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A SYNTHESIS OF C-23 AND C-24 DIASTEREOMERS OF 5α-DINOSTERANE[1]

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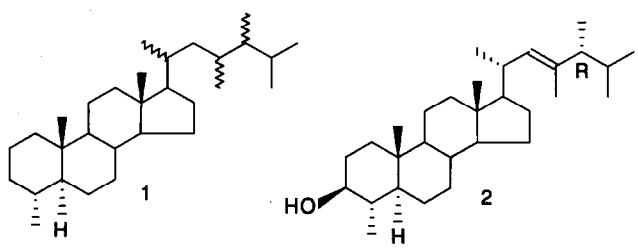
Abstract. Stereoselective routes for the preparation of C-23 and C-24 diastereomers of the C_{30} biological marker, 5α-dinosterane (**1**), involved the alkylation of (20S)-20-(iodomethyl)-4α-methyl-5α-pregnane (**7**) with either a saturated ester, methyl 3,4-dimethylpentanoate (**9**), followed by reduction to give principally the *erythro*-diastereomers or the alkylation of **7** with an α,β-unsaturated ester, methyl 3,4-dimethylpentenoate (**12**), followed by reduction to give principally the *threo*-diastereomers.

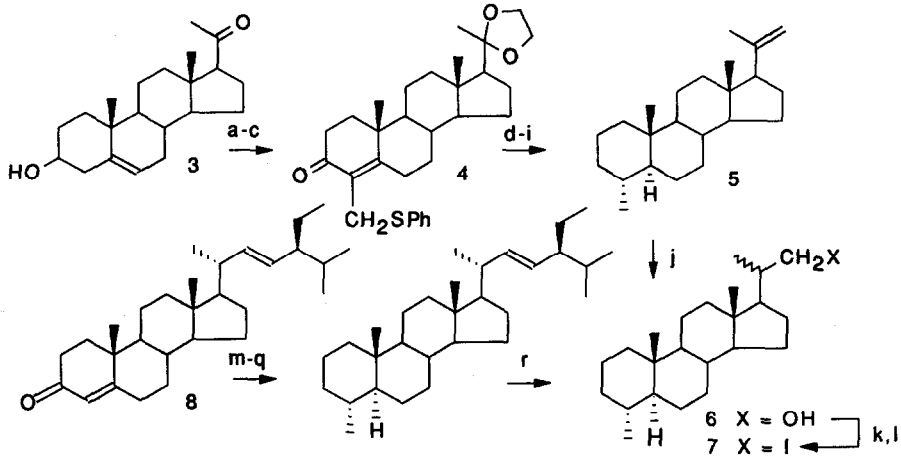
The formation of petroleum from biological materials under the conditions of high temperature and pressure present during sedimentation and maturation results in the conversion of terpenoid natural products to the corresponding hydrocarbons called biological markers.[2] Authentic samples were needed to define the stereochemistry of 5α-dinosteranes (**1**) detected in crude oils.[2,3] We report stereoselective syntheses of various C-23 and C-24 diastereomers of 5α-dinosterane (**1**), a C_{30} biological marker derived from dinosterol[4] (**2**) or related sterols.



We opted to construct 5α-dinosterane (**1**) using an alkylation of an acyclic ester with a C_{23} sterane electrophile since this approach offered the opportunity to control C-23 and C-24 stereochemistry. As shown in Scheme 1, synthesis of an appropriate electrophile, 20-(iodomethyl)-4α-methyl-5α-pregnane (**7**), from pregnenolone (**3**) required the introduction of the 4α-methyl group, 5α-stereochemistry, and a one-carbon homologation of the C-20 ketone. The key step in the synthesis employed the Kirk-Petrow thiophenoxymethylation[5] to obtain the α-(thiophenoxymethyl)enone **4** and a lithium in ammonia reduction of **3** to effect both desulfurization and enone reduction. Deoxygenation at C-3,[6] hydrolysis of the ketal, a

Wittig reaction with methylenetriphenylphosphorane, and hydroboration-oxidation delivered the alcohols **6** as a mixture of separable C-20 epimers. These epimers were independently converted to the iodides **7** in a standard fashion. As shown in Scheme 1, a second, efficient route to **7** employed (*22E*)-stigmasta-4,22-dien-3-one (**8**) and the same Kirk-Petrow approach[5] for introducing the 4α-methyl group.

Scheme 1

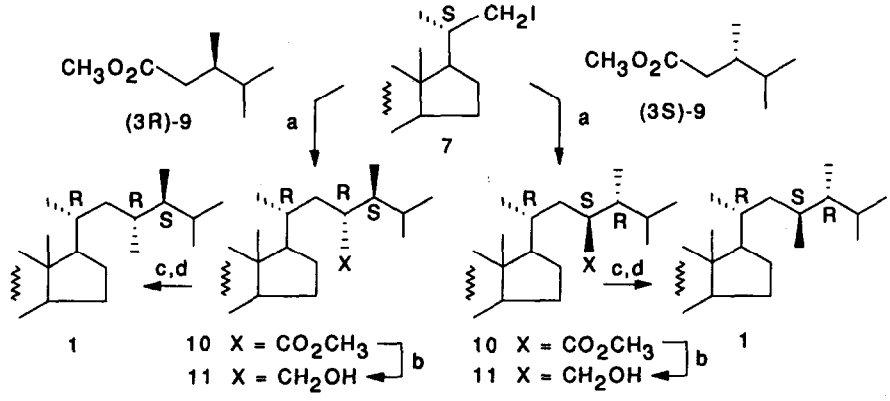


a, $HOCH_2CH_2OH$, p-TsOH (79%); b, $Al(Oi\text{-}Pr)_3$, 1-methyl-4-piperidone (78%); c, PhSH, HCHO, Et_3N (54%); d, Li, NH_3 (54%); e, $LiAlH_4$, THF (87%); f, PhOC(S)Cl, Py, CH_2Cl_2 (78%); g, $(n\text{-}C_4H_9)_3SnH$, AIBN, C_6H_6 (82%); h, 1:2.5:5.5 HCl-HOAc-THF, 25°C (86%); i, $Ph_3P{=}CH_2$, KOt-C_5H_{11}, benzene (91%); j, diborane, THF followed by NaOH, H_2O_2 (81%); k, Et_3N, MsCl; l, NaI, acetone (75% for steps k,l); m, PhSH, HCHO, Et_3N (62%); n, Li, NH_3; o, $NaBH_4$ (54% for steps n, o); p, PhOC(S)Cl, Py, CH_2Cl_2; q, $(n\text{-}C_4H_9)_3SnH$, AIBN, C_6H_6 (81% for steps p,q); r, O_3 followed by $(CH_3)_2S$ and $NaBH_4$ (81%).

The alkylation of acyclic, chiral *saturated* esters[7] with the sterane electrophile **7** provided access to the *erythro*-diastereomers of **1**. As shown in Scheme 2, the alkylation of methyl (3S)- or (3R)-3,4-dimethylpentanoate[8] (**9**) with (20S)-**7** led to the *erythro*-diastereomers, (23R,24S)-**10** and (23S,24R)-**10**, respectively, as the major diastereomers.[9] Both (20R)- and (20S)-**7** were available (Scheme 1), but only alkylation studies using (20S)-**7** that leads to the natural 20R steranes are presented here. Reduction of the mixture containing principally (23R,24S)-**10** or (23S,24R)-**10** to the corresponding primary alcohols **11** permitted the chromatographic separation of the major *erythro*-diastereomers from the minor *threo*-diastereomers. An X-ray crystallographic study of one isomer, (20R,23S,24R)-5α-dinosteran-29-ol (**11**), confirmed the stereochemical assignments. This particular structure determination represented a significant challenge in that the unit cell displayed three different conformers aligned in a pattern in which the single hydroxyl group in the side chain forms an interesting hydrogen-bonded, spirocyclic polymer. Full details of this structure determination will be given elsewhere.[10] The further reduction of the principal

alcohols **11** provided access to the *erythro*-diastereomers, (20R,23R,24S)- and (20R,23S,24R)-5α-dinosterane (**1**).

Scheme 2

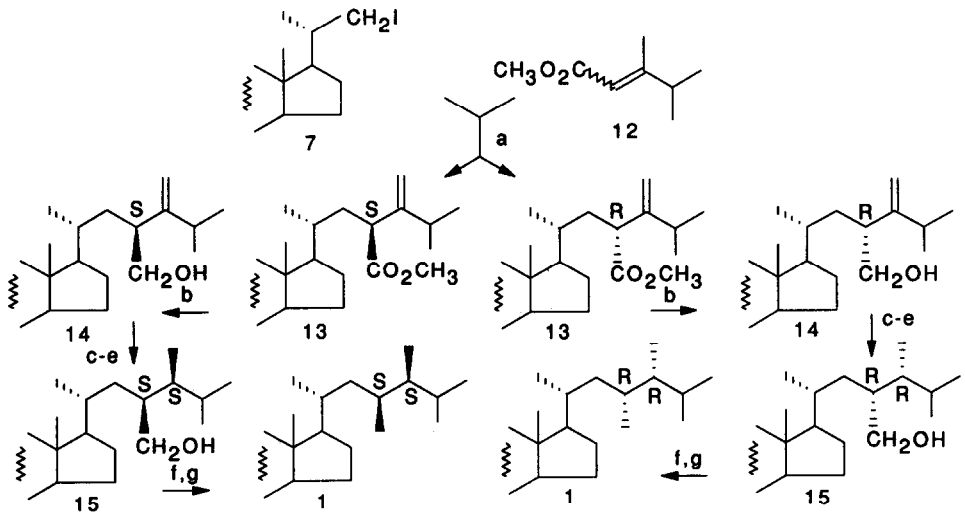


a, LDA, HMPA, THF, -78°C (83% for (3R)-**9**; 81% for (3S)-**9**); b, $LiAlH_4$ followed by SiO_2 separation (86%); c, MsCl, Et_3N (93%); d, $LiAlH_4$ (96%).

The alkylation of an acyclic *unsaturated* ester[7] with the sterane electrophile **7** provided access to the *threo*-diastereomers of **1**. As shown in Scheme 3, the alkylation of methyl 3,4-dimethyl-2-pentenoate (**12**) with (20S)-**7** led to a mixture of β,γ-unsaturated esters, (23S)-**13** and (23R)-**13**, in a 1:2 ratio. The reduction of the mixture of esters **13** provided the chromatographically separable allylic alcohols (23S)-**14** and (23R)-**14**, respectively. The individual hydrogenation of these homoallylic alcohols to the saturated alcohols exhibited no diastereoselectivity at C-24. However, the individual reduction of the tert-butyldimethylsilyl ethers of these homoallylic alcohols provided principally (23S,24S)-**15** and (23R,24R)-**15**, respectively.[11] The further reduction of these alcohols provided *threo*-diastereomers, (20R,23S,24S)- and (20R,23R,24R)-5α-dinosterane (**1**).

In summary, the alkylation of the saturated ester, methyl (3S)- or (3R)-3,4-dimethylpentanoate (**9**), provided access to the *erythro*-diastereomers of 5α-dinosterane, (20R,23R,24S)-**1** and (20R,23S,24R)-**1** as the major products, whereas the alkylation of the α,β-unsaturated ester, methyl 3,4-dimethyl-2-pentenoate (**12**) followed by a diastereoselective reduction, provided access to the *threo*-diastereomers, (20R,23S,24S)-**1** and (20R,23R,24R)-**1**. Current studies using (20R)- or (20S)-**7** and other esters will define the factors that influence diastereoselection in the alkylation of achiral and chiral esters with chiral electrophiles and will be reported in due course.[12]

Scheme 3



a, LDA, HMPA, THF, -78°C (72%); b, $LiAlH_4$ followed by SiO_2 separation (96%); c, TBSCl, imidazole; d, H_2, PtO_2; e, $(n\text{-}C_4H_9)_4NF$ (*ca.* 90% for steps c,d,e); f, MsCl, Et_3N; g, $LiAlH_4$ (*ca.* 95% for steps f,g).

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8. (a) Leutenegger, U.; Madin, A.; Pfaltz, A. Angew. Chem., Inter. Ed. Engl. 1989, **28**, 60; (b) Matt, P.; Pfaltz, A. Tetrahedron Assym. 1991, **2**, 691. We thank Professor Andreas Pfaltz for providing the semicorrin catalyst.
9. The alkylation of (3R)-**9** (note: the R-stereocenter in **9** becomes the C-24S stereocenter in **10**) with (20S)-**7** led to the (20R,23R,24S)-**10** and (20R,23S,24S)-**10** in a 4:1 ratio as determined by analysis and separation of the alcohols **11** derived from **10**. The alkylation of (3S)-**9** with (20S)-**7** led to the (20R,23S,24R)-**10** and (20R,23R,24R)-**10** in a 4:1 ratio.
10. We thank the Center for Computational Sciences at the University of Kentucky for making the Cambridge Structural Database available locally.
11. The reduction of the TBS ether of (23S)-**14** gave (23S,24S)-**15** and (23S,24R)-**15** (structure not shown in Scheme 3) in a 3:1 ratio. The reduction of the TBS ether of (23R)-**14** gave (23R,24R)-**15** and (23R,24S)-**15** (structure not shown in Scheme 3) in a 3:1 ratio.
12. All compounds were characterized using IR, ^1H and ^{13}C NMR, mass spectrometry and combustion analysis.

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