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Studies towards the Synthesis of 16α-Carboxyprednisolones. Chemistry of C16/C17 Fused Bromoisoxazolines

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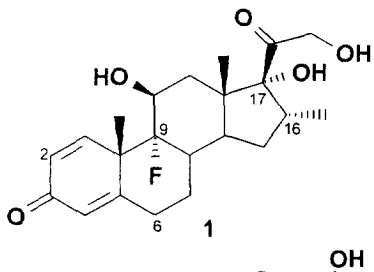
Abstract: Bromonitrile-N-oxide adds to the enone **9b/c** completely regio- and stereoselectively to form the bromoisoxazoline **10b/c**. The latter can be transformed into the nitrile **11**, previously hydrolyzed[14] to the target 16α-carbomethoxyprednisolone **4a** a potentially locally active antiinflammatory steroid. The methoxyisoxazoline **12**, prepared from **10b** has proved surprisingly resistant to reductive cleavage of the N-O bond. © 1997 Elsevier Science Ltd.

A variety of positions in corticosteroids have been functionalized in efforts to improve the anti-inflammatory profile of such compounds. Generally structural changes in the immediate vicinity of the functional groups of corticoid derivatives have resulted in significantly altered biological activity. Some examples are steroids with one or more of the following structural modifications: 2-methyl, 6-methyl, 6- and/or 9-halo, C16,C17 acetals or acetonides, C17,C21 mono- or diesters.[2] With regard to the hydroxyacetyl C17 side chain, the neighbouring position C16 has been the attention of functional variation. Amongst these, the C16α-methyl derivative *dexamethasone* **1** is marketed for asthma and dermatitis.[3] 16α– or 16β-methylation potentiates anti-inflammatory activity as compared to the parent steroid prednisone. A 16-methyl substituent also serves to attenuate the *in vivo* metabolic conversion to the corresponding 17-keto ste·oid. More recently C16,C17 fused ring steroids such as *deflazacort* **2**[4] and *SQ26,490* **3**[5] have appeared.



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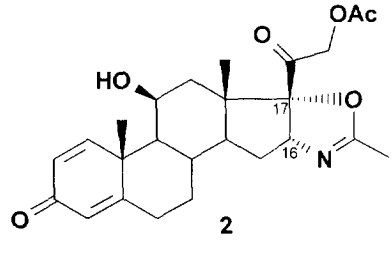

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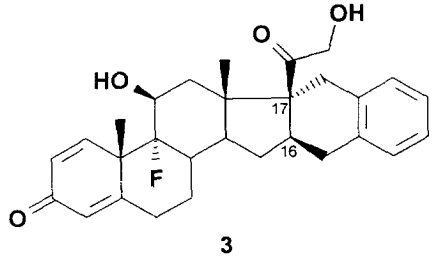

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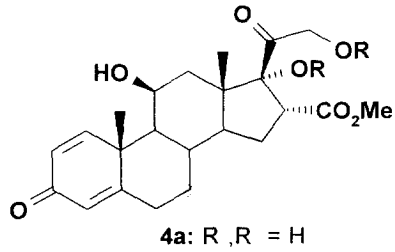
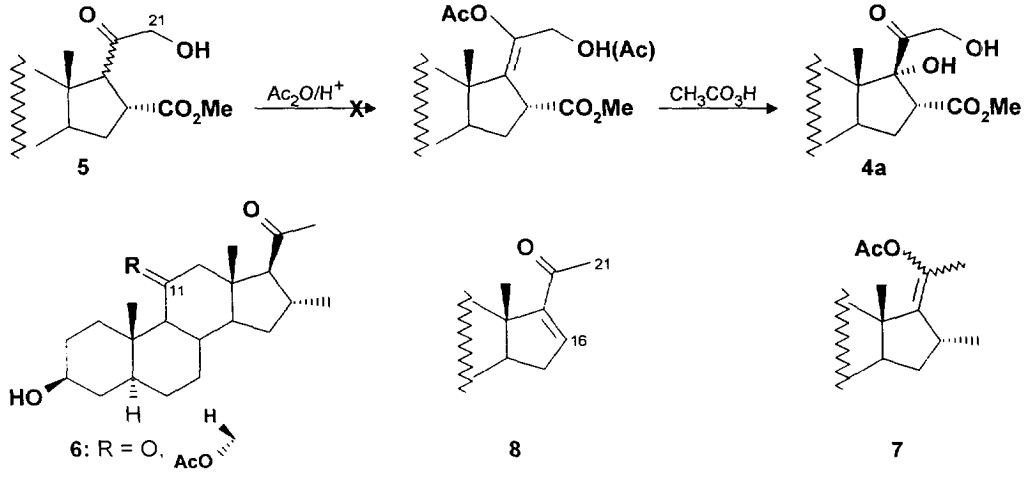


4a: R ,R = H
4b: R ,R = acetonide

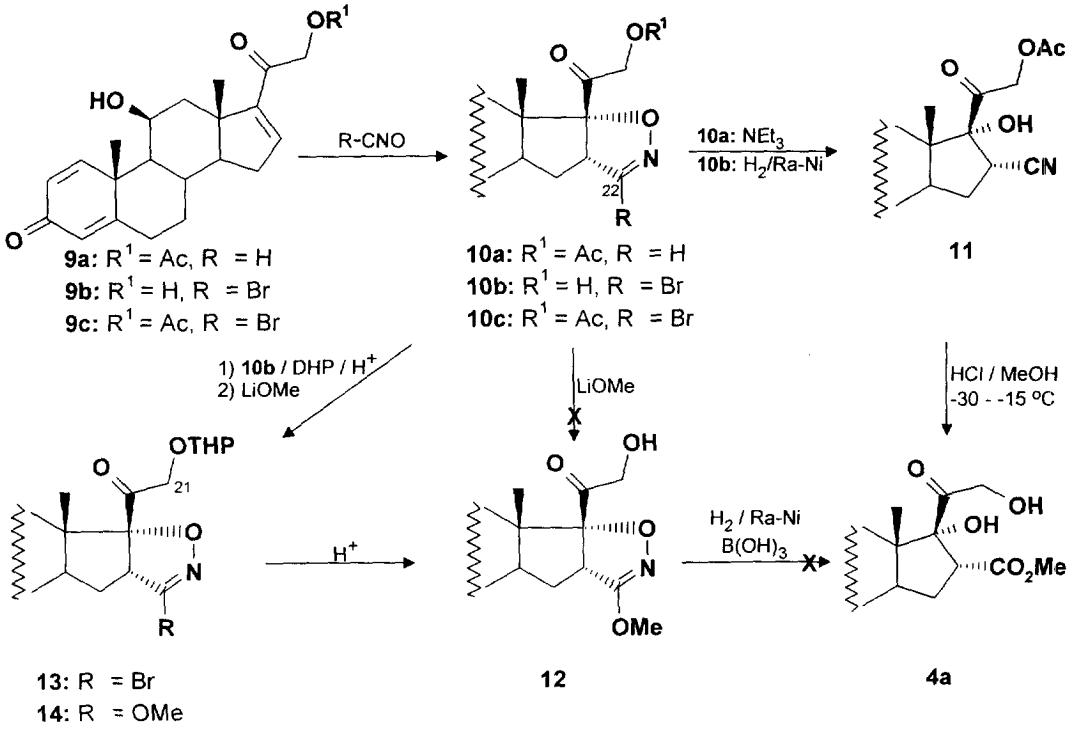
Derivatives of steroid acids have been advanced as locally active anti-inflammatory principles, the rationale being, that metabolic hydrolysis of the acid derivative would lead to inactive and readily excreted carboxylic acids with low systemic side effects.[6] Within this context Lee has recently advocated C-16α carboxy derived steroids to fulfill such a prerequisite.[7] The lead compound methyl 11β,17α,21-trihydroxy-3,20-dioxo-pregna-1,4-diene-16α-carboxylate (P16CM) **4a** was topically 14 times more potent than prednisolone in the croton oil induced ear edema model and locally 5.5 times more active in the cotton pellet granuloma assay in rats.[8] Further derivatization of **4a** to **4b** increased the topical acitvity.[9]

The original synthesis of **4a** was lengthy and low yielding.[7] In particular the key introduction of the 17α-hydroxy function into **4a**, from **5**, by means of the classical enol acetate oxidation route[7,10-13] was reported by Lee to "not yield the desired result."[14] Heusler *et al.*[15] discussed the steric consequences of introducing a C16 methyl group into the D-ring of corticoids. Thus, whilst 17-deoxypregnane derivatives (AB rings *cis*)[11] or -allopregnane derivatives (AB rings *trans*)[12] with either 16α- or 16β-methyl substituents successfully yielded to enol acetylation, Heusler's group was not able to carry out the same 17α enol acetylation/hydroxylation sequence in, for example, allopregnane derivatives **6** where C11 was substituted. Even though an enol acetate such as **7** could be formed by alternative means via conjugate methyl addition to **8** and O-acetylation of the resultant enolate anion, the subsequent hydroxylation of **7** proceeded only sluggishly and in low yield. These workers ascribe this behaviour to the steric encumberance imparted upon the steroid D-ring by C16 methyl substitution preventing both the C17 rehybridization in the course of enolization as well as the approach of the oxidant to the C17-C20 double bond in the enol acetate. In the light of these considerations we believe that the reason for the lack of success in enolacetate formation from **5** lies in the increased steric hinderance imposed both by the C16α-CO_2Me and C21-OH groups. It is clear, that this scenario is even more demanding than the classical case where C16 bears "only" a methyl group and C21 is unsubstituted.



We were recently engaged in a program to synthesize (P16CM) **4a** and could not reproduce Lee's originally reported procedure for the conversion of **5** to **4a**.[7] Prompted by the recent disclosure from this group of an alternative and much shorter synthesis of **4a**[14] which proceded via fulminic acid cycloaddition to enone **9a** and subsequent manipulation of the resulting isoxazoline **10a** (**9a** ---> **10a** ---> **11** ---> **4a**), we would like to report our own independant and similar efforts in this field.

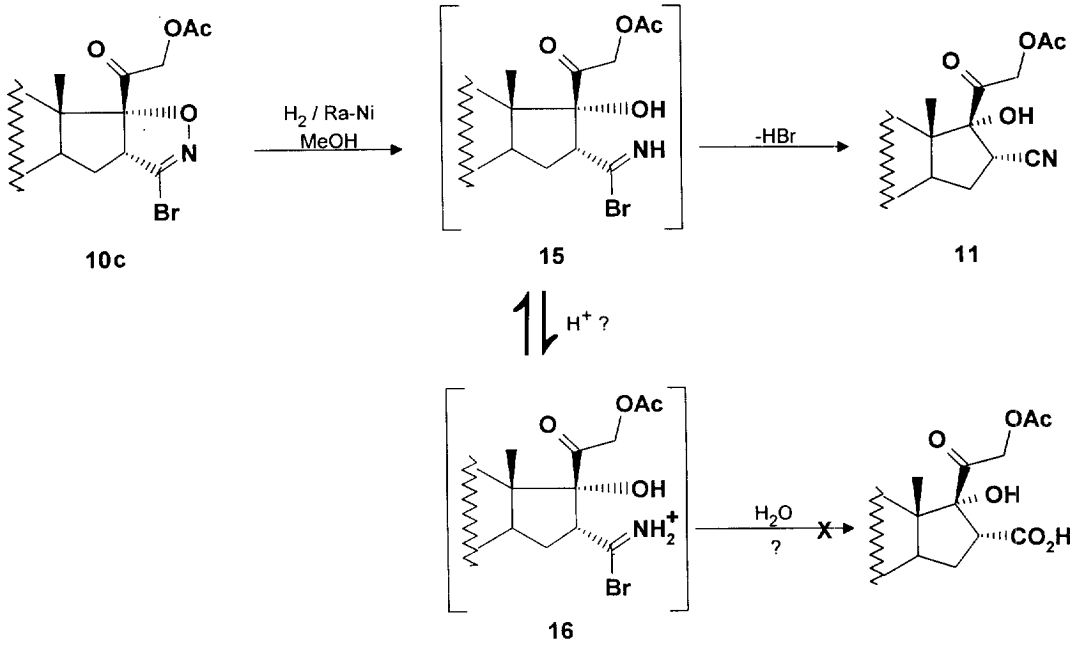
Anticipating difficulty with the generally vigorous conditions required for nitrile hydrolysis we sought to avoid proceding through an intermediate such as **11**, and instead prepare C22 directly at the correct carboxy oxidation level in the cycloaddition step. To this end we adopted the bromonitrile oxide 1,3-dipole[16-18] which smoothly added to the dihydroxy enone **9b** completely regio- and stereoselectively from the α-face in high yield to afford the bromoisoxazoline **10b**. In analogy to literature precedent, we then attempted to substitute a methoxy group for bromine,[17-20] (**10b/c** ---> **12**) thus setting up the isoxazoline for hydrogenolysis[18,20,21] which we hoped would give the dihydroxy methyl ester **4a** directly.



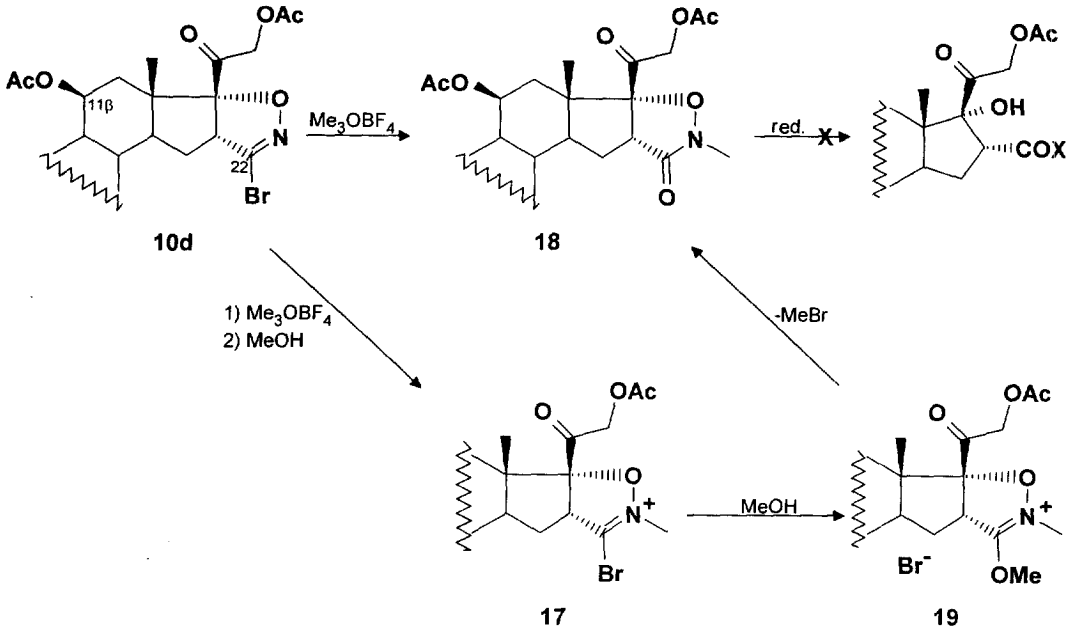
We were disappointed to find, that all attempts at substituting methoxy for bromo in the bromoisoxazoline **10b/c** were unsuccessful, yielding increasingly complex reaction mixtures with greater

reaction times and/or temperature. The desired methoxy analogue **12** could not be isolated. This lack of success applied to both the C21 acetate **10c** and the free hydroxy compound **10b**.

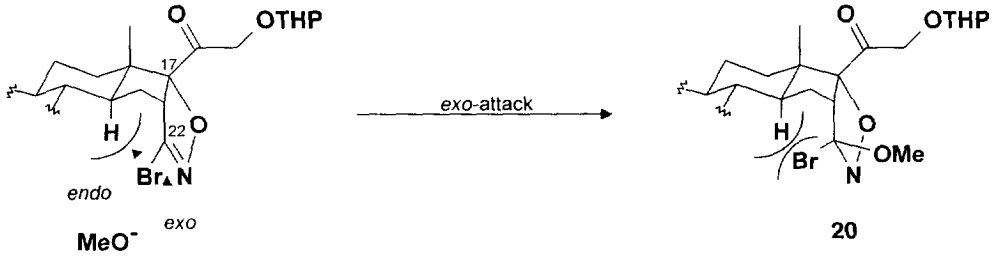
Direct hydrogenolysis of **10c** using the standard conditions (H_2 / Raney-Ni / $B(OH)_3$)[18,20,21] gave the nitrile **11** (~100% crude) described by Lee and already transformed into the target **4a**.[14] In the assumption that N-O bond hydrogenolysis is immediately followed by HBr elimination from the bromoimine intermediate **15** we attempted to suppress this by performing the hydrogenolysis in strongly acidic media in the hope that a protonated species **16** might succumb to preferential hydrolysis rather than elimination. These hopes were unfortunately not borne out in practice. With a variety of acid catalysts we invariably produced the nitrile **11** and with prolonged reaction times dienone hydrogenation began to occur as well.



In a different approach we sought to improve the reactivity of bromoisoxazolines **10** by increasing the electrophilicity of the C22 trigonal center. N-methylation with Meerwein's salt[22] of the C11β-acetoxy bromoisoxazoline **10d** invariably produced the isoxazolidinone **18** indicating that indeed an N-methylated intermediate such as **17** is more susceptible to nucleophilic exchange of the bromine atom. Attempts to reductively cleave **18** however were unsuccessful with a variety of conditions tried. Expectations that a substrate such as methoxyiminium ion **19** might yield more readily to N-O bond cleavage and subsequent hydrolysis were thwarted by virtue of the fact that all efforts aimed at its preparation resulted in **18**, leading us to conclude, that **19**, if formed, immediately stabilizes itself by loss of MeBr to give isoxazolidinone **18**.



Being thwarted in this route we returned to the original plan of nucleophilic bromine substitution using methoxide. Anticipating that the problem in substituting bromine for methoxy in **10b/c** lay in the C21 free hydroxy group we protected it as the base stable THP ether. Indeed, treatment of C21 protected derivative **13** with LiOMe in warm methanol, albeit for considerably long reaction times, cleanly provided the methoxyisoxazoline **14**, which could be cleanly converted to the 11β,21-diol **12**. The conditions required for the substitution of the bromine atom were paticularly forcing (MeOH / 50 °C / >24 h) when compared to the methods typically employed for this type of conversion;[17-20] (rt-reflux / 0.5-several h). This can be rationalized as follows. Approach of a nucleophile to the trigonal center (C22) from the preferred *exo* (top) face would not only be impeded by the C17β THP-oxyacetate function, but also force the large bromine atom into a sterically very encumbered *endo* orientation in the ensuing tetrahedral intermediate **20**. The alternative *endo* approach of MeO^- is equally sterically disfavoured.



With **12** now in hand, it remained only to reductively cleave the methoxyisoxazoline function. The most common conditions for this, namely hydrogenolysis in acidic methanol in the presence of Raney-Nickel as catalyst[17,18,20] which, according to literature precedent ought to give the methyl ester, resulted only in unchanged starting material and, with longer reaction times, slow dienone olefin hydrogenation. To this date we have been unsuccessful in carrying out the transformation of **12** to **4a** with a numerous variety of reducing conditions, obtaining either unchanged isoxazoline (usually in the case of shorter reaction times) or a whole plethora of products at least some of which arise from olefin reduction. Certainly steric factors are largely responsible for this, especially in the cases of catalytic hydrogenation and those involving transition metal complexes,[23] but we also believe that a higher reduction potential of the methoxyisoxazoline function as compared to the bromo analogue makes the former more reluctant to react with, for example, sodium amalgam or metal ions such as Ti(III).[24]

Conclusion. We have shown, that bromonitrile oxide adds in high yield and completely regio- and stereoselectively to the pregnatrienone **9b/c** to provide the bromoisoxazoline **10b/c**, which in turn can be converted to the hydroxynitrile **11** (in overall quantitative crude yield). Since the latter has been successfully transformed into the C16α-carbomethoxy pregnane derivative **4a**[14] this constitutes a formal synthesis of this member of a new class of antiinflammatory steroids with potentially reduced systemic action. Further it is possible to substitute the C22 bromine substituent at what is evidently a sterically very restricted environment. Despite this, the resulting methoxyisoxazoline is surprisingly reluctant to submit to reductive cleavage. We are continuing to address this problem and will report the results of our efforts at an appropriate opportunity.

EXPERIMENTAL

Melting points are corrected. ^{1}H NMR (200, 360, 400MHz) and ^{13}C NMR (90, 100MHz) spectra were recorded on Varian *Gemini-200*, Bruker *AM-360* and Bruker *AMX-400* instruments respectively using residual $CHCl_3$ protons as references. Infra-red spectra were recorded on a Bruker *IFS 66* apparatus and mass spectra on a VG *70-SE* instrument. Flash chromatography was carried out using silica gel (Merck, Kieselgel 60, 230-400 mesh) and analytical tlc was done on precoated Kieselgel 60 F_{254} glass plates. AR grade solvents (Fluka) and commercial reagents (Fluka, Aldrich) were used without further purification in all cases.

11β,21-Dihydroxy-3,20-dioxopregna-1,4-diene-[17α,16α]-3'-bromoisoxazoline (10b): A mixture of enone **9b** (600 mg, 1.75 mmol), dibromoformaldoxime[16a] (430 mg, 2.12 mmol, 1.2 eq) and $NaHCO_3$ (2.9 g, 35 mmol) in EtOAc (150 ml) was stirred at room temperature for six days. The reaction mixture was filtered through hyflo and concentrated to afford an ocre foam (840 mg, 100%, **10b** as the only product by nmr spectroscopy), which in practice could be carried on without further purification. Usually chromatography on

silica gel resulted in considerable loss of material and was avoided wherever possible! For analytical purposes the crude product was crystallized from MeOH to afford white blocks, mp = 165 °C (dec.) (sweats above 135 °C). ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.23 (d, J = 11 Hz, 1H), 6.28 (dd, J = 11, 2 Hz, 1H), 6.02 (br s, 1H), 4.67 (d, J = 20 Hz, 1H), 4.53 (br d, J = 3 Hz, 1H), 4.28 (d, J = 20 Hz, 1H), 4.10 (dd, J = 8, 1 Hz, 1H), 2.58 (br dddd, J = 13, 13, 6, <1 Hz, 1H), 2.37 (m, 1H), 2.29-1.69 (m, 8H), 1.48-1.38 (m, 1H), 1.46 (s, 3H), 1.29-1.09 (m, 2H), 1.05 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 206.78, 186.30, 169.20, 155.57, 142.39, 128.01, 122.62, 103.89, 69.50, 66.99, 58.28, 54.65, 50.64, 49.13, 43.82, 40.21, 33.77, 31.69, 30.85, 30.43, 21.11, 17.79; IR (KBr) ν_{max} 3435 br, 1725, 1658, 1616 cm^{-1}; MS (FAB) *m/e* 464/466 (100, MH^+), 446/448 (36), 386 (11); Anal. ($C_{22}H_{26}BrNO_5$) calcd.: C, 56.91, H, 5.64, N, 3.02, Br, 17.21; found: C, 56.49, H, 5.66, N, 3.13, Br, 17.60.

21-Acetoxy-11β-hydroxy-3,20-dioxopregna-1,4-diene-[17α,16α]-3'-bromoisoxazoline (10c): A mixture of enone **9c** (6 g, 14 mmol), dibromoformaldoxime[16a] (2.9 g, 14.3 mmol, 1.02 eq) and $NaHCO_3$ (18 g, 35 mmol) in EtOAc (300 ml) was stirred at room temperature for five days. The reaction mixture was diluted with CH_2Cl_2 (150 ml), filtered through hyflo and concentrated to afford a pale-yellow solid (9.58g, 100%, **10c** as the only product by nmr data), which in practice could be carried on without further purification. Usually chromatography on silica gel resulted in considerable loss of material and was avoided wherever possible! A small portion was flash chromatographed. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.23 (d, J = 11 Hz, 1H), 6.28 (dd, J = 11, 2 Hz, 1H), 6.02 (br s, 1H), 4.98 (d, J = 20 Hz, 1H), 4.77 (d, J = 20 Hz, 1H), 4.53 (br s, 1H), 4.01 (dd, J = 8, 1 Hz, 1H), 2.58 (br ddd, J = 13, 13, 6 Hz, 1H), 2.42-0.92 (m, 11H), 2.18 (s, 3H), 1.46 (s, 3H), 1.07 (s, 3H).

21-Tetrahydropyranyloxy-11β-hydroxy-3,20-dioxopregna-1,4-diene-[17α,16α]-3'-bromoisoxazoline (13): A solution containing the bromoisoxazoline **10b** (2.07 g, 4.46 mmol), dihydropyran (1.6 ml, 17.69 mmol, 4 eq) and PPTS (500 mg) in CH_2Cl_2 (300 ml) was stirred at room temperature for 75 min. The reaction solution was shaken with sat aq $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to afford a white solid (2.63 g, 100%). This material was very pure by nmr and could be used as such. For purification the product could be taken up in CH_2Cl_2/EtOAC and crystallized by preferential evaporation of CH_2Cl_2, providing a white powder which after renewed crystallization from MeOH gave fine white flakes (diastereomer ratio undetermined), mp 215-220 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.21 (d, J = 11 Hz, 1H), 6.28 (dd, J = 11, 2 Hz, 1H), 6.02 (dd, J = <1, <1 Hz, 1H), 4.71/4.67 (2 x d, J = 20 Hz, 1H), 4.70/4.62 (2 x dd, J = 3, 3 Hz, 1H), 4.53 (m, 1H), 4.40/4.34 (2 x d, J = 20 Hz, 1H), 4.10 (dd, J = 8, 1 Hz, 1H), 3.85 (m, 1H), 3.51 (m, 1H), 2.58 (br dddd, J = 13, 13, 6, <1 Hz, 1H), 2.37 (m, 1H), 2.29-1.07 (m, 8H), 1.46 (s, 3H), 1.07/1.04 (2 x s, 3H); IR (KBr) ν_{max} 3477 br, 1728, 1658, 1618 cm^{-1}; MS (FAB) *m/e* 548/550 (100, MH^+), 530/532 (23); Anal. ($C_{27}H_{34}BrNO_6$) calcd.: C, 59.13, H, 6.25, N, 2.55, Br, 14.57; found: C, 58.72, H, 6.10, N, 2.67, Br, 14.3.

21-Tetrahydropyranyloxy-11β-hydroxy-3,20-dioxopregna-1,4-diene-[17α,16α]-3'-methoxyisoxazoline (14): A solution of the THP ether **13** (1.426 g, 2.6 mmol) in dry MeOH (30 ml) and dry DME (40 ml) was treated with a 0.62M solution of LiOMe in MeOH (9.5 ml, 5.89 mmol, 2.26 eq), stirred at 50 °C for 24 h and at room temperature for another 4 days. The reaction mixture was concentrated to a small volume, quenched with sat aq NH_4Cl and extracted with EtOAc (4x). The organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated giving an ocre foam (1.63 g) which was used directly in the next step. In another run, flash chromatography of the product (eluent: EtOAc/hexane, 2:1) gave methoxyisoxazoline **14** as a colourles gum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 11 Hz, 1H), 6.28 (dd, *J* = 11, 1 Hz, 1H), 6.03 (s, 1H), 4.79/4.73 (2 x d, *J* = 18 Hz, 1H), 4.71/4.65 (2 x dd, *J* = 3, 3 Hz, 1H), 4.53 (br s, 1H), 4.43/4.38 (2 x d, *J* = 18 Hz, 1H), 3.95-3.75 (m, 1H), 3.84 (d, *J* = 9 Hz, 1H), 3.79 (s, 3H), 3.52 (m, 1H), 2.58 (br ddd, *J* = 14, 14, 6 Hz, 1H), 2.37 (m, 1H), 2.28-1.10 (m, 8H), 1.46 (s, 3H), 1.03/1.01 (2 x s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.5/204.9, 186.4, 169.6/169.5, 169.3, 155.7, 128.0, 122.6, 104.4, 99.3, 97.6, 70.6/69.4, 69.7, 62.5/61.8, 57.4, 54.8, 50.8, 49.4, 48.6/48.5, 43.8, 40.0, 33.8, 31.8, 30.5, 30.2, 30.0, 25.2, 21.1, 19.2, 18.6, 17.5; IR (KBr) ν_{max} 3441 br, 1728, 1662, 1624 cm^{-1}; MS (FAB) *m/e* 500 (85, MH^+), 482 (18), 416 (100), 398 (75).

11β,21-Dihydroxy-3,20-dioxopregna-1,4-diene-[17α,16α]-3'-methoxyisoxazoline (12): The crude product **14** (1.63 g) from the foregoing reaction was dissolved in MeOH (100 ml), treated with PPTS (100 mg) and stirred at rt for 4 days before concentrating. The residue was taken up in EtOAc, filtered through a plug containing alternate layers of hyflo and silica gel and concentrated again to result in an ocre foam (1.13g, 100% crude from **13**) whose nmr indicated clean diol **12**. A small portion was flash-chromatographed (eluent: EtOAc/cyclohexane, 5:1) to give the methoxyisoxazoline **12** as a colourles gum, which was treated with Et_2O and rubbed with a glass rod to provide a white amorphous solid, mp = 100 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 9 Hz, 1H), 6.27 (d, *J* = 9 Hz, 1H), 6.02 (s, 1H), 4.71 (d, *J* = 20 Hz, 1H), 4.52 (br s, 1H), 4.28 (d, *J* = 20 Hz, 1H), 3.82 (d, *J* = 8 Hz, 1H), 3.78 (s, 3H), 2.58 (ddd, *J* = 14, 14, 6 Hz, 1H), 2.35 (m, 1H), 2.29-1.12 (m, 11H), 1.45 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.7, 181.3, 164.5, 164.1, 150.5, 123.0, 117.6, 98.6, 64.7, 62.1, 52.5, 49.8, 45.8, 44.9, 43.8, 38.8, 34.9, 28.8, 26.7, 25.6, 20.3, 16.1, 12.6; IR (KBr) ν_{max} 3433 br, 1722, 1658, 1623 cm^{-1}; MS (FAB) *m/e* 416 (35, MH^+), 398 (12), 356 (6).

11β,21-Diacetoxy-3,20-dioxopregna-1,4-diene-[17α,16α]-N-methylisoxazolidin-3-one (18): A solution of **10d** (1g, 1.82 mmol) (prepared analogously to **10b/c**) in $MeNO_2$ (200 ml) was treated with Me_3OBF_4 (2.6g, 57.8 mmol, 9.6eq) and stirred at rt overnight. EtOAc was added to the solution and this was shaken with water and brine. Drying (Na_2SO_4), filtration and concentration gave a brown residue which was flash-chromatographed with EtOAc to afford a white solid (700 mg, 77%). Recystallisation from Et_2O provided white rhombic blocks, mp 175 - 177 °C. ^{1}H NMR (360 MHz, $CDCl_3$) δ 6.93 (d, *J* = 11 Hz, 1H), 6.28 (dd, *J* =

11, 1 Hz, 1H), 6.04 (dd, J = <1, <1 Hz, 1H), 5.57 (ddd, J = 5, 5, 5 Hz, 1H), 4.88 (d, J = 20 Hz, 1H), 4.82 (d, J = 20 Hz, 1H), 3.60 (br d, J = 10 Hz, 1H), 3.13 (s, 3H), 2.55 (br ddd, J = 14, 14, 6 Hz, 1H), 2.39 (m, 1H), 2.28-1.10 (m, 9H), 2.17 (s, 3H), 2.12 (s, 3H), 1.29 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.14, 185.63, 171.35, 170.05, 169.60, 167.57, 153.77, 128.56, 123.04, 97.99, 70.52, 67.25, 53.43, 51.69, 48.41, 42.77, 34.96, 33.55, 32.17, 31.66, 31.33, 30.44, 21.74, 20.75, 20.34, 16.31; IR (KBr) ν_{max} 1735, 1705, 1664, 1628 cm^{-1}; MS (FAB) *m/e* 500 (94, MH^+), 440 (100); Anal. ($C_{27}H_{33}NO_8$) calcd.: C, 64.92, H, 6.66, N, 2.80; found: C, 64.53, H, 6.52, N, 2.82.

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2. For a good review including many examples of these and other, newer steroidal anti-inflammatory agents see: Lee, H. J.; Heimann, A. S.; Taraporewala, I. B. in *New Developments in Antirheumatic Therapy*, Rainsford, K. D.; Velo, G. P., Eds., Inflammation and Drug Therapy Series, Vol. III, MPT, Lancaster, UK, **1989**, *Ch.* 6, 153-186.
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