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# Stereocontrolled synthesis of contignasterol's side chain

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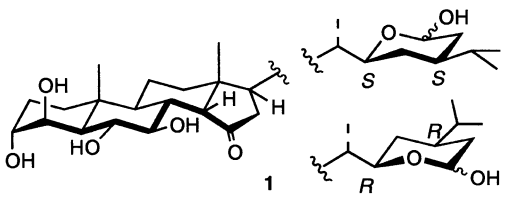
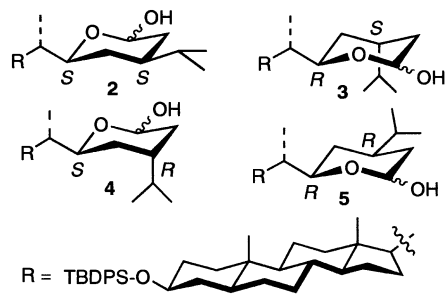
**Abstract**—The four models of the contignasterol's side chains (**2**–**5**) have been stereospecifically prepared. The key reaction in the synthesis is a dimethylaluminum chloride-mediated 'ene' reaction between the steroid derivative **6** and the *pseudo*-enantiomeric aldehydes **7** and **8**. © 2001 Elsevier Science Ltd. All rights reserved.

The recent isolation of potent anti-inflammatory compounds, such as contignasterol[1] (**1**), a highly oxygenated steroid isolated from the sponge *Petrosia contignata* Thiele, and xestobergsterol,[2] has been followed by extensive biological studies[3] but few synthetic works.[4]

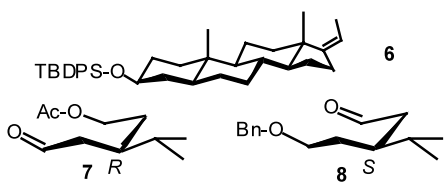


As a part of our studies on the synthesis of steroids we focused our attention on contignasterol (**1**), a polyhydroxysteroid presenting in its structure a 15-keto functionality, a rare CD-*cis* ring junction and an unprecedented side chain hemiacetal tetrahydropyranyl. Accurate NMR studies by Andersen et al.[1] allowed the partial structural assignment of **1**. The relative stereochemistries at C-22 and C-24 side chain's stereogenic centers were established to be (22*S*,24*S*) or (22*R*,24*R*). Attempts to determine the absolute configuration on a derivative of **1**, gave ambiguous results.[1]

In order to assign the absolute configurations at the stereogenic centers of the contignasterol's side chain and with the idea to settle the basis for future investigations toward its total synthesis, here we report the stereospecific synthesis of the four side-chain models **2**–**5**, the formation of the related acetates, and the assignment of the target side chain's stereochemistries.



Our approach, an extension of the method developed by Koreeda and co-workers,[5] relies on a stereospecific pericyclic coupling between the protected (*Z*)-17(20)-ethylidene steroid **6** and the partner *pseudo*-enantiomeric aldehydes **7** and **8**.



The chosen strategy allows the stereocontrolled simultaneous introduction of all the side chain's stereogenic centers (C-20, C-22 and C-24).

Our first goal was the preparation of the (*Z*)-3β-[(*tert*-butyldiphenylsilyl)oxy]-5α-pregn-17-(20)-ene (**6**). This was obtained in a two-step sequence[6] (98% overall yield) starting from the commercially available *epi*-androsterone (**9**), as reported in Scheme 1.

The synthesis of the aldehydes **7** and **8** was achieved from (*R*)-limonene (**11**) in seven and nine steps (22 and 10% overall yield, respectively; Schemes 2 and 3).[7]

*Keywords*: contignasterol; anti-inflammatory compounds; steroids; marine metabolites.

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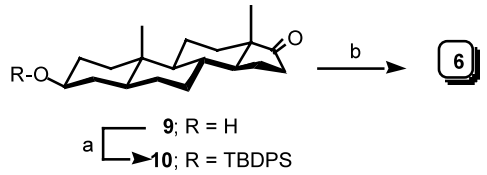
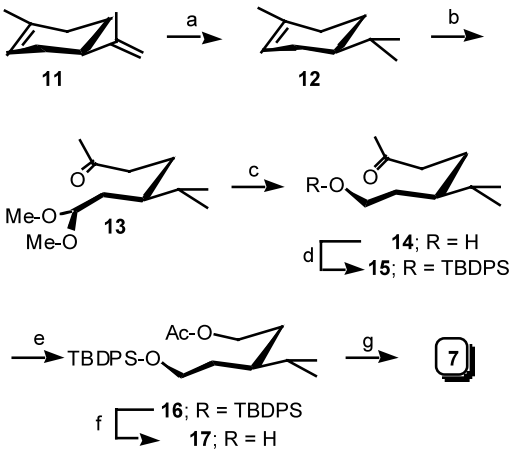
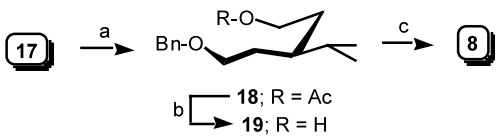



**Scheme 1.** *Reagents and conditions*: (a) 1.4 equiv. DBU, 1.2 equiv. TBDPSCl, $CH_2Cl_2$, overnight, quant.; (b) 2.7 equiv. *t*-BuOK, 3.0 equiv. $EtPPh_3Br$, THF, 3 h, reflux, 98%.




**Scheme 2.** *Reagents and conditions*: (a) 1 equiv. $H_2$, $PtO_2$, MeOH; (b) (i) $O_3$, $CH_2Cl_2$, MeOH, −60°C, 1 h, (ii) 2.8 equiv. $Me_2S$, 0.07 equiv. *p*-TsOH, MeOH, −60→0°C, 1 h, 60%, overall; (c) (i) 3% $HClO_4$ in $H_2O$/THF (1:1). quant., (ii) 1.2 equiv. $LiAl(OC(C_2H_5)_3)_3H$, THF, −78°C, 1 h, 98%; (d) 1.4 equiv. DBU, 1.2 equiv. TPBDSCl, $CH_2Cl_2$, overnight, 96%; (e) 3 equiv. MCPBA, $CHCl_3$, reflux, 48 h, quant.; (f) 1.1 equiv. TBAF, THF, 0°C, 1 h, 60%; (g) 2 equiv. PDC, $CH_2Cl_2$, MS 4 Å, 2 h, 66%.




**Scheme 3.** *Reagents and conditions*: (a) 1.1 equiv. $Ag_2O$, 1.3 equiv. BnBr, $CH_2Cl_2$, 57%; (b) $K_2CO_3$, MeOH, 40°C, 8 h, 81%; (c) 2 equiv. PDC, $CH_2Cl_2$, MS 4 Å, 2 h, 66%.

The synthesis of **7** started with a selective hydrogenation of **11** to give (*R*)-menthene (**12**). Oxidative cleavage of the double bond and subsequent in situ protection of the unstable aldehyde (not isolated) gave the keto-acetal **13**. The keto-alcohol **14** was formed by mild hydrolysis of the corresponding dimethyl acetal (3% solution of $HClO_4$ in THF/$H_2O$), followed by chemoselective reduction with lithium tris[(3-ethyl-3-pentyl)oxy]aluminohydride.[7a] Protection of the hydroxy group as *t*-butyldiphenylsilyl ether was necessary to ensure a quantitative yield in the Baeyer–Villiger reaction step.[7a] Fluoride induced desilylation[8] and pyridinium dichromate (PDC) oxidation[9] gave the enantiopure building block **7**.

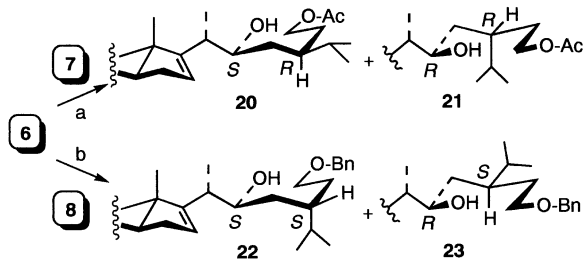
The synthesis of **8** (Scheme 3) was achieved through benzylation of the alcohol **17**,[10] $K_2CO_3$-induced deacetylation of the ether **18** and Cr(VI)-mediated oxidation of the free primary alcohol.

The continuation of the synthesis required the coupling of the steroid **6** with the partner aldehydes **7** and **8** (Scheme 4). Both the 'ene' reactions were accomplished uneventfully. As expected the (20*S*,22*S*) adducts **20** and **22** were prevalent and easily separated from their (20*S*,22*R*) minor epimers **21** and **23**.[11]

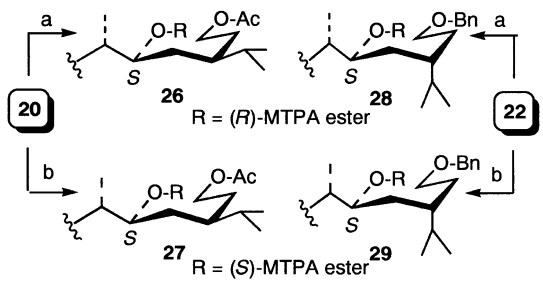
The indicated stereochemistries were assigned on the strength of comparative analysis with the results of Koreeda and co-workers.[5] The (*S*)-C-22 absolute configuration of the major adducts **20** and **22** was confirmed according the modified Mosher's esters method[12] (Scheme 5) through comparison of the $^1H$ NMR and COSY spectra of the α-methoxy-α-(trifluoromethyl)phenylacetate (MTPA) derivatives **26**–**29**.[13]

The stage was now set for the construction of the side chain tetrahydropyran present in **1**. Deprotection of the adducts **20**–**23** (Scheme 6) and stereoselective $\Delta^{16}$-hydrogenation, afforded the four stereoisomeric diols **30**–**33**.

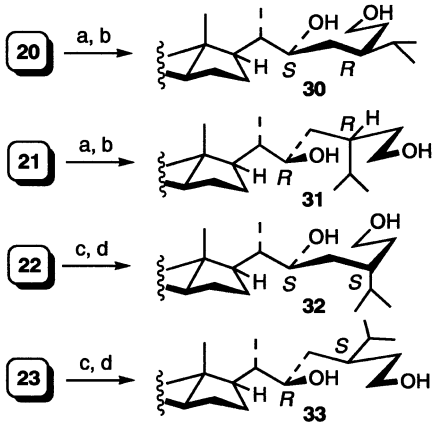
The β-orientation of the side chain was assigned according literature data.[14] It is known, in fact, that the stereoselectivity of the hydrogenation depends on the CD-ring junction: CD-*trans* junction induces the formation of β-oriented side chains (natural configuration); CD-*cis* junction brings to unnatural C-17α side chains.




**Scheme 4.** *Reagents and conditions*: (a) 3.1 equiv. **7**, 6.2 equiv. $Me_2AlCl$, $CH_2Cl_2$, −78→−30°C, 6 h, **20**: 80%, **21**: 16%; (b) 3.1 equiv. **8**, 6.2 equiv. $Me_2AlCl$, $CH_2Cl_2$, −78→−30°C, 6 h, **22**: 50%, **23**: 10%.



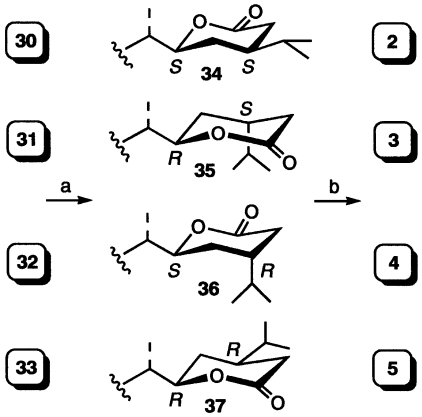

**Scheme 5.** *Reagents and conditions*: (a) 3 equiv. (*S*)-(+)-MTPA-Cl, pyr., 0.5 h, quant.; (b) 3 equiv. (*R*)-(−)-MTPA-Cl, pyr., 0.5 h, quant.



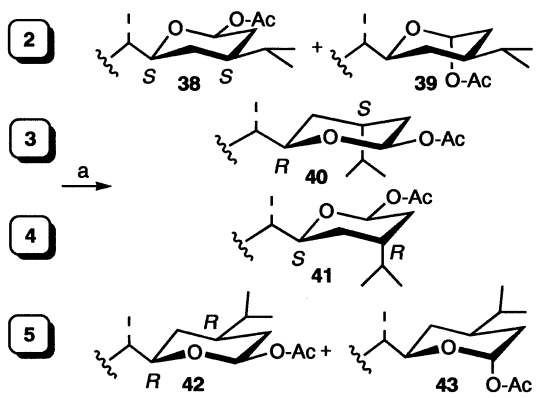

**Scheme 6.** *Reagents and conditions*: (a) $K_2CO_3$, MeOH; (b) $H_2$, Pt/C, EtOH, quant. (two steps); (c) $H_2$, Pd/C, EtOH; (d) $H_2$, Pt/C, EtOH, quant. (two steps).

The side-chain cyclization was oxidatively achieved using the ruthenium complex $(PPh_3)_3RuCl_2$ (Scheme 7).[15] The δ lactones (**34**–**37**) were reduced with DIBAL-H[16] affording the desired lactols **2**–**5** in excellent yields.

The assignment of the side chain's stereogenic centers was possible only after acetylation of the free hydroxy groups[17] (Scheme 8). Surprisingly, lactols **3** and **4** gave




**Scheme 7.** *Reagents and conditions*: (a) 1 equiv. $RuCl_2(PPh_3)_3$, benzene, 6 h (**34**: 70%; **35**: 70%; **36**: 88%, **37**: 87%); (b) 3 equiv. DIBAL-H, $CH_2Cl_2$, −78°C (**2**: 93%; **3**: 98%; **4**: 76%, **5**: 83%).

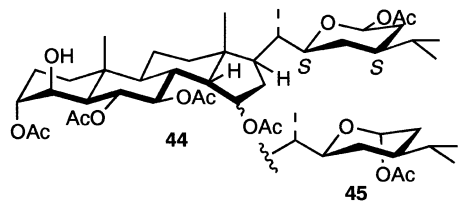



**Scheme 8.** *Reagents and conditions*: (a) $Ac_2O$, pyr., 24 h, 50–60%.

predominantly the supposed C-29 equatorial acetoxy epimers **40** and **41** ($^1$H NMR analysis).[18]

Table 1 shows the similarity of the $^1$H NMR values between compound **44**,[1] synthesized by Andersen, through reduction and acetylation of contignasterol and our models **38** and **42**, thus confirming the (22*S*,24*S*) or (22*R*,24*R*) Andersen's relative stereochemistry assignment. The (22*S*,24*S*) side chain's absolute configurations are suggested for contignasterol considering:

1. that the resonance value of H-29 in synthetic **38** is almost coincident with the resonance value found in the pentaacetate **44** (**44**: $\delta_{H\text{-}29}=5.75$; **38**: $\delta_{H\text{-}29}=5.76$ while for **42**: $\delta_{H\text{-}29}=5.93$);
2. the almost identical $^1$H NMR values showed by the minor epimers **45** and **39** found in mixture with **44** and **38**, respectively (see Table 1).[19]




In conclusion the synthesis and a tentative assignment of the side chain's absolute configurations of contignasterol have been reported. Future efforts in our laboratory will be directed to the total synthesis of **1**.

**Table 1.** Comparison of selected $^1$H NMR data ($C_6D_6$, 400 MHz) among models **38**–**43** and the pentaacetate derivatives of contignasterol **44** and **45** (multiplicities and coupling constants are reported in parenthesis)

| $^1$H at C | **38** | **39** | **40** | **41** | **42** | **43** | **44** | **45** |
|---|---|---|---|---|---|---|---|---|
| 21 | 1.11 (d, 6.8) | – | 1.08 (d, 6.8) | 1.10 (d, 6.7) | 1.12 (d, 6.8) | – | 1.03 (d, 6.8) | – |
| 22 | 3.50 (dd, 10.1, 2.0) | 3.96 (m) | 4.10 (dt, 10.8, 3.8) | 4.04 (bd, 10.3) | 3.52 (bd, 11.1) | 4.09 (bd, 11.7) | 3.54 (dd, 9.4, 5.9) | 3.96 (m) |
| 26 | 0.75 (d, 6.8) | – | 0.81 (d, 7.0) | 0.83 (d, 7.0) | 0.76 (d, 6.8) | – | 0.74 (d, 6.8) | – |
| 27 | 0.76 (d, 6.8) | – | 0.83 (d, 7.0) | 0.83 (d, 7.0) | 0.78 (d, 6.8) | – | 0.76 (d, 6.8) | – |
| 29 | 5.76 (dd, 9.5, 2.2) | 6.49 (d, 2.7) | 6.82 (dd, 5.0, 4.9) | 6.35 (dd, 5.0, 4.9) | 5.93 (dd, 9.8, 1.9) | 6.59 (bs) | 5.75 (dd, 9.7, 2.2) | 6.49 (d, 2.7) |
| $COCH_3$ | 1.76 (s) | 1.75 (s) | 1.73 (s) | 1.73 (s) | 1.73(s) | 1.74 (s) | 1.76 (s) | 1.76 (s) |

## Acknowledgements

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7. For the first steps, see: (a) Mase, T.; Ichita, J.; Marino, J. P.; Koreeda, M. *Tetrahedron Lett.* **1989**, *30*, 2075–2078; (b) Hudlicky, T.; Fleming, A.; Radesca, L. *J. Am. Chem. Soc.* **1989**, *111*, 6691–6707.
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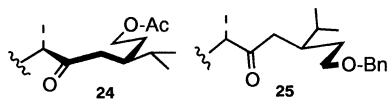
11. When less than 2.0 equiv. of the Lewis acid were used, an Oppenauer-like oxidation gives variable amounts of the ketones **24** and **25** (10–15%). Interestingly, the reduction of those ketones with $NaBH_4$ in absolute ethanol/THF (95:5) affords preferentially the alcohols **21** and **23** (**24**→**21**: 56%, **20**: 14%; **25**→**23**: 58%, **22**: 12%).

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13. $\Delta\delta=\delta_S-\delta_R$ ($CDCl_3$, 400 MHz): **26** and **27**: $H_{20}$: $\Delta\delta=+0.01$ ppm, $CH_3$-21: $\Delta\delta=+0.08$ ppm, $H_{16}$: $\Delta\delta=+0.08$ ppm, $H_{23}$: $\Delta\delta=-0.07$ ppm, $H'_{23}$: $\Delta\delta=-0.09$ ppm, $CH_3$-26: $\Delta\delta=-0.01$ ppm; $CH_3$-27: $\Delta\delta=-0.01$ ppm; **28** and **29**: $H_{20}$: $\Delta\delta=+0.04$ ppm, $CH_3$-21: $\Delta\delta=+0.08$ ppm, $H_{16}$: $\Delta\delta=+0.11$ ppm, $H_{23}$ and $H'_{23}$: $\Delta\delta=-0.04$ ppm, $CH_3$-26: $\Delta\delta=-0.06$ ppm, $CH_3$-27: $\Delta\delta=-0.03$ ppm.
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17. The acetylation 'eliminates the effects of the hemiacetal epimerization which complicates the $^1$H NMR'.[1]
18. The absence of the epimer with the axial acetoxy group can be understood considering the unfavorable C-24/C-29 1,3-diaxial interaction.
19. The $^1$H NMR data shown in Table 1 for the minor epimer **45** were not reported by Andersen et al.[1] even though its resonances are evident in the spectrum of **44**, kindly provided to us by Professor R. Andersen.