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A Convenient Synthesis of the Side-Chain of Sterols

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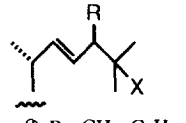
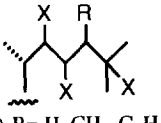
Abstract: *Potassium t-butoxide-induced Ramberg-Bäcklund rearrangement of chlorosulfones formed from a cyclopregnane-20-thiomethanol derivative has been shown to give Δ^{22}-unsaturated steroids with high* trans *stereoselectivity.*

A huge number of exotic sterols[1] have been characterised in plants and animals over the past thirty years.[2] Whatever their origin, these modified steroids are structurally characterised by the appendage of a dehydrogenated and/or hydroxylated androstane skeleton to a so-called modified side-chain. A few of the more common structures are shown.



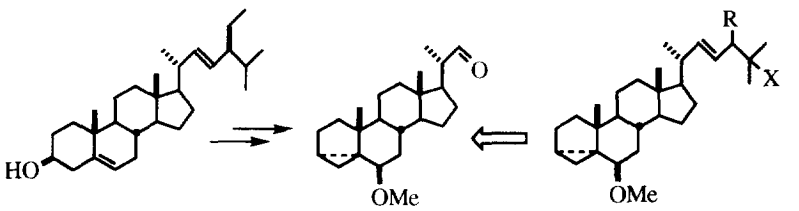
α (or β)-R= CH_3, C_2H_5
X= H, OH
type a



α (or β)-R= H, CH_3, C_2H_4OH
X= H, OH
type b

The structural complexity of these sterols, combined with their scarcity and their interesting biological -*inter alia* antibiotic, phytohormonal, antifeedant- properties, has induced a thriving synthetic activity.[2a, 3]

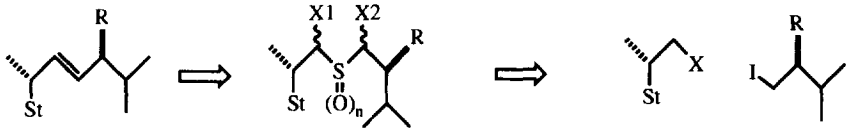
A useful strategy for preparing steroids bearing a side-chain of *type a* is based on the use of stigmasterol **1**, a readily available sterol of vegetal origin. Protection of the ring unsaturation in **1** by performing a homoallylic rearrangement, followed by cleavage of the residual carbon-carbon double bond affords the aldehyde **2**, which can be converted into *type a* derivatives by means of appropriate olefination reagents.[4]



1 **2** **3**

Complications can rise occasionally however, resulting essentially from the sensitivity of aldehyde **2** and, in a lesser extent, from the incomplete stereoselectivity of the used reagents.[4f]

As part of our ongoing work on the synthesis of polyhydroxylated steroids,[5] we needed to prepare compounds related to **3b**. Having prepared **2** from stigmasterol as described,[4a] we noted that some epimerisation took place effectively at C-20, in the aldehyde **2**, either during its purification by chromatography (silica gel) or on attempted condensation with a lithiosulfone.[6] This prompted us to study the following scheme in order to avoid the aforementioned difficulties.



3a, R=H
3b, R=C_2H_5

9a-b, n=0; X_1,X_2=H
10a, n=2; X_1,X_2=H
11a-b, n=0; X_1(or X_2)=H; X_2(or X_1)=Cl
12a-b, n=2; X_1(or X_2)=H; X_2(or X_1)=Cl

4, X=OH **8a-b**
5, X=I
6, X=SC(O)CH_3
7, X=SH

St=(3α,5α)-cyclo-(6β)-methoxy-pregnane

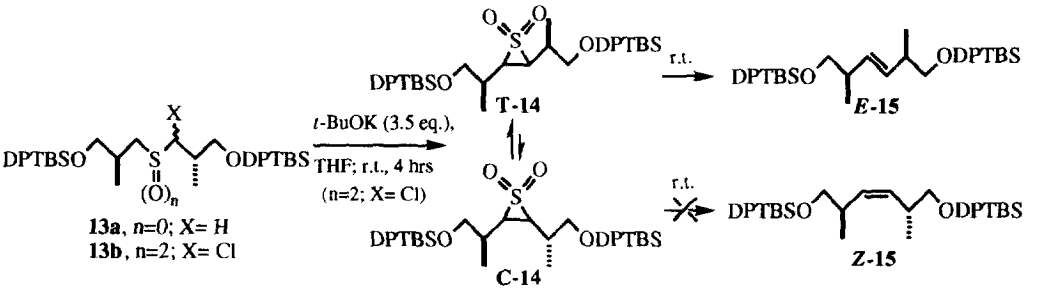
Ozonolysis of compound **3b** under improved conditions was immediately followed by LAH reduction.[7] The resulting alcohol **4** was converted into the iodide **5** (87%). Treatment of **5** by sodium thioacetate in acetone[8] gave the thioacetate **6** (90%), which, by reduction (LAH, THF), furnished the pure thiol **7** (96%). Stereochemical integrity at C-20 could be ascertained for each step of the sequence by NMR spectroscopy, indeed an accurate diagnostic presently. Condensation of the sodium salt of **7** with the iodides **8a-b** (NaH, DMF; r.t., overnight) gave the sulfides **9a** (85%) and **9b** (87%), respectively. Sulfide **9a** was eventually oxidised (MCPBA, $NaHCO_3$) into the corresponding sulfone **10a**.

First attempt to convert directly the sulfone **10a** into the corresponding olefin by using improved modifications of the Ramberg-Bäcklund rearrangement (RBR)[9] proved disappointing. Subsequent efforts to chlorinate **9a**, in order to obtain **11a** (hence **12a**, after MCPBA oxidation), by using recommended reagents[9d, 10] were also ineffective: complex mixtures resulted. Consequently, our quest of suitable conditions was pursued with a simpler, more accessible model substrate, **13a**.[11a]

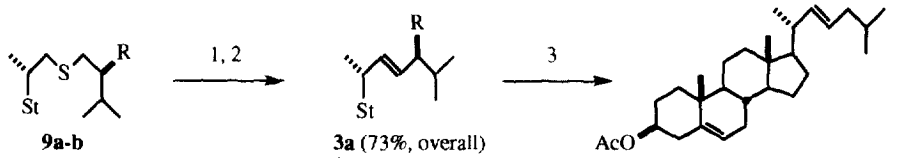
After much experimental work, it appeared that, according to a procedure described by Paquette,[12a] addition of the sulfide **13a** to a preheated (90°C; bath) solution of NCS (1 eq.) in CCl_4, followed by filtration of the formed succinimide after a few minutes and treatment of the filtrate by MCPBA (1 eq.) in the presence of $NaHCO_3$ (1.5 eq.) resulted in the clean formation of the chlorosulfone **13b** in good yield (83%; overall). Treating this chlorosulfone with *t*-BuOK (2eq.), a base known for promoting the *E* selectivity in relevant cases,[12b] in THF, for 2 hours at room temperature, resulted in the formation of a less polar compound, which proved (NMR) to be the pure *trans* RBR product ***E*-15**,[11b] accompanied by the *cis* episulfone **C-14**,[11c] we confused initially with the starting chlorosulfone **13b** (about the same Rf in TLC). The apparent stability of this episulfone was confirmed independently by heating a $CDCl_3$ solution of **C-14** in a NMR-tube: the *cis* olefin ***Z*-15** was not formed at an appreciable rate before the temperature reached 80°C (bath).

Taking advantage of earlier Bordwell's results,[12b,c] we then treated the episulfone **C-14** by an excess of base (3.5 eq.; in THF) for a longer time (4 h), still at room temperature, with the hope that **C-14** would be epimerised into the *trans* sulfone **T-14**, leading thus to the desired *trans* compound ***E*-15**. This occurred effectively and subsequent treatment of a THF solution of chlorosulfone **13b** by *t*-BuOK (3.5 eq.; 4 hours at room temperature) resulted in the isolation of pure ***E*-15** (87%; 73% overall, from **13a**).

On the whole, this stereoselective olefination process is likely to occur as outlined below.



Applying these chlorination/oxidation conditions to sulfides **9a** and **9b** gave, respectively, the chlorosulfones **12a** and **12b**, as mixture of isomers. Finally, reaction of these chlorosulfones with excess *t*-BuOK gave in high yield the corresponding unsaturated steroids **3a** and **3b**, which were identified either by subsequent transformation[4a] into the known acetate **16** (**3a**) or by comparison with an authentic sample (**3b**).[13]



9a-b

3a (73%, overall)
3b (70%, overall)

16 (89%), m.p.120-121°C(MeOH);
$[\alpha]_D$ -61, *c*=1.5 (CH_2Cl_2)

Reagents and conditions: 1- NCS (1 eq.), CCl_4; 90°C, 15 mn; then, MCPBA (1 eq.), $NaHCO_3$ (1.5 eq.); r.t., 3 hrs; 2- *t*-BuOK (3.5 eq.), THF; r.t., 3-4 hrs; 3- $Zn(OAc)_2$ (8 eq.), AcOH, reflux, 2hrs.

In conclusion, in proper conditions, the Ramberg-Bäcklund reaction is highly efficient for preparing stereoselectively (*E*)-Δ^{22}-steroids from alcohol **4**, a stable product easily available from stigmasterol.

Acknowledgements: We thank the "Ministère de l'Enseignement, de la Recherche, et de la Technologie" for a grant (to T. S.).

References and Notes

1- Vitamin D metabolites have to be included.

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6- Lithiated *iso*-amyl phenylsulfone was tested as a possible reagent for preparing **3a** from **2** by a Julia-Paris-Kocienski coupling reaction. Apart the moderate yield, the recovered aldehyde **2** was contaminated with its epimer (at C-20), which was characterised as the corresponding alcohol, ***epi*-4**, after reduction (LAH, THF) and chromatography (silica gel, CH_2Cl_2/ether); ^{13}C NMR: *i)* ***epi*-4**:12.72, 13.15, 16.77, 19.36, 21.56. 22.8, 24.12, 25.02, 27.75, 30.53, 33.43, 35.12, 35.32, 38.03, 39.79, 42.65, 43.46, 48.11, 52.68, 56.5, 56.64, 66.97, 82.46; *ii)* **4**: 12.36, 13.15, 16.84, 19.32, 21.48, 22.79, 24.33, 24.96, 27.84, 30.52, 33.36, 35.13, 35.22, 38.83, 40.16, 42.87, 43.36, 48.05, 52.7, 56.26, 56.52, 67.66, 82.41.

7- The ozonolysis was performed in methylene chloride, at -78°C. After the characteristic blue color developped, argon was bubbled until the coloration was discharged. Dimethylsulfide (2 eq.) was added and the cooling bath was removed. After stirring for 3 hours, the solvents were distilled off (Vigreux column). The residue was taken up in THF and the resulting solution was slowly added to a slurry of LAH (2.5 eq.) in THF (ice bath). Stirring at r.t. for two hours was followed by the addition of water. The organic layer was dried (Na_2SO_4) and the solvents were removed by distillation (Vigreux column). The resulting oil was chromatographed over silica gel (CH_2Cl_2/ether), which gave successively: *i)* (2*S*)-2-ethyl-3-methyl-butanol (Bp_{15} 90-92°C (60%); $[\alpha]_D$ -9.2, c=5.5 CH_2Cl_2); *ii)* the alcohol **4** (73%; m.p. 66-67°C; $[\alpha]_D$ +40 (c=9, CH_2Cl_2). Both alcohols were converted into the corresponding iodide with PPh_3-I_2-imidazole in ether/acetonitrile (Millar, J. G., Underhill, E. W. *J. Org. Chem. 1986*, **51**, 4726-4728).

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11- a) Prepared from methyl (*S*)-3-hydroxy-isobutyrate (Schmittberger, T.; Uguen, D. *Tetrahedron Lett.*, **1995**, *36*, 7445-7448). $[\alpha]_D$ +6 (c=2, CH_2Cl_2); b) The *E* stereochemistry became apparent, in ^1H NMR, only after monodesilylation (TBAF) of ***E*-15**; then, $J_{CH=CH}$≈15.5Hz); c) The assigned *cis* stereochemistry is supported by the AB pattern of the signals displayed by the thiirane-dioxide protons of **C-14** (roughly, two d. of d. centered at 5.3 and 5.5 ppm, respectively) in ^1H NMR (200MHz; $CDCl_3$).

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13- Selected data: *i)* **7**: m.p. 48-49°C; $[\alpha]_D$ +73 (c=10, CH_2Cl_2); C, H (%): 76.18, 10.56 (calc.: 76.06, 10.34); ^{13}C NMR: 12.54, 13.16, 17.84, 19.35, 21.5, 22.61, 24.21, 25.03, 27 .99, 30.54, 31.72, 33.42, 35.14, 35.27, 38.27, 40.13, 42.83, 43.41, 48.03, 54.34, 56.38, 56.60, 82.37; *ii)* **9a**: $[\alpha]_D$ +85 (c=7, CH_2Cl_2); ^{13}C NMR: 12.36, 13.16, 18.88, 19.35, 21.52, 22.37, 22.47, 22.81, 24.25, 25.03, 27.49, 28.32, 30.55, 31.04, 33.41, 35.14, 35.29, 36.8, 38.92, 39.88, 40.14, 43.04, 43.42, 48.04, 55.65, 56.43, 56.6, 82.41; *iii)* **9b**:$[\alpha]_D$ +139 (c=4.7, CH_2Cl_2); ^{13}C NMR: 12.05, 12.38, 13 .16, 18.86, 19.27, 19.36, 21.56, 22.61, 22.82, 24.27, 25.04, 26.99, 28.34, 28.76, 30.57, 33.44, 34.79, 35.14, 35.34, 36.82, 40.17, 40.51, 43.08, 43.45, 45.97, 48.06, 55.73, 56.45, 56.63, 82.47; *iv)* **13b** (mixture of 2 diastereomers): C, H (%): 66.56, 7.56 (calc.: 66.58, 7.41); *v)* ***E*-15**: $[\alpha]_D$ +4 (c=8, CH_2Cl_2); C, H (%): 77.23, 8.28 (calc.: 77.36, 8.42); ^{13}C NMR: 17.94, 19.36, 26.95, 39.39, 68.69, 127.63, 129.54, 132.55, 134.04, 135 ,65; *vi)* **3a**: ^{13}C NMR: 12.52, 13.16, 15.38, 20.53, 21.58, 22.35, 22.41, 22.85, 24.28, 25.05, 28.25, 28.85, 29.79, 30.57, 33.44, 35.14, 35.37, 40.25, 40.29, 42.06, 42.77, 43.48, 48.15, 56.18, 56.64, 56.70, 82.51, 126.27, 138.26. All ^{13}C NMR spectra were recorded at 50MHz on $CDCl_3$ solutions.

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