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Chemoselective hydrogenation of 17α-hydroxy-6-methylen-pregna-4,9(11)-diene-3,20-dione. Synthesis of fluorometholone

Andrés Marcos-Escribano [a], Francisco A. Bermejo [a,*], Antonio Lorente Bonde-Larsen [b], Jesús Iglesias Retuerto [b]

[a] Departamento de Quimica Orgánica, Universidad de Salamanca, Pza de la Merced s.n., 37008 Salamanca, Spain
[b] Ragactives, Parque Tecnológico de Boecillo, Parcela 105, 47151 Boecillo, Valladolid, Spain

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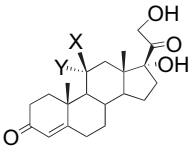
ABSTRACT

The development of an efficient hydrogenation method of 17α-hydroxy-6-methylen-pregna-4,9(11)-diene-3,20-dione by using wet (10%) Pd on carbon and triethylamine led us to the corresponding 6α-methyl-pregnane in good yield. This chemoselective process allowed us to set up a large-scale procedure for the synthesis of the ophthalmic drug fluorometholone with 45% overall yield.

1. Introduction

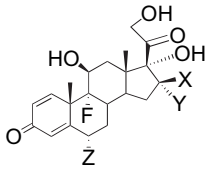
Since the introduction of cortisone **1**, in 1948, and hydrocortisone **2**, in 1951, anti-inflammatory steroids have remained an important and irreplaceable drug class (Fig. 1). They inhibit the inflammatory response to a variety of inciting agents and probably delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary and fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation.[1]



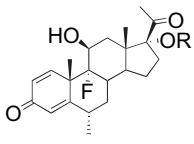
Cortisone **1:** X, Y= O
Hydrocortisone **2**: X= OH; Y= H

Figure 1.

A natural extension of corticoid research involved the examination of compounds containing both a 9α-fluoro group and a double bond between positions 1 and 2. Most known fluorinated analogues such as triamcinolone (9α-fluoro-11β,16α,17α,21-tetrahydroxy-pregna-1,4-diene-3,20-dione) **3**, dexamethasone (9α-fluoro-11β, 17α,21-trihydroxy-16α-methylpregna-1,4-dien-3-one) **4**, betamethasone (9α-fluoro-11β,17α,21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione) **5**, and fluocinolone (6α,9α-difluoro,11β,16α17α, 21-tetrahydroxypregna-1.4-diene-3,20-dione) **6** are potent anti-inflammatory agents (Fig. 2).[2]



3: X=H; Y=OH; Z= H
4: X= H; Y= CH_3; Z= H
5: X= CH_3; Y= H; Z= H
6: X=H, Y= OH; Z= F



7a: R= H
7b: R= $COCH_3$

Figure 2.

It is known that the 9α-fluoro group increases the anti-inflammatory potency, but it also markedly increases the mineralocorticoid potency. Fluorometholone **7a** and fluorometholone acetate **7b** are both corticosteroids used for their glucocorticoid activity in the treatment of allergic and inflammatory conditions of the eye. Fluorometholone has a 40-fold more powerful anti-inflammatory activity than hydrocortisone, without intraocular pressure being

* Corresponding author. Tel.: +34 923 294481; fax: +34 923 294574.
E-mail address: fcobmjo@usal.es (F.A. Bermejo).

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affected significantly. In addition, the immunosuppressive action of fluorometholone **7a** is less pronounced than that of dexamethasone **4**. Prolongued use of corticoids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision, and later subcapsular cataract formation. In comparison with other corticosteroids, fluorometholone is more rapidly degraded in the tissue and therefore has less effect on introcular pressure. Mainly for this reason, fluorometholone is the 'drug of choice' for long-term ophthalmic anti-inflammatory treatment.[3–6]

The synthesis of fluorometholone **7a** was first described in a US patent in 1959[7] and used either the 6α-methyl-prednisolone 21-acetate **8** or the 11β,17-dihydroxy-6α-methyl-1,4-pregnadien-3,20-dione **9** as starting material (Fig. 3).[8] In both cases, a five-step sequence was applied to obtain the target molecule in reasonable yields. Later on, Lincoln et al. described the synthesis of **7a** starting from 11β,17-dihydroxy-6α-methyl-4-pregnen-3,20-dione **10**, and made use of a last fermentation step to introduce the 1,2-double bond in the pregnane skeleton.[9] The same group described a procedure starting from 17α-hydroxyprogesterone **11**, which led to the isolation of **7a** by application of a 12-step sequence that included two fermentation reactions to introduce the 11β-hydroxy function and the 1,2-double bond.[10] In 1973 a French patent described a new route to **7a**, starting from 9α-fluoro-11β,17-dihydroxy-1,4-pregnadien-3,20-dione **12**, which first introduced the methyl at C-6 through formylation of the dienol ether with the Vilsmeier reagent, and then made use of the DDQ to introduce the 1,2-unsaturation.[11]

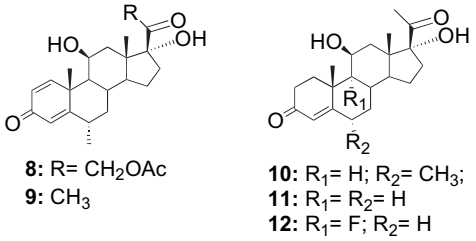


Figure 3.

The isolation of the fluorometholone acetate **7b** from **7a** was described by Kagan and Magerlein in 1960[12] and an US Patent from 1982 described several base-catalyzed acylations with enol esters in the pregnane series.[13]

2. Results and discussion

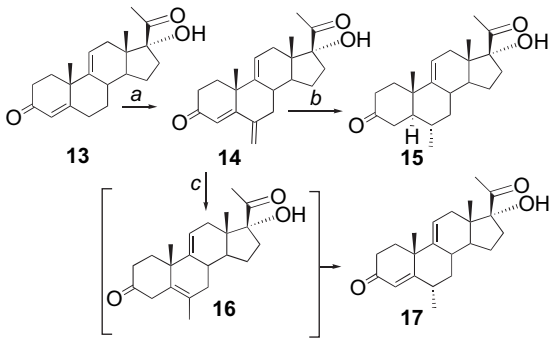
With the aim of setting up a large-scale procedure for the synthesis of fluorometholone, we focused our attention on the stereoselective introduction of the methyl at C-6 by the hydrogenation of 6-methylenpregnane derivatives, and then setting the hydroxy and fluoride functionalities at C-9 and C-11, respectively, by the C9–C11 β-epoxide opening procedure.

2.1. Functionalization at C-6

2.1.1. Mannich reaction at C-6. Transformation of 17α-hydroxy-4,9(11)-pregnadien-3,20-dione **13**[14] into the pregnantriene **14** was achieved in 85% yield by standard procedures.[15]

2.1.2. Chemoselective hydrogenation of the methylene group at C-6. Hydrogenation of **14** with (10%) Pd on carbon (wet) in ethanol led to the unsaturated ketone **15** in 70% yield after equilibration with HCl.

It has been reported that triethylamine retards hydrogenation of the carbon–carbon double bond in α,β-unsaturated ketones.[16] The addition of triethylamine to a dichloromethane solution of **14** afforded, by stirring the reaction mixture under a hydrogen atmosphere in the presence of (10%) Pd on carbon (wet) and further treatment with HCl, the 6α-methyl-pregnane **17** in 75% yield (Scheme 1).



Scheme 1. (a) $HC(OEt)_3$, THF/EtOH, *p*-TsOH, *N*-Me aniline, (40%) HCHO, 40 °C, HCl, H_2O, 84%; (b) H_2, 10% Pd(C), EtOH, 70%; (c) H_2, Pd(C), Et_3N, DCM, HCl, 75%.

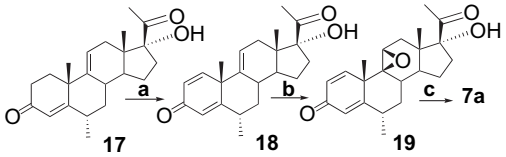
We assume that under these conditions **14** would be transformed into the pregnadiene **16**, which would be rearranged to the thermodynamically-controlled reaction product **17**, under acidic conditions.

The high yield obtained in the hydrogenation reaction of **14** prompted us to complete the synthesis of **7a**, starting from **17** by application of a three-step sequence, which included, $\Delta^{1,2}$ dehydrogenation, $\Delta^{9,11}$ epoxidation, and stereoselective hydrofluoric acid ring opening.

2.1.3. Dehydrogenation. The 1,2-dehydrogenation of **17** using either DDQ or chloranil and bis(trimethylsilyl)trifluoroacetamide (BSTFA) under acidic catalysis afforded the desired dehydrogenated product **18** in only 36% isolated yield. This particular transformation was recently described by our group to proceed successfully on 6-methylenandrostane derivatives on the occasion of the synthesis of exemestane.[17] However, transformation into the silylenol ether proceeded successfully under basic conditions by treatment of **17** with *tert*-butyldimethylsilyltrifluoromethanesulphonate and diisopropylethylamine in dichloromethane. Then, the 1,2-dehydrogenation reaction took place successfully by the addition of pyridine and chloranil.

The isolation of the trienone **18** was achieved by flash chromatography of the crude reaction product in 67% yield.

*2.1.4. Synthesis of fluorometholone **7a**.* With the trienone **18** in our hands, we successfully obtained the epoxide **19** steroselectively through the intermediate halohydrin. Treatment of **18** with 1,3-dibromo-5,5-dimethylhydantoin in perchloric acid followed by basic work up led to the isolation of the epoxide **19** in 92% yield. The epoxide ring opening reaction was achieved by standard treatment of **19** with 70% hydrofluoric acid to afford fluorometholone **7a**,[18] in 85% yield (Scheme 2).



Scheme 2. (a) $^tBuMe_2OSO_2CF_3$, DIPEA, CH_2Cl_2, chloranil, Py, 65%; (b) DBH, $HClO_4$, K_2CO_3, 70%; (c) HF, 85%.

3. Conclusion

The chemoselective hydrogenation of the 6-methylene double bond of 17-hydroxy-6-methylen-4,9(11)-pregnadien-3,20-dione

was the key step in the synthesis of fluorometholone **7a**, starting from 17-hydroxy-4,9(11)-pregnadien-3,20-dione **13**. The target molecule was successfully achieved by application of a five-step reaction sequence in 45% overall yield.

4. Experimental

4.1. General experimental methods

Melting points are uncorrected. ^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. IR spectra were recorded either in $CHCl_3$ solution or in NaCl plates, unless otherwise noted, on an FTIR instrument. HRMS determinations (EI) were recorded at the Mass Spectrometry Service of the University of Salamanca, Spain. All reactions were conducted under a positive pressure of argon, utilizing standard bench-top techniques for handling of air-sensitive materials. Chemicals and solvents were obtained from commercial sources and used as received with the exception of tetrahydrofuran, benzene, toluene, and dioxane, which were distilled from sodium and benzophenone. The 10% palladium on activated charcoal has been obtained from Fluka (Cat. No. 75993). Unless specified otherwise, the yields reported are for chromatographically pure isolated products.

4.2. 6-Methylen-17α-hydroxy-pregna-4,9(11)-diene-3,20-dione (14)

The steroidal diketone **13** (56 g, 170 mmol) and *p*-toluenesulfonic acid monohydrate (9 mmol) were dissolved in a mixture of THF (385 mL) and ethanol (45 mL) at 37 °C under argon. Triethyl orthoformate (38 mL, 230 mmol) was added via syringe. After 2.5 h, *N*-methylaniline (19 mL, 176 mmol) and 40% formaldehyde (16 mL) were consecutively added. After 3.5 h of additional stirring at 40 °C, 37% hydrochloric acid (100 mL) was added and the reaction mixture was kept under stirring at 40 °C for 3 h. The suspension was cooled to room temperature, poured into water, and cooled to 5 °C while stirring. After 30 min, the steroid was filtered, suspended in water at 15 °C, filtered again, and dried. Compound **14** was afforded (49 g, 84%) pure. Mp: 185–186 °C; $[\alpha]_D^{20}$ +217.5 (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 730, 911, 1227, 1356, 1665, 2951, 3452; ^{1}H NMR ($CDCl_3$) (200 MHz) δ (ppm): 0.67 (s, 3H), 1.25 (s, 3H), 0.5–3.0 (m, 15H), 2.27 (s, 3H), 5.01 (t, *J*=2.0 Hz, 1H), 5.13 (t, *J*=2.0 Hz, 1H), 5.58 (d, *J*=3.0 Hz, 1H), 5.91 (s, 1H); ^{13}C NMR ($CDCl_3$) (50 MHz) δ (ppm): 15.2, 24.6, 26.2, 27.5, 32.2, 33.3, 33.7, 34.0, 37.8, 40.0, 41.4, 46.8, 48.0, 89.5, 114.0, 119.2, 121.7, 143.1, 145.5, 167.4, 199.5, 211.1; HRMS-EI (M+H) calcd for $C_{22}H_{29}O_3$ 341.2111, found 341.2112.

4.3. 6α-Methyl-17α-hydroxy-pregna-9(11)-ene-3,20-dione (15)

The 6-methylene steroidal derivative **14** (1.07 g, 3.16 mmol) and palladium over charcoal 10% (50% wet, 0.1 g/g) were suspended in ethanol (25 mL) keeping the reaction mixture under hydrogen pressure (5 atm) and gently stirred for 7 h. The reaction mixture was filtered over Celite, and the solid gently extracted with ethanol. The organic phase was concentrated up to 25 mL and 37% HCl (8.5 mL, 0.25 mL) was added, followed by 20 h of stirring. Once the isomerization process was completed, a saturated $NaHCO_3$ solution (25 mL) was added and organic phase was extracted with ethyl acetate, washed with brine (3×25 mL), dried (Na_2SO_4), and evaporated to obtain **15** (0.81 g, 57%) pure. Mp: 105 °C; $[\alpha]_D^{20}$ −7.6 (*c* 1.6, $CHCl_3$); IR (Nujol) ν (cm^{-1}): 723, 898, 1378, 1463, 1716, 2728, 2916, 3487; ^{1}H NMR ($CDCl_3$) (400 MHz) δ (ppm): 0.68 (s, 3H), 1.04 (d, *J*=7.28 Hz, 3H), 1.21 (s, 3H), 2.26 (s, 3H), 0.5–2.8 (m, 19H), 5.42 (d, *J*=6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) (100 MHz) δ (ppm): 14.4, 15.3, 21.6, 25.0, 27.6, 32.0, 32.2, 32.7, 33.7, 38.2, 38.3, 39.4, 39.8, 43.2, 46.8, 46.9, 47.9, 89.7, 117.0, 145.8, 211.4, 212.3; HRMS-EI (M+Na) calcd for $C_{22}H_{32}O_3Na$ 367.2244, found 367.2241.

4.4. 6α-Methyl-17α-hydroxy-pregna-4,9(11)-diene-3,20-dione (17)

The 6-methylene steroidal derivative **14** (18 g, 54 mmol) and palladium (10%) over charcoal (50% wet, 0.1 g/g) were suspended in dichloromethane (350 mL) and triethylamine (5 mL, 38 mmol) was added via syringe; the reaction mixture was stirred under a hydrogen atmosphere for 6 h. The reaction mixture was filtered over Celite, and the solid washed five times with DCM. The organic phase was evaporated off and the solid was redissolved in THF (350 mL). HCl (37%, 11 mL, 135 mmol) was added and the reaction mixture was stirred for an additional 12 h. Once the isomerization process was completed, the reaction mixture was evaporated, redissolved in methanol (30 mL), and poured very slowly into water (200 mL). The suspended solid was filtered and dried, yielding **17** (14.35 g, 61%) pure. Mp: 180–183 °C; $[\alpha]_D^{20}$ +38.6 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 736, 918, 1242, 1359, 1664, 1709, 2968, 3448; ^{1}H NMR ($CDCl_3$) (400 MHz) δ (ppm): 0.67 (s, 3H), 1.09 (d, *J*=12.6 Hz, 3H), 1.32 (s, 3H), 2.26 (s, 3H), 2.82 (s, 1H, OH), 0.5–2.6 (m, 15H), 5.52 (d, *J*=5.8 Hz, 1H), 5.77 (s, 1H); ^{13}C NMR ($CDCl_3$) (100 MHz) δ (ppm): 15.3, 18.1, 24.6, 27.2, 27.5, 32.2, 33.7, 33.8, 34.0, 34.0, 37.2, 41.3, 46.6, 47.4, 89.5, 118.4, 121.2, 144.0, 172.8, 199.6, 211.2; HRMS-EI (M+Na) calcd for $C_{22}H_{30}O_3Na$ 365.2087, found 365.2098.

4.5. 6α-Methyl-17α-hydroxy-pregna-1,4,9(11)-triene-3,20-dione (18)

To a solution of the steroidal diketone **17** (0.05 g, 0.14 mmol) in DCM (0.5 mL), diisopropylethylamine (0.1 mL, 0.45 mmol) and *tert*-butyldimethylsilyltrifluoromethanesulphonate (TfOTBDMS, 0.08 mL, 0.35 mmol) were added successively via syringe. The reaction mixture was stirred at 10 °C for 3 h, after which water (1 mL) was added and stirring was maintained for an additional 60 min. The organic phase was extracted and pyridine (0.02 mL, 0.28 mL) and chloranil (0.04 g, 0.15 mmol) were added. The mixture was stirred at 15 °C for 16 h, after which 5% $NaHSO_3$ (1 mL) was added, filtered over Celite, and extracted three times with DCM. The combined organic phases were washed with water (3×15 mL), brine (3×15 mL), dried (Na_2SO_4), and evaporated to afford a residue that was fractionated by chromatography on silica gel. Elution with 1:1 hexane/ethyl acetate gave **18** (0.035 g, 67%) pure. Mp: 197–205 °C; $[\alpha]_D^{20}$ +45.7 (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 743, 924, 1015, 1177, 1385, 1469, 1625, 1664, 1697, 2936, 3474; ^{1}H NMR ($CDCl_3$) (200 MHz) δ (ppm): 0.70 (s, 3H), 1.14 (d, *J*=6.4 Hz, 3H), 1.40 (s, 3H), 2.26 (s, 3H), 0.5–3.0 (m, 12H), 5.52 (d, *J*=5.4 Hz, 1H), 6.06 (s, 1H), 6.27 (d, *J*=10.2 Hz, 1H), 7.18 (d, *J*=10.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) (50 MHz) δ (ppm): 15.2, 17.6, 24.8, 27.1, 27.5, 32.3, 33.2, 33.7, 36.6, 43.6, 46.1, 46.9, 47.8, 89.4, 120.4, 121.1, 126.9, 142.7, 155.2, 169.7, 186.4, 211.0; HRMS-EI (M+Na) calcd for $C_{22}H_{28}O_3Na$ 363.1931, found 363.1939.

4.6. 6α-Methyl-9,11β-epoxy-17α-hydroxy-pregna-1,4-diene-3,20-dione (19)

To a solution of the steroidal diketone **18** (2 g, 6 mmol) in 20 mL of a mixture acetone/water 6:1 70% perchloric acid (0.07 mL, 1.2 mmol) was added dropwise, and the temperature fixed at 25 °C. 1,3-Dibromo-5,5-dimethylhydantoin (DBH, 1.2 g,

4 mmol) was added and the reaction mixture was stirred for 4.5 h. The solution was poured into 200 mL of a mixture of acetone/water 1:1, and 10% $NaHSO_3$ (10 mL) and K_2CO_3 (3.6 g, 26 mmol) were added and the mixture stirred for a further 4 h. The acetone was evaporated off and the solution was cooled to 0–5 °C. The suspension was filtered and the solid was washed with cold water. The steroid **19** (1.9 g, 92%) was isolated pure. Mp: 183 °C; $[\alpha]_D^{20}$ +22.4° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν (cm^{-1}): 730, 918, 1132, 1249, 1372, 1664, 1709, 2929, 3416; ^1H NMR ($CDCl_3$) (200 MHz) δ (ppm): 0.85 (s, 3H), 1.13 (d, *J*=6.4 Hz, 3H), 1.38 (s, 3H), 2.18 (s, 3H), 3.12 (br s, 1H, OH), 3.29 (s, 1H), 0.5–3.5 (m, 11H), 6.08 (s, 1H), 6.16 (dd, J_1=10.2 Hz, J_2=1.7 Hz, 1H), 6.55 (d, *J*=10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) (50 MHz) δ (ppm): 17.4, 17.9, 24.1, 24.8, 27.3, 30.6, 31.6, 32.8, 34.4, 42.4, 44.2, 46.2, 50.2, 63.4, 67.0, 89.2, 121.6, 127.6, 152.9, 168.4, 186.3, 210.3; HRMS-EI (M+Na) calcd for $C_{22}H_{28}O_4Na$ 379.1879, found 379.1870.

4.7. 6α-Methyl-9α-fluoro-11β,17α-dihydroxy-pregna-1,4-diene-3,20-dione (7a)

Hydrofluoric acid (70%, 2.2 mL, 94.3 mmol) was placed in a plastic or Teflon round-bottomed flask at −40 °C and the steroidal epoxide 19 (1.0 g, 2.8 mmol) was added portionwise maintaining the temperature below −35 °C. After 4 h, the solution was slowly poured into 20% NH_4OH (36 mL) at −10 °C. The stirred suspension was warmed up to 0 °C, filtered, and washed with cold water (10 mL). After drying, the fluorohydrin **7a** (0.85 g, 80%) was obtained pure. Mp: 297 °C; $[\alpha]_D^{20}$ +50.2 (*c* 0.4, $CHCl_3$); IR (KBr) ν (cm^{-1}): 888, 988, 1075, 1201, 1307, 1348, 1447, 1656, 1713, 2879, 2921, 2944, 2971, 3393; ^1H NMR (DMSO-d_6) (400 MHz) δ (ppm): 0.75 (s, 3H), 1.06 (d, *J*=6.4 Hz, 3H), 1.48 (s, 3H), 2.07 (s, 3H), 1.2–2.9 (m, 11H), 4.12 (d, *J*=5.7 Hz, 1H), 5.24 (br s, 1H, C11-OH), 5.27 (s, 1H, C17-OH), 5.90 (s, 1H), 6.23 (dd, J_1=10.1 Hz, J_2=1.8 Hz, 1H), 7.28 (d, *J*=10.0 Hz, 1H); ^{13}C NMR (DMSO-d_6) (100 MHz) δ (ppm): 16.4, 17.3, 23.0, 23.4, 26.6, 31.7, 31.8, 33.4 (d), 35.6, 36.3, 44.0, 45.3, 48.1 (d), 70.5 (d), 88.9, 101.2 (d), 121.5, 128.6, 153.3, 169.9, 185.3, 209.7; HRMS-EI (M+Na) calcd for $C_{22}H_{29}O_4FNa$: 399.1942, found: 399.1955.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2009.08.030.

References and notes

1. Avery, M. A.; Wollfrey, J. R. Antiinflammatory steroids. In *Therapeutic Agents*; Wolf, M. E., Ed.; Burger's Medicinal Chemistry and Drug Discovery; Wiley-Interscience: New York, NY, 1997; Vol. 5, pp 281–376.
2. Brueggemeier, R. W.; Miller, D. D.; Witiak, D. T. In *Principles of Medicinal Chemistry*; Foye, W. O., Lemke, T. L., Williams, D. A., Eds.; Williams and Wilkins: Baltimore, MD, 1995; pp 444–498.
3. Cahn, M. M.; Levy, E. J. *Clin. Med.* **1963**, *70*, 571–576.
4. Noojin, R. O.; Osment, L. A.; Douglass, H. J. *Clin. Med.* **1963**, *70*, 747–751.
5. Rostenberg, A. *J. New Drugs* **1961**, *1*, 118–121.
6. Cahn, M. M.; Levy, E. J. *J. New Drugs* **1961**, *1*, 262–267.
7. Lincoln, F. H.; Schneider, W. P.; Spero, G. B. U.S. Patent 2,867,637, 1959; *Chem. Abstr.* **1959**, *53*, 9297.
8. Spero, G. B.; Thompson, J. L.; Lincoln, F. H.; Schneider, W. P.; Hogg, J. A. *J. Am. Chem. Soc.* **1957**, *79*, 1515–1516.
9. Lincoln, F. H.; Schneider, W. P.; Spero, G. B. U.S. Patent 2,867,638, 1959; *Chem. Abstr.* **1959**, *53*, 9297c.
10. Lincoln, F. H.; Schneider, W. P.; Spero, G. B. French Patent 1,330,110, 1958; *Chem. Abstr.* **1964**, *61*, 7084a.
11. Plasseraud, C.; Gutmann, D.; Lemoine, J. FR Demande 2,223.364, 1973; *Chem. Abstr.* **1975**, *82*, 156581.
12. Magerlein, B. J.; Kagan, F. *J. Org. Chem.* **1960**, *25*, 1675–1676.
13. Burke, H. J.; Hessler, E. J. U.S. Patent 4,346,037, 1982; *Chem. Abstr.* **1983**, *98*, 4716j.
14. Bucourt, R.; Nedelec, L.; Gasc, J. C.; Pierdet, A. Ger. Offen. 2,110,140, 1971; *Chem. Abstr.* **1971**, *75*, 151986a.
15. Lombardi, P. *Biochim. Biophys. Acta* **2002**, *1587*, 326–337 and references therein.
16. (a) Pizey, J. S. *Synthetic reagents*; Malsted: New York, NY, 1974; Vol. II, pp 180–193; (b) The catalyst depression effect of the Pd/C and triethylamine combination has been successfully applied on chemoselective hydrogenations, see: Sajiki, H.; Hirota, K. *Tetrahedron* **1998**, *54*, 13981–13996 and references therein.
17. Marcos-Escribano, A.; Bermejo, F. A.; Lorente Bonde-Larsen, A.; Iglesias Retuerto, J.; Herráiz-Sierra, I. *Tetrahedron* **2009**, *65*, 7587–7590.
18. Park, Y. J.; Lee, M. Y.; Cho, S. I. *J. Korean Chem. Soc.* **1992**, *36*, 812–817.