iodohydrin **11** produced only ether **26** (Fig. 1), indicating the critical role sustained by the mesylate group in the formation of **24**. The base-promoted elimination of sulfene from a mesylate is an unusual reaction, although evidence of sulfene formation from methanesulfonyl chloride in the presence of pyridine has been reported.[26] With this idea in mind, the reaction cascade depicted in Scheme 4 is proposed to explain the base-promoted formation of **24** from **13**.

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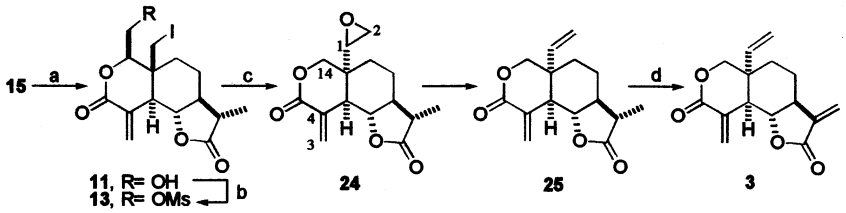
† Compound **15**: white powder; 169–170°C; $[\alpha]_D^{25}$ +60.6 (*c* 0.53, $CHCl_3$); IR (film) ν_{max} 3477, 2939, 1779, 1720, 1627, 1185 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.63 (1H, d, J=2.5 Hz, H-3a), 6.10 (1H, d, J=2.5 Hz, H-3b), 4.28 (1H, t, J=5.2 Hz, H-1), 3.97 (1H, t, J=10.3 Hz, H-6), 3.78 (2H, m, H-2), 2.66 (1H, dt, J=2.5, J=10.3 Hz, H-5), 2.34 (1H, dq, J=12.4, J=6.9 Hz, H-11), 1.25 (3H, d, J=6.9 Hz, H-13), 0.95 (3H, s, H-14); NOE-dif experiments: H irradiated (NOE observed), H-1 (H-5), H-2 (H-1, H-14), H-5 (H-1), H-6 (H-11, H-14), H-14 (H-6, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.3 (s, C-12), 164.1 (s, C-15), 133.5 (s, C-4), 130.2 (t, C-3), 89.7 (d, C-1), 79.3 (d, C-6), 61.3 (t, C-2), 51.8 (d, C-7), 49.9 (d, C-5), 40.5 (d, C-11), 38.4 (s, C-10), 34.3 (t, C-9), 22.7 (t, C-8), 13.9 (q, C-14), 12.5 (q, C-13); NMR assignments have been made with the aid of 2D NMR experiments; EIMS *m*/*z* (rel. int.) 280 (4) $[M]^+$, 249 (100), 203 (34), 175 (28), 147 (22), 91 (44), 55 (56); HRFABMS *m*/*z* 281.1391 (calcd for $C_{15}H_{21}O_5$ 281.1389); anal. C, 63.76; H, 7.56%, calcd for $C_{15}H_{20}O_5$, C, 64.27; H, 7.19%.

‡ Compound **24**: oil, ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.76 (1H, t, J=1.0 Hz, H-3a), 5.98 (1H, t, J=1.0 Hz, H-3b), 4.55 (1H, d, J=12.3 Hz, H-14a), 4.14 (1H, dd, J=12.3, J=1.6 Hz, H-14b), 3.89 (1H, dd, J=10.7 Hz, H-6), 2.95 (1H, dd, J=3.9, J=2.8 Hz, H-1), 2.82 (1H, dd, J=3.9 Hz, H-2a), 2.79 (1H, dd, J=3.9, J=2.8 Hz, H-2b), 2.66 (1H, da, J=10.7 Hz, H-5), 2.37 (1H, dq, J=12.5, J=6.9 Hz, H-11), 1.30 (3H, d, J=6.9 Hz, H-13); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 177.95 (s, C-12), 163.71 (s, C-15), 135.17 (t, C-3), 131.41 (s, C-4), 81.01 (d, C-6), 70.01 (t, C-14), 56.99 (d, C-1), 50.11 (d, C-7), 45.84 (t, C-2), 42.82 (d, C-5), 41.53 (d, C-11), 29.77 (t, C-9), 23.02 (t, C-8), 12.61 (q, C-13). HRFABMS *m*/*z* 301.1056 (calcd for $C_{15}H_{18}O_5Na$ 301.1052).



Scheme 3. Reagents, conditions and yields. (a) HgO, I_2, hν (two 100 W tungsten filament lamps), CH_2Cl_2/CCl_4, reflux, 8 h, 49%; (b) MsCl, Et_3N, CH_2Cl_2, 75%; (c) DBU, THF, 0°C, 43%; (d) Ref. 15

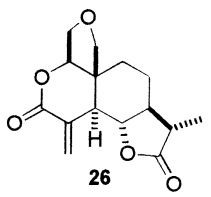
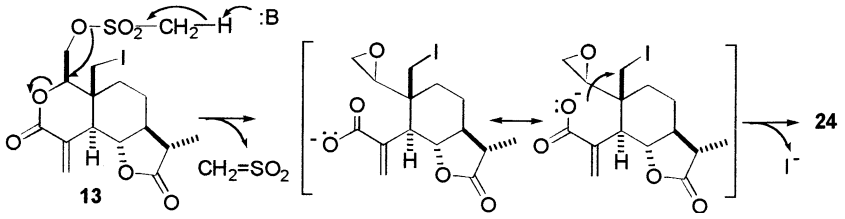


Figure 1.



Scheme 4. Mechanism proposed for the chemical transformation of **13** into **24**

The direct transformation from **13** into **24** reduces the number of steps foreseen in retrosynthetic Scheme 1. This fact, together with the excellent yields reported for the procedures used to restore the $\Delta^{11,13}$ double bond of **3** (in contrast to those for Δ^3),[7,15] are encouraging incentives to complete the syntheses of **1**–**3** following the strategy developed through this work.

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