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Synthesis of Calicoferol E and Astrogorgiadiol, Two Marine 9,10-Secosteroids

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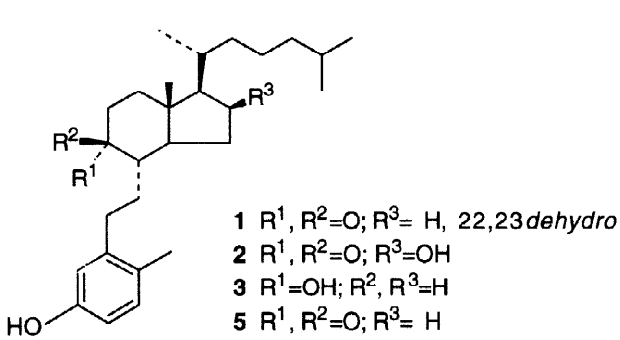
Abstract

The synthesis of two marine 9,10-secosteroids, calicoferol E and astrogorgiadiol, has been achieved starting from vitamin D_3. The conceived approach establishes a general convergent strategy toward the synthesis of 9,10-secosteroids.

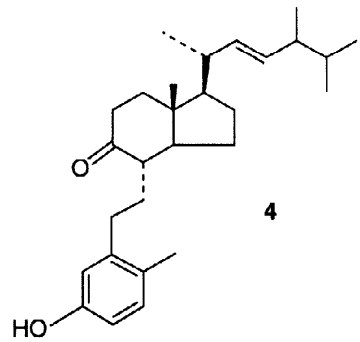
Keywords: Marine metabolites; Sterols; Radical reactions.

Among the unusual marine steroids there is a small group of 9,10-secosteroids that show interesting bioactivities [1]. Calicoferol A (**1**) and B (**2**), isolated from a gorgonian of the genus *Calicogorgia* [2], are toxic against brine shrimp larvae; astrogorgiadiol (**3**), isolated from a gorgonian of the genus *Astrogorgia* [3], inhibits cell division in fertilised starfish eggs, while calicoferol D (**4**), isolated from a gorgonian of the genus *Muricella* [4], exhibits potent activity against *Herpes simplex* viruses I and II and *polio* virus.

Due to their interesting bioactivities, and as a part of our synthetic studies on marine steroids [5,6], we report here a convergent route for the synthesis of calicoferol E [4] (**5**) and astrogorgiadiol (**3**), amenable to the synthesis of other members of this family of natural products.



1 R^1, R^2=O; R^3= H, 22,23*dehydro*
2 R^1, R^2=O; R^3=OH
3 R^1=OH; R^2, R^3=H
5 R^1, R^2=O; R^3= H



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In the successful synthetic plan (Scheme 1) we have presumed that the electrophilic hydrindan core (**6**) could be accessible from vitamin D_3, through the known Grundmann's ketone (**7**) [7-9]. In the key step we planned the introduction of the C_8 aromatic fragment **8** through an ionic or radical coupling to **6**. Target 9,10-secosteroids **5** and **3** could finally be generated by deprotection and stereoselective reduction of the formed adduct.

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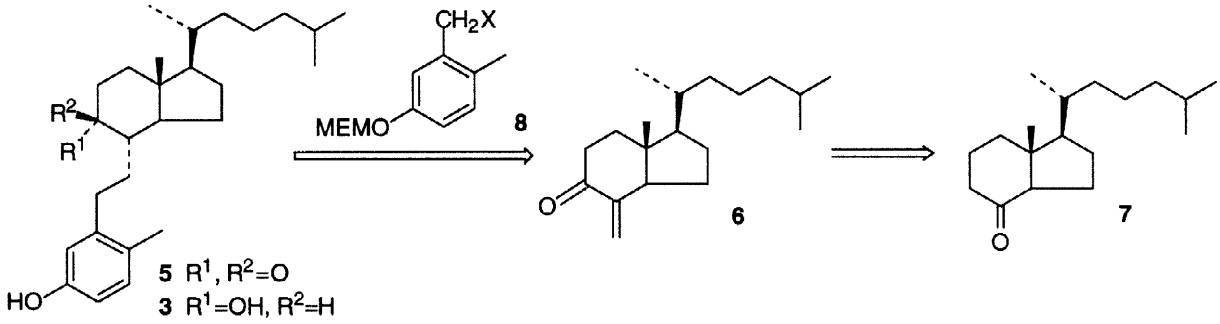
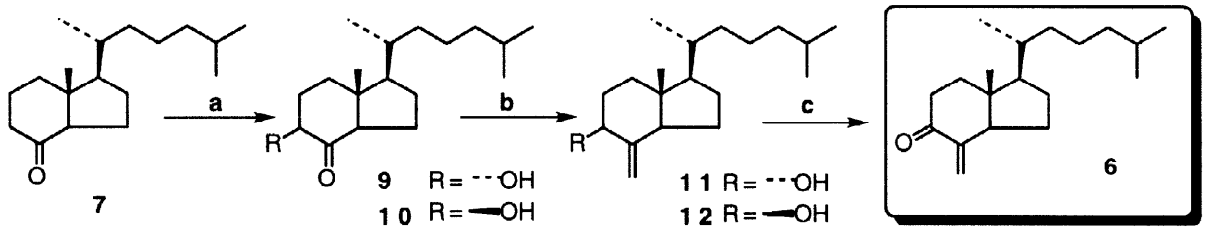
Scheme 1



For the synthesis of the hydrindan portion (Scheme 2) we took advantage of the recently synthesized α-hydroxy Grundmann's ketone [10]. A 7.2 : 1 mixture of the α- and β-epimers **9** and **10** was prepared in 82% yield by treating the kinetic enolate of **7** ($NaN(SiMe_3)_2$, -78°C) with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide) (MoOPH), prepared according to the Mimoun's procedure [11,12]. Methylenation of the unprotected α-hydroxy ketones **9** and **10** with Nysted's reagent [13] gave the allylic alcohols **11** and **12**. Oxidation of the mixture of **11** and **12** with tetra-*n*-propylammonium perruthenate (TPAP) and N-methylmorpholine N-oxide (NMO) [14] gave the α,β-unsaturated ketone **6**[1] in 72% yield. The ketone **6** was previously prepared through a tedious procedure [15] as a possible starting material for the synthesis of vitamin D analogs.

Scheme 2[a]



[a]*Reagents and Conditions*: **a**. $NaN(SiMe_3)_2$, THF , -78°C; MoOPH , -60°C, 82%; **b**. Nysted, $TiCl_4$, CH_2Cl_2-THF, r.t., 50%; **c**. TPAP, NMO, m.s., CH_2Cl_2, r.t., 72%.

The synthesis of the aromatic fragment is presented in Scheme 3. Treatment of the readily available 2-methyl-5-nitrobenzoic acid (**13**) with absolute ethanol/H_2SO_4 [16] afforded the ethyl ester **14**. This was catalytically reduced [17] to the 2-methyl-5-aminobenzoic ester (**15**) in quantitative yield and then converted to phenol **16** *via* the diazonium salt, by radical oxidation in presence of copper salts [18]. Conversion of **16** to the corresponding MEM-ether (**17**) [19] and reduction with an excess of $LiAlH_4$ [17] afforded the benzyl alcohol **18**, which was converted [20] to the benzyl chloride **19**. Finally, sodium iodide displacement [21] furnished the iodide **20**[2] in 33% overall yield from **13**.

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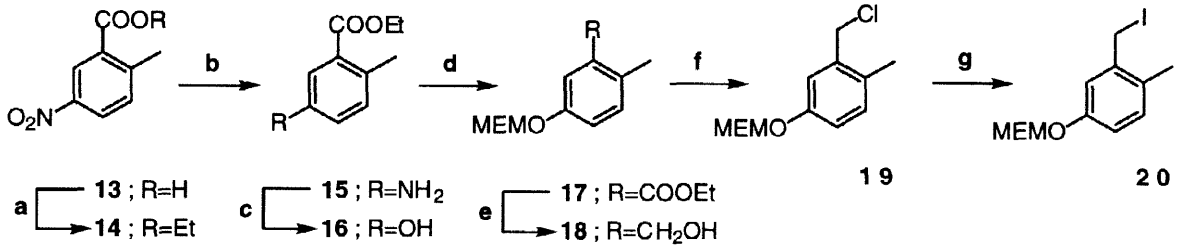
[1] ^{1}H-NMR δ ($CDCl_3$, 250 MHz): 0.73 (3H, s, CH_3-18), 0.87 (6H, d, J=6.5 Hz, CH_3-26 and CH_3-27), 0.94 (3H, d, J=6.0 Hz, CH_3-21), 5.00 (1H, t, J=2.2 Hz, H-7), 5.91 (1H, t, J=2.2 Hz, H-7'). ^{13}C-NMR δ ($CDCl_3$, 62.5 MHz): 11.7, 18.7, 22.5, 22.8, 23.2, 23.8, 28.0, 28.9, 29.7, 35.9, 36.3 (x 2), 39.4, 43.2, 54.2, 55.6, 118.0, 147.6, 202.3. EI-MS *m/z*: 276 (M^+), 247, 205, 163. $[\alpha]_D$=+39.3° (c=0.9, $CHCl_3$).

[2] ^{1}H-NMR δ ($CDCl_3$, 400 MHz): 2.26 (3H, s, Ar-CH_3), 3.38 (3H, s, $OCH_2OCH_2CH_2OCH_3$), 3.56 (2H, m, $OCH_2OCH_2CH_2OCH_3$), 3.82 (2H, m, $OCH_2OCH_2CH_2OCH_3$), 4.39 (2H, s, CH_2I), 5.23 (2H, s, $OCH_2OCH_2CH_2OCH_3$), 6.88 (1H, dd, J=8.3, 2.5 Hz, H-2), 7.01 (1H, d, J=2.5 Hz, H-4), 7.03 (1H, d, J=8.3 Hz, H-1). ^{13}C-NMR δ ($CDCl_3$, 100 MHz): 4.9, 18.0, 59.0, 67.5, 71.5, 93.6, 116.3, 116.9, 129.8, 131.8, 137.9, 155.6.

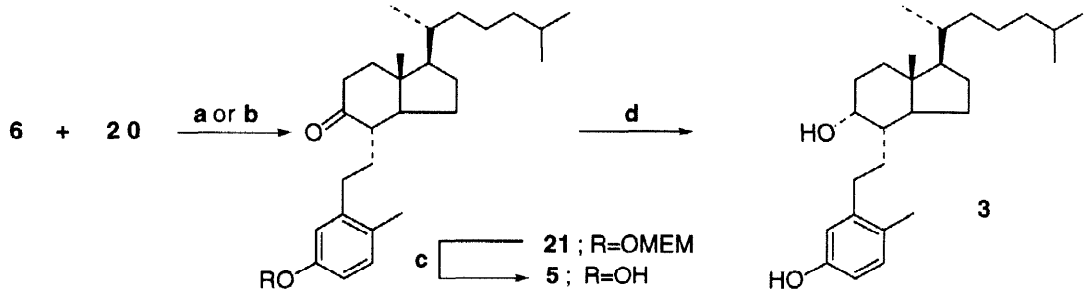
Scheme 3[a]



[a]*Reagents and conditions*: **a**. EtOH, H_2SO_4, traces, 94%; **b**. H_2, Pd/C, EtOH, r.t., 100%; **c**. *i*. $NaNO_2$, H_2SO_4, H_2O, 0°C; *ii*. $Cu(NO_3)_2 \cdot 2{,}5\ H_2O$, Cu_2O, H_2O, r.t., 81%; **d**. $EtN(i\text{-}Pr)_2$, MEMCl, CH_2Cl_2, r.t., 75%; **e**. $LiAlH_4$, THF, r.t., 84%; **f**. LiCl, MsCl, 2,6-lutidine, DMF, 0°C, 82%; **g**. NaI, $NaHCO_3$, acetone, reflux, 81%.

Preliminary attempts to couple the hydrindan **6** with the aromatic fragment were made by use of a copper-mediated 1,4-addition of a Grignard reagent formed from chloride **19**, a route which was previously reported for the synthesis of (+)-estrone 3-methyl ether [22]. However these efforts were hampered by extensive Wurtz coupling of **19** during the reaction with magnesium. The coupling of the two compounds (Scheme 4) was then accomplished *via* radical coupling using both the Giese-Chatgilialoglu's procedure with tris(trimethylsilyl)silane (TTMSS) as radical mediator [23-27], and the Hershberger's procedure, using tributylgermanium hydride as agent for the reductive coupling [28].

Scheme 4[a]



[a]*Reagents and conditions*: **a**. TTMSS, AIBN, toluene, 80°C, 28% (38%, based on recovered starting material); **b**. Bu_3GeH, AIBN, acetonitrile, reflux, 21%; **c**. HCl, MeOH, r.t., 61%; **d**. $K(sec\text{-}Bu)_3BH$, r.t., 81%.

The success of C-C bond formation by means of these methodologies depends on the ability to optimise reactivities and concentrations of the radical species in the path followed by the radical chain. We thus performed the reaction varying the time of addition of reactants and of radical precursors. Although an excellent diasteroselectivity in the formation of the adduct **21** was observed in both reactions (^{1}H-NMR analysis), low yields were obtained (28% and 21%, respectively, scheme 4).

Deprotection of compound **21** furnished calicoferol E (**5**)[3]. Stereoselective reduction of **5** using K-Selectride® [29] gave astrogorgiadiol (**3**)[4]. The optical rotations, ^{1}H- and ^{13}C-NMR

[3] ^{1}H-NMR δ ($CDCl_3$, 400 MHz): 0.87 (6H, d, J=6.5 Hz, CH_3-26, CH_3-27), 0.93 (3H, d, J=6.5 Hz, CH_3-21), 0.98 (3H, s, CH_3-18), 2.24 (3H, s, CH_3-19), 6.57 (1H, dd, J=8.1, 2.7 Hz, H-2), 6.67 (1H, d, J=2.7 Hz, H-4), 6.98 (1H, d, J=8.1 Hz, H-1). ^{13}C-NMR δ ($CDCl_3$, 100 MHz): 11.5, 18.4, 18.5, 22.5, 22.8, 23.8, 25.1, 27.6, 28.0, 29.0, 31.0, 35.6, 35.9, 38.3, 38.5, 39.4, 42.8, 50.4, 55.0, 55.2, 112.5, 115.7, 128.0, 131.0, 142.5, 153.7, 213.4. EI-MS *m/z*: 398 (M^+), 277, 268, 264, 249, 223. $[\alpha]_D$=+21.6° (c=0.6, $CHCl_3$).

[4] ^{1}H-NMR δ ($CDCl_3$, 400 MHz): 0.69 (3H, s, CH_3-18), 0.86 (3H, d, J=6.6 Hz, CH_3-26 or CH_3-27), 0.87 (3H, d, J=6.6 Hz, CH_3-27 or CH_3-26), 0.92 (3H, d, J=6.5 Hz, CH_3-21), 2.22 (3H, s, CH_3-19), 2.42 (1H, ddd, J=13.5, 10.7, 3.4 Hz, H-6), 2.69 (1H, ddd, J=13.5, 11.1, 3.4 Hz, H-6'), 4.05 (1H, bs, H-9), 6.57 (1H, dd, J=8.1, 2.7 Hz, H-2), 6.65 (1H, d, J=2.7 Hz, H-4), 6.97 (1H, d, J=8.1 Hz, H-1).^{13}C-NMR δ ($CDCl_3$, 100 MHz): 11.5, 18.4, 18.5, 22.5, 22.8, 23.8, 25.1, 27.6, 28.0, 29.0, 31.0, 35.6, 35.9, 38.3, 38.5,

spectra of **3** and **5** are in excellent agreement with those of the natural products. Pharmacological studies are in progress.

To sum up, the first convergent synthesis of marine 9,10-secosteroids has been achieved. The synthetic strategy can be expanded to other members of this family of natural products. Somewhat disappointing was the yield of the coupling step, even if it shows high level of stereoselectivity.

Acknowledgements

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39.4, 42.8, 50.4, 55.0, 55.2, 112.5, 115.7, 128.0, 131.0, 142.5, 153.7, 213.4. EI-MS *m/z* =400 (M^+), 382, 367. $[\alpha]_D$=- 4.6° (c=0.2, $CHCl_3$).