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Synthesis of (+)-Vernolepin Related Compounds from Germacranolides

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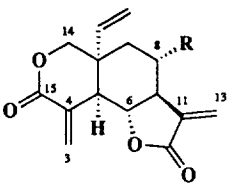
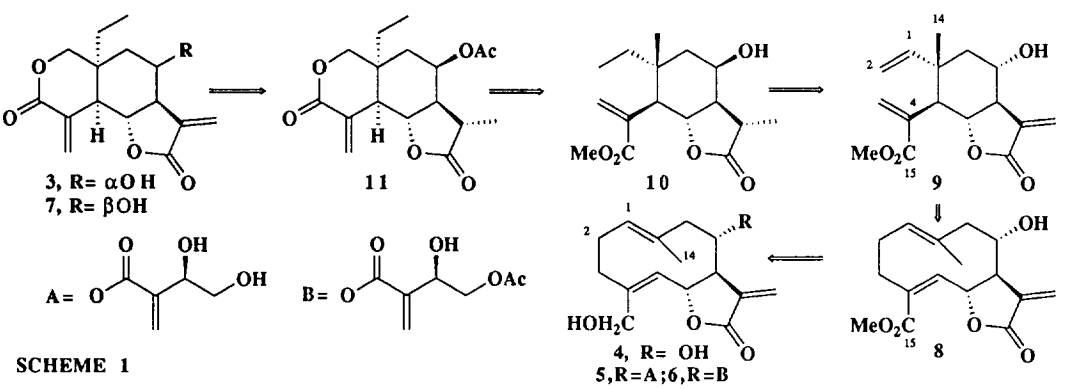
Abstract: (+)-8-O-acetyl-1,2,11,13-tetrahydro-8-*epi* -vernolepin (**11**) was synthesized from salonitenolide (**4**). The key steps were the Cope rearrangement of the germacradiene skeleton to elemadiene and the long-range functionalization at C-14, which allows the intramolecular cyclisation necessary for the formation of the δ-lactone ring of **11**.

(+)-Vernolepin[1] (**1**) is a sesquiterpene dilactone with spasmolytic, anti-aggregating and de-aggregating activities,[2] as well as antitumoral activity *in vitro* and *in vivo* .[3] It has been synthesized as a racemic mixture by several authors[4] and, recently, two enantioselective procedures,[5,6] which take place in a number of steps, have been described. The antitumoral power of **1** resides basically in the α-methylene-γ-lactone group and is enhanced by the additional α-methylene-δ-lactone.[3b] However, the hydroxyl at C-8 and the angular vinyl groups seem to be irrelevant for the activity. Thereby 8-deoxyvernolepin[7] (**2**) and 1,2-dihydrovernolepin[3b] (**3**) have an activity analogous to that of **1** against the tumoral cell lines assayed. Some procedures[8] for the preparation of (+)-8-deoxyvernolepin (**2**), starting from α-santonin , have been developed. But **2** lacks the OH group at C-8 , which could be chemically employed for the introduction of lateral chains in order to modulate the activity of vernolepin. In this paper, a new strategy for the enantioselective synthesis of vernolepin derivatives, functionalized at C-8, is described.



1, R= OH
2, R= H



3, R= αOH
7, R= βOH

11

10

9

4, R= OH
5,R=A;6,R=B

8

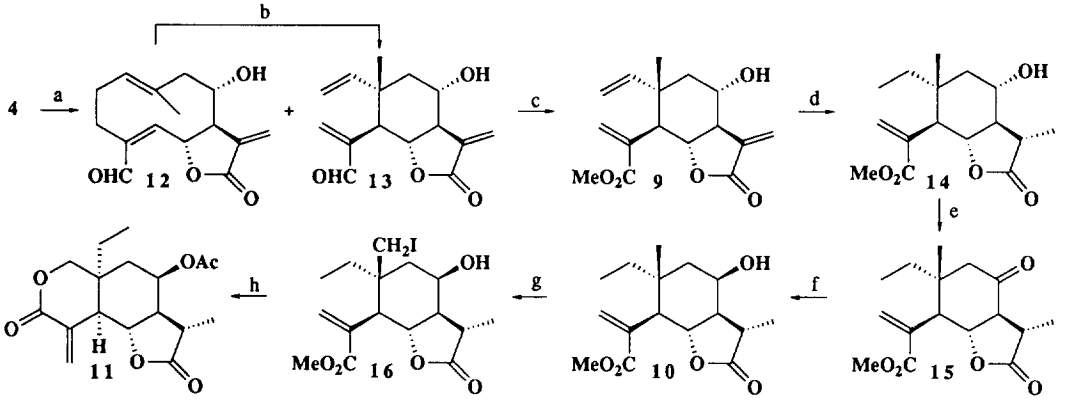
A=

B=

SCHEME 1

Salonitenolide (**4**), cnicin (**5**) and monoacetylcnicin (**6**) are germacranolides found abundantly in the Plant Kingdom. Besides other Compositae, they occur in notable quantities in distinct species of the *Centaurea* genus,[9] from which they can be extracted by simple immersion of the fresh plant material in organic solvents.[9b] Furthermore, selective saponification of the lateral chains of **5** and **6** generated **4**.[9b] These observations prompted the authors to use these compounds as starting material in a retrosynthetic scheme (Scheme 1) designed for the enantioselective preparation of 1,2-dihydro-8-*epi* -vernolepin (**7**).The key steps of the retrosynthetic scheme are the Cope rearrangement of the germacradiene skeleton to elemadiene and the introduction of a functional group at C-14 of **10**, which allows the intramolecular cyclisation necessary for the formation of the δ-lactone ring of **11**.

Taking Scheme 1 into account, the authors obtained (+)-8-O-acetyl-1,2,11,13-tetrahydro-8-*epi*-vernolepin (**11**) from **4** in eight steps at good yields (Scheme 2).

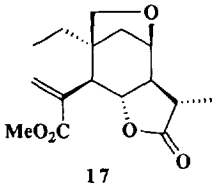


SCHEME 2. Reagents and conditions : a) TPAP (0.06 equiv), NMO (1.6 equiv), molecular sieves 4Å, THF, rt, 1h. b) Toluene, reflux, 10 min, 75% overall yield of **13**. c) (i) $NaClO_2$ (9.2 equiv), 2-methyl-2-butene (excess), NaH_2PO_4/H_2O (0.8M, 7 equiv), t-BuOH, rt, 2h; (ii) CH_2N_2 (excess), Et_2O, -15°C, 15 min, 84% overall yield. d) H_2 (atmospheric pressure)/Pd/C, MeOH, rt, 5h, 95% yield. e) PCC (2 equiv), NaOAc (0.5 equiv), CH_2Cl_2, 18h, 87%. f) L-Selectride® (1 equiv), THF, -78°C, 40 min, 98%. g) $PhI(OAc)_2$ (1.9 equiv), I_2 (0.75 equiv), cyclohexane, hν (200 W tungsten-filament lamp), 40°C, 8h, 68%. h) (i) Ac_2O (excess), pyridine, rt, 12h; (ii) NaOAc (1 equiv), DMF, reflux, 1h 30 min, 86% overall.

The regioselective oxidation of the primary hydroxyl group of **4**, with tetrapropylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO) generated a 38% yield of the 15-oxogermacranolide **12** and 38% of the elemanolide **13** (14% of **4** was recovered). The formation of **13**, during a reaction taking place at room temperature, indicated the facility with which the Cope rearrangement occurs once the formyl group at C-15 has been formed. With this idea in mind, the preparation of the germacranolide **8** (Scheme 1) was discarded and **12** was heated in toluene under reflux. After ten minutes **12** had almost completely been rearranged to **13** (98% yield).

The treatment of **13** with sodium chlorite was found to be the best method for the oxidation of the conjugated aldehyde. In the ^1H NMR spectrum of the methyl ester **9**,[10] the coupling constant between H-5 and H-6 was 11.9 Hz, indicating their *trans* -diaxial arrangement. The α disposition of the new C-13 methyl group in the tetrahydrogenate **14** was established on the basis of the NOEs observed between H-13 (1.33 ppm, d, $J_{11,13}$= 6.9 Hz) and H-7 (1.71 ppm, ddd, $J_{6,7}$= 10.7, $J_{7,8}$= 10.5 , $J_{7,11}$= 12.1 Hz) and between H-11 (2.56, dq) and H-6 (4.24 ppm, dd, $J_{5,6}$= 11.9 Hz). The inversion of the configuration of C-8 was carried out in two steps: oxidation of **14** and stereoselective reduction of the ketone **15**. In the ^1H NMR spectrum of the alcohol **10**, the coupling constant $J_{7,8}$ was 2.2 Hz, showing the equatorial position of H-8.

Long-range functionalization at the C-14 methyl group of **10**, generated the iododerivative **16**.[11] Its CIMS shows the $[M+H]^+$ ion at *m/z* 423, in agreement with the molecular formula $C_{16}H_{23}IO_5$, and in its ^1H NMR spectrum the diastereotopic hydrogens of the iodomethylene group resonate as two coupled signals (J= 9.6 Hz) centered at 3.22 and 4.04 ppm. Iodohydrins like **16** have been described in the hypoiodite reaction.[12] These intermediates generally evolve to cyclic ethers such as **17**. In the case described here, however, together with **16** only 13% of **17** was obtained (9% of **10** was recovered). Analysis by molecular mechanics of **16** showed its minimum energy conformation (depicted in Figure 1). The bulky iodine atom of C-14 is directed to the outside of the molecule and the methoxycarbonyl group is located facing the opposite side of the same carbon. Thereby, nucleophilic OH attack on C-14 is difficult.



17

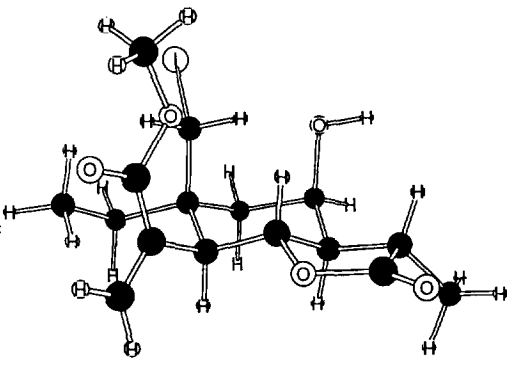


FIGURE 1

Finally, **16** was acetylated and treated with NaOAc in DMF under reflux. The nucleophilic intramolecular substitution of the iodine atom took place and **11**[13] was obtained. In its ^1H NMR spectrum, the characteristic signals of the δ-lactone of (+)-vernolepin[1] appeared at 4.69 (d, H_a-14) and 3.95 (dd, H_b-14) ppm.

Oxidation of the selenide formed via enolate is a well established method for restoring the $\Delta^{11(13)}$ double bond of (+)-vernolepin related compounds.[8]

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10. Compound **9**: White crystals, m.p. 124-126° C; $[\alpha]_D$ +105.0 (c 0.98, $CHCl_3$); IR ν_{max} ($CHCl_3$) 3465, 2934, 1749, 1718,1629, 1279, 1138, 970 cm^{-1}; CIMS *m/z* (rel. int.) 293 $[M+H]^+$ (80), 275 $[293-H_2O]^+$ (100), 243 $[275-CH_3OH]^+$ (76); ^1H NMR ($CDCl_3$, 300 MHz) δ: 6.36 (1H, s, H_a-3), 6.12 (1H, d, H_a-13), 5.98 (1H, d, H_b-13), 5.48 (1H, s, H_b-3), 4.89 (1H, d, H_a-2), 4.83 (1H, d, H_b-2), 4.18 (1H, dd, H-6), 4.06 (1H, dddd, H-8), 3.66 (3H, OMe), 3.14 (1H, br d, H-5), 2.67 (1H, dddd, H-7), 2.49 (1H, OH), 1.84 (1H, dd, Hβ-9), 1.64 (1H, br dd, H_α-9), 0.96 (3H, s, H-14) ppm; J (Hz): $1,2_a$=10.7, $1,2_b$= 17.3, 5,6=11.9, 6,7=11.1, 7,8=10.2 , $7,13_a$=3.1 , $7,13_b$=3.0 , $8,9_\alpha$=10.7 , $8,9_\beta$=4.3 , 8,OH=5.1 , $9_\alpha,9_\beta$=13.1; ^{13}C NMR ($CDCl_3$, 75 MHz) δ (from C-1 to C-15): 145.4, 112.3, 127.5, 135.7, 48.6, 77.7, 54.7, 67.2, 49.2, 41.9, 137.4, 170.0, 120.5, 17.6, 167.6, 51.9 ($CO_2\underline{C}H_3$) ppm.
11. Compound **16**: Oil, $[\alpha]_D$ +10.5 (c 0.98, $CHCl_3$); IR ν_{max} (film) 3502, 2933, 1774, 1717, 1625, 1438, 1263, 1174, 1014, 756 cm^{-1}; CIMS *m/z* (rel. int.) 423 $[M+H]^+$ (13), 405 $[423-H_2O]^+$ (6), 295 [423-HI]+ (13), 57 (100); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.50 (1H, s, H_a-3), 5.69 (1H, s, H_b-3), 4.79 (1H, dd, H-6), 4.29 (1H, m, H-8), 4.04 (1H, d, H_a-14), 3.75 (3H, s, OMe), 3.38 (1H, br d, H-5), 3.22 (1H, dd, H_b-14), 2.74 (1H, dq, H-11), 2.24 (1H, dd, Hβ-9), 1.92 (1H, br s, OH), 1.75 (1H, ddd, H-7), 1.61 (1H, ddd, H_α-9), 1.58 (1H, dq, H_a-1), 1.22 (3H, d, H-13), 1.04 (1H, dq, H_b-1), 0.84 (3H, t, H-2) ppm; J (Hz): $1_a,1_b$=14.7 , $1_a,2=1_b,2$=7.4, 5,6=12.1 , 6,7=10.7 , 7,8=2.3 , 7,11=12.6 , $8,9_\alpha$=2.6 , $8,9_\beta$=3.1 , $9_\alpha,9_\beta$=15.4 , $9_\alpha,14_b$=2.0 , 11,13=7.0 , $14_a,14_b$=9.6 ; ^{13}C NMR (100 MHz, $CDCl_3$) δ (C-1 to C-15): 32.3, 8.1, 129.3, 136.1, 45.7, 75.7, 56.3, 65.2, 40.3, 41.7, 37.2, 178.6, 12.3, 22.2, 167.5, 52.4 ($CO_2\underline{C}H_3$) ppm.
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13. Compound **11**: Oil, $[\alpha]_D$ +27.0 (c 0.10, $CHCl_3$); IR ν_{max} (film) 2971, 2935, 1782, 1742, 1718, 1620, 1378, 1235, 1164, 1045, 1015 cm^{-1}; CIMS *m/z* (rel. int.) 323 $[M+H]^+$ (100), 295 $[323-CO]^+$ (56), 279 $[323-CO_2]^+$ (42); ^1H NMR (400 MHz, $CDCl_3$) δ: 6.73 (1H, d, H_a-3), 5.90 (1H, dd, H_b-3), 5.32 (1H, ddd, H-8), 4.69 (1H, d, H_a-14), 4.30 (1H, dd, H-6), 3.95 (1H, dd, H_b-14), 2.65 (1H, br dd, H-5), 2.37 (1H, dq, H-11), 2.09 (3H, s, $COC\underline{H}_3$), 1.84 (1H, ddd, H_α-9), 1.74 (1H, dd, Hβ-9), 1.62 (1H, dq, H_a-1), 1.44 (1H, dq, H_b-1), 1.24 (3H, d, H-13), 0.89 (3H, t, H-2) ppm; J (Hz): $1_a,1_b$=14.7 , $1_a,2=1_b,2$=7.5 , $3_a,3_b$=0.8 , $3_b,5$=1.4 , 5,6=11.6 , 6,7=10.8 , 7,8=2.3 , 7,11=12.7 , $8,9_\alpha$=2.5 , $8,9_\beta$=3.8 , $9_\alpha,9_\beta$=16.0 , $9_\alpha,14_b$=2.0 , 11,13=6.9 , $14_a,14_b$=12.2; ^{13}C NMR (100 MHz, $CDCl_3$) δ (C-1 to C-15): 30.1, 7.1, 136.0, 130.6, 48.1, 76.0, 52.8, 66.3, 35.3, 37.9, 37.6, 177.2, 12.5, 70.6, 164.0, 169.7 ($O\underline{C}OCH_3$), 21.1 ($OCO\underline{C}H_3$) ppm.

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