Drugs of the Future 1999, 24(5): 488-501

CCC: 0377-8282/99

Eplerenone

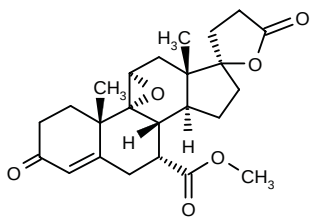
Prop INN; USAN

Antihypertensive
Treatment of Heart Failure
Aldosterone Antagonist

Epoxymexrenone
CGP-30083
SC-66110

9α,11α-Epoxy-3,5'-dioxospiro[androst-4-ene-17,2'(*R*)-tetrahydrofuran]-7α-carboxylic acid methyl ester

9α,11α-Epoxy-17β-hydroxy-3-oxo-17α-pregn-4-ene-7α,21-dicarboxylic acid γ-lactone 7-methyl ester



$C_{24}H_{30}O_6$ Mol wt: 414.4950

CAS: 107724-20-9

EN: 261466

Synthesis

Eplerenone was prepared by several related ways:

1) Microbiological hydroxylation of canrenone (I) provided the 11α-hydroxy derivative (II), which was converted to the enamino compound (IV) by the addition of cyanide, followed by cyclization with acetone cyanohydrin (III) in the presence of triethylamine and lithium chloride in DMF or, alternatively, by treatment with sodium cyanide and sulfuric acid. Hydrolysis of enamine (IV) with HCl in methanol/water gave diketone (V), and further reaction of (V) with sodium methoxide in refluxing methanol gave hydroxyester (VI). The mesylation of the 11α-hydroxyl group of (VI) with mesyl chloride and triethylamine in dichloromethane yielded sulfonate (VII), which by treatment with potassium formate in a mixture of formic acid and acetic anhydride at 100 °C afforded olefine (VIII). Other conditions for this reaction were potassium acetate in trifluoroacetic acid/trifluoroacetic anhydride, isopropenyl acetate and *p*-TsOH, or thermoelimination in DMSO at 80 °C. Alternatively, hydroxyester (VI) was converted directly into olefin (VIII) by reaction with sulfuryl chloride at –70 °C and treatment with imidazole at room temperature. Finally, epoxidation of (VIII) was performed by reaction with H_2O_2 in the presence of trichloroacetamide or trichloroacetonitrile and K_2HPO_4, giving eplerenone (1, 2). Scheme 1.

2) Alternatively, canrenone (I) was converted to mexrenone (XI) by a similar sequence, including cyanide addition to give enamine (IX), hydrolysis to diketone (X) and ring opening with NaOMe to (XI). The microbiological oxidation of mexrenone (XI) yielded either the 9α (XII) or the 11β (XIII) hydroxylated compounds, which were dehydrated to the olefin (VIII), whose epoxidation, as before, afforded eplerenone (1, 2). Scheme 2.

3) The reaction of enol ether (XIV) with the sulfonium ylide from trimethylsulfonium methylsulfate and KOH in DMSO/THF at 80 °C afforded epoxide (XV), which was converted to the lactone-carboxylic acid ester (XVI) by treatment with diethyl malonate and sodium ethoxide in refluxing ethanol. The decarboxylation of (XVI) by heating with NaCl in moist DMF yielded (XVII), which by hydrolysis of its enol ether group with AcOH in boiling ethanol/water provided dienone (XVIII). The oxidation of (XVIII) to trienone (XIX) was performed by means of a sequence consisting of halogenation with *N*-bromosuccinimide and then dehydrohalogenation with DABCO and LiBr in DMF (or by treatment with DDQ or chloranil). Using the analogous reactions as in Scheme 1, (XIX) was converted to enamine (XX), then hydrolized to diketone (XXI) and treated with NaOMe to give the already reported dienone (VIII), and was finally converted to eplerenone (1, 2). Scheme 3.

4) Alternatively, lactone (XVIII), obtained from enol ether (XIV) as in Scheme 3, was epoxidized as before to give (XXII), which was dehydrogenated using either DDQ or chloranil to afford dienone (XXIII). Finally, (XXIII) was converted into the enamine (XXIV) as already reported,

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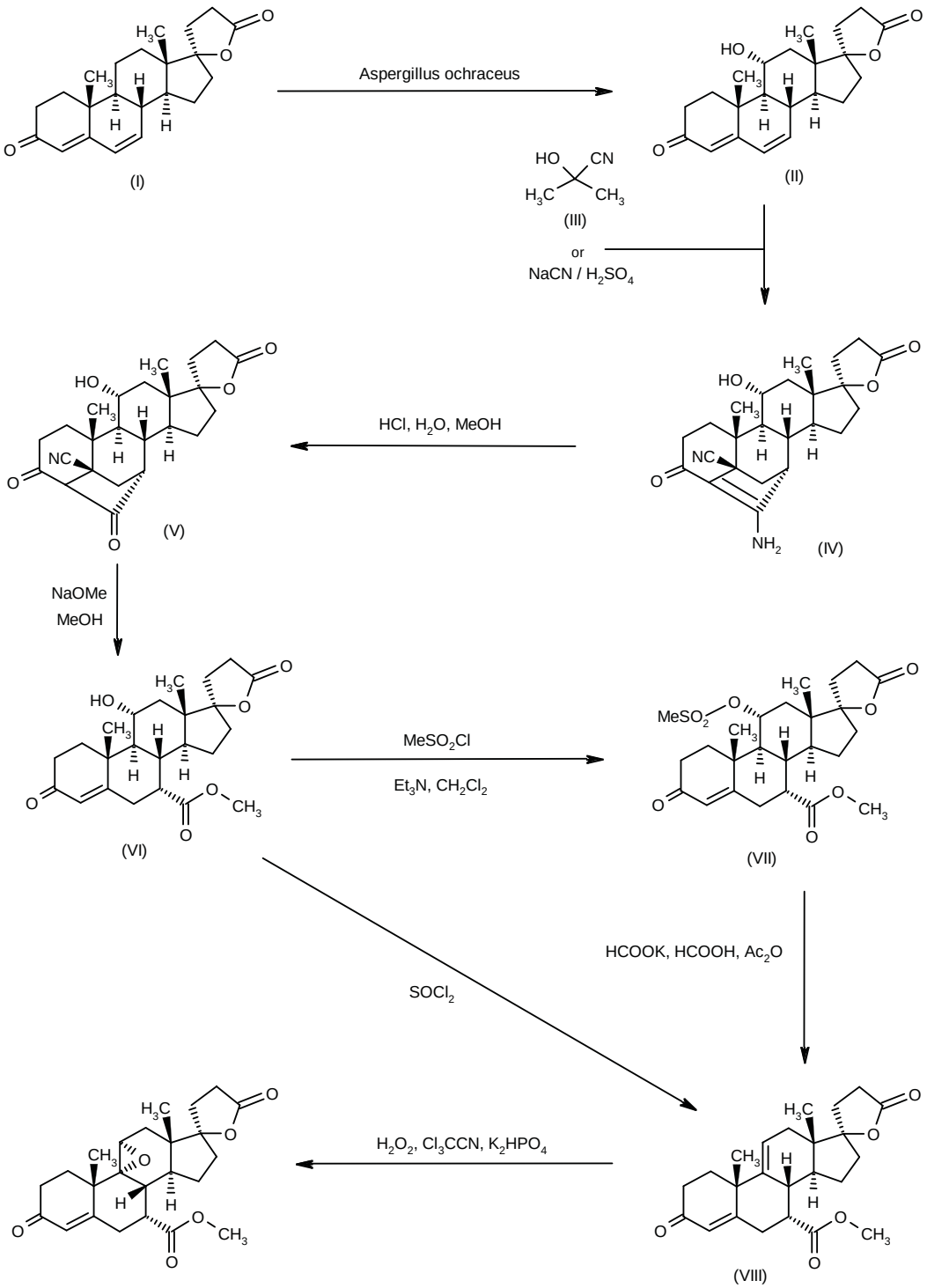
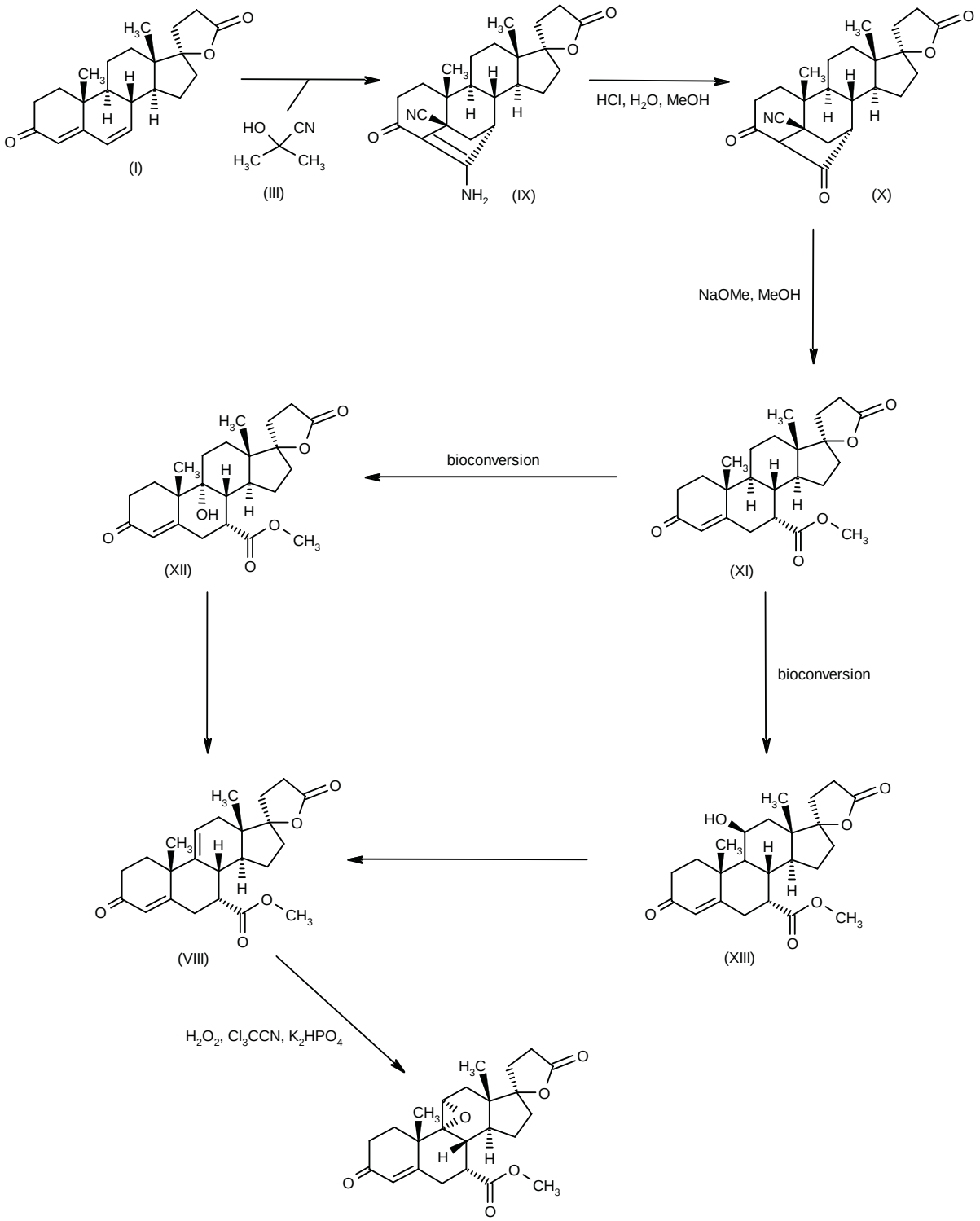
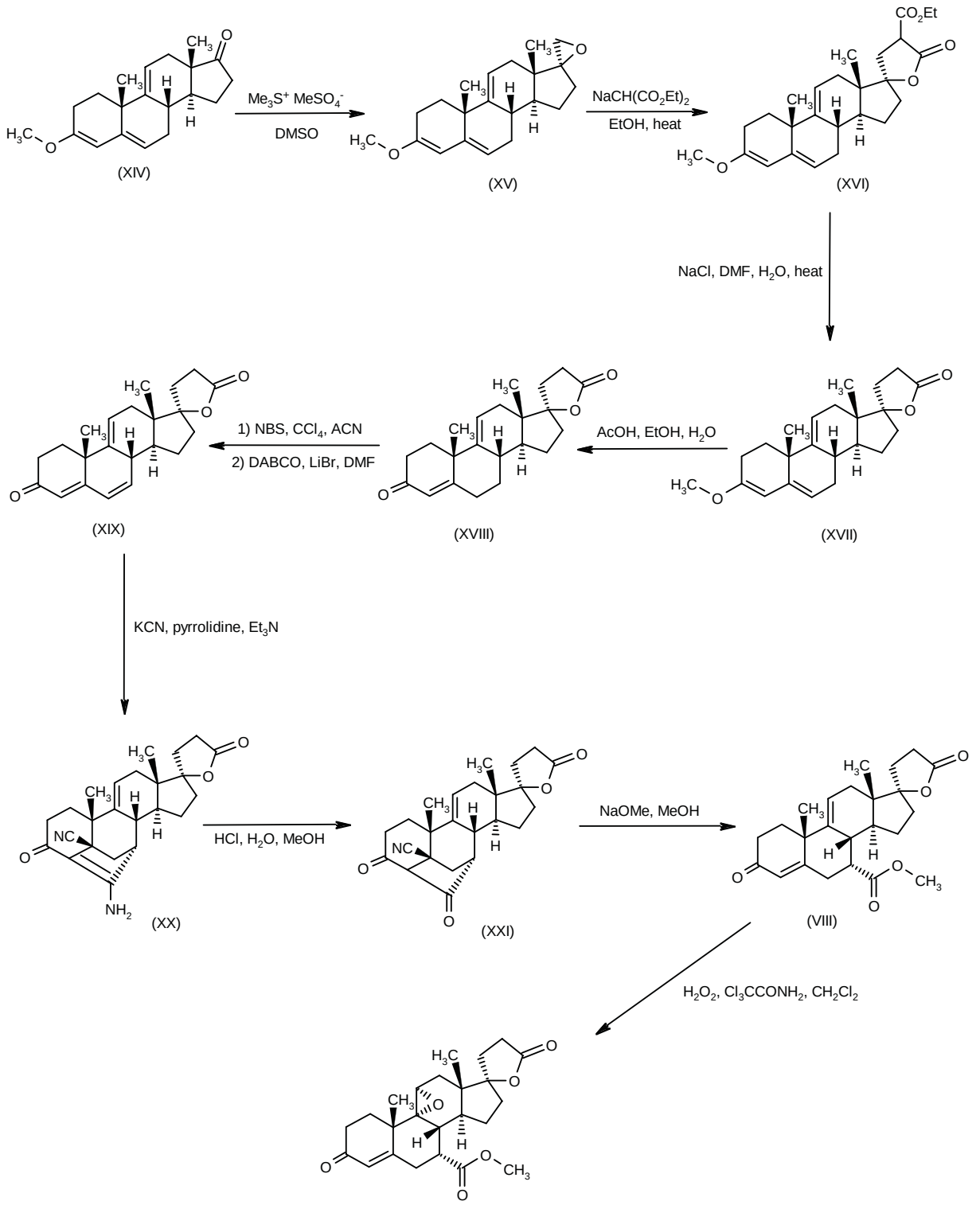
Scheme 1: Synthesis of Eplerenone



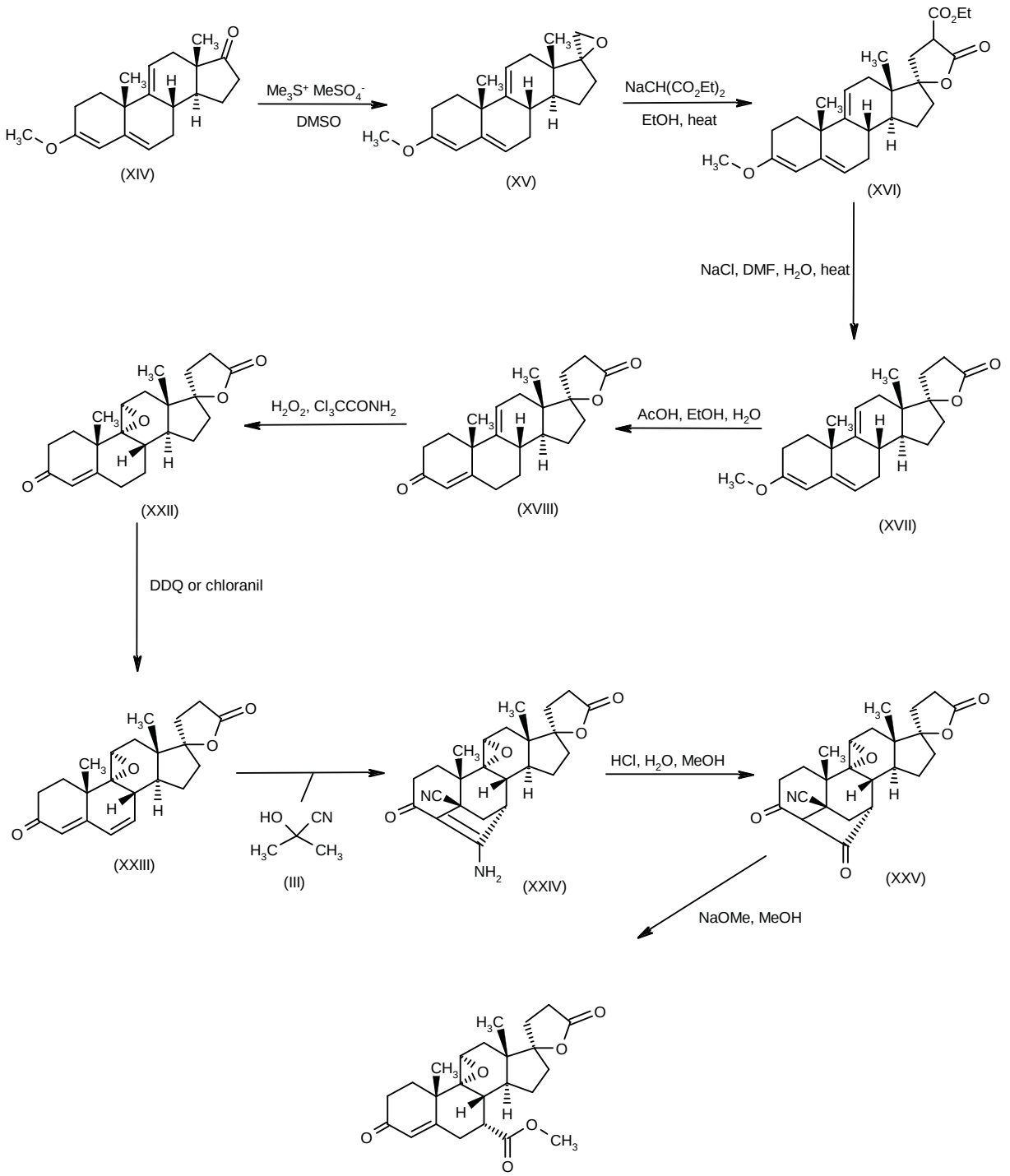
Scheme 2: Synthesis of Eplerenone



Scheme 3: Synthesis of Eplerenone



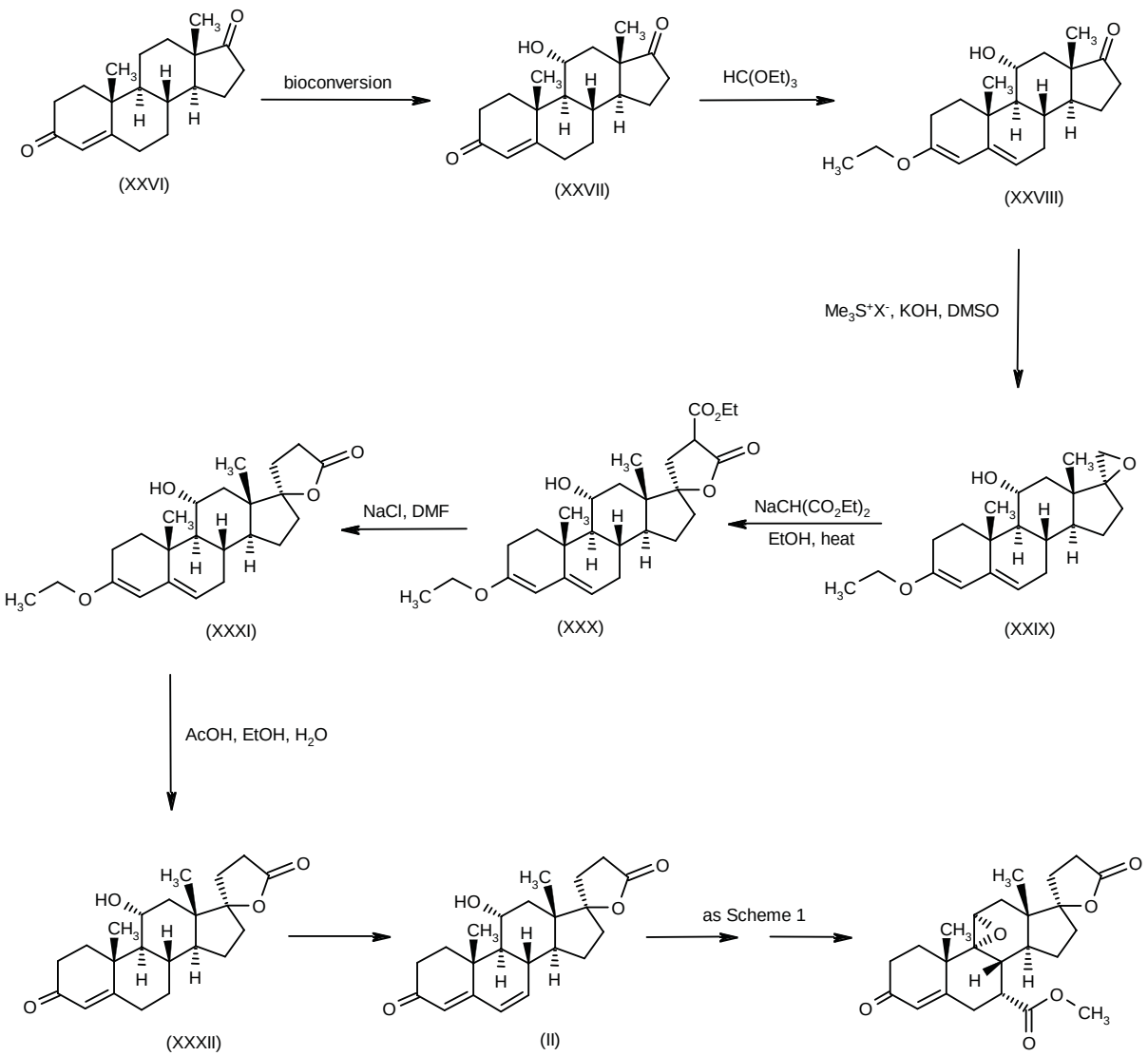
Scheme 4: Synthesis of Eplerenone



then hydrolyzed to diketone (XXV) and treated with NaOMe, yielding eplerenone (1, 2). Scheme 4.

5) Microbiological oxidation of androstenedione (XXVI) produced the 11α-hydroxy compound (XXVII), which was converted to enol ether (XXVIII) by treatment with triethyl orthoformate and *p*-toluenesulfonic acid. Compound (XXVIII) was submitted to a reaction sequence analogous to Scheme 3, producing epoxide (XXIX), lactone-carboxylic acid ester (XXX), decarboxylated compound (XXXI) and enone (XXXII). This com-

Scheme 5: Synthesis of Eplerenone



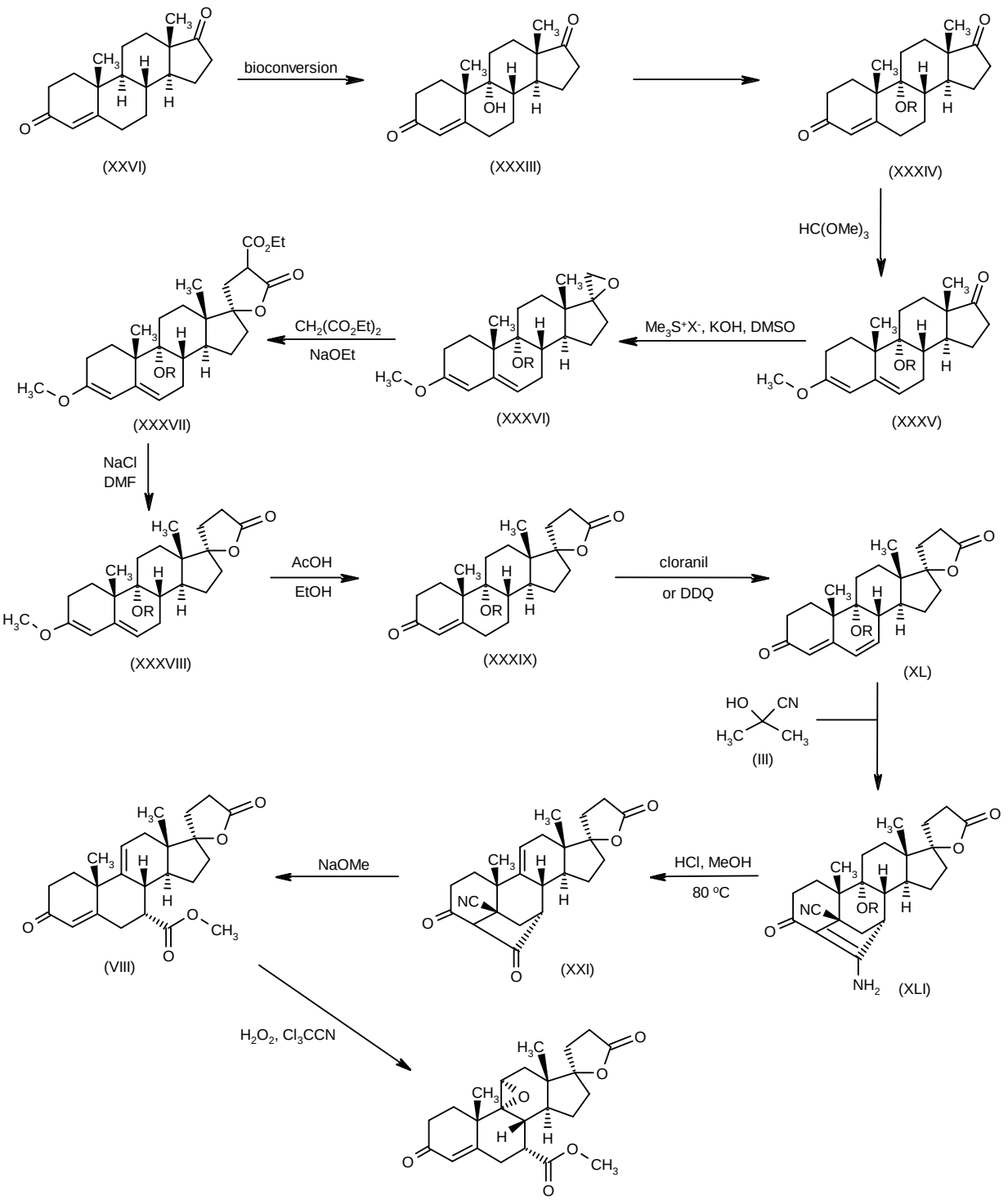
pound was dehydrogenated as before to dienone (II), which was finally converted to eplerenone by the synthetic steps described in Scheme 1 (1, 2). Scheme 5.

6) Microbiological oxidation of androstenedione (XXVI) produced the 9α-hydroxy compound (XXXIII), which was protected, yielding the ether (XXXIV). The reaction of (XXXIV) with trimethyl orthoformate afforded the enol ether (XXXV), which by a reaction sequence analogous to Scheme 3 provided epoxide (XXXVI), lactone-carboxylic acid ester (XXXVII), decarboxylated lactone (XXXVIII) and finally enone (XXXIX). Dehydrogenation of (XXXIX) with DDQ or chloranil afforded dienone (XL), which by reaction with acetone cyanohydrin in a sequence analogous to Scheme 1 gave enamine (XLI). The treatment of (XLI) with HCl in methanol at 80 °C yielded the already described unsaturated diketone (XXI), which was worked up as described in Scheme 3, giving eplerenone (1, 2). Scheme 6.

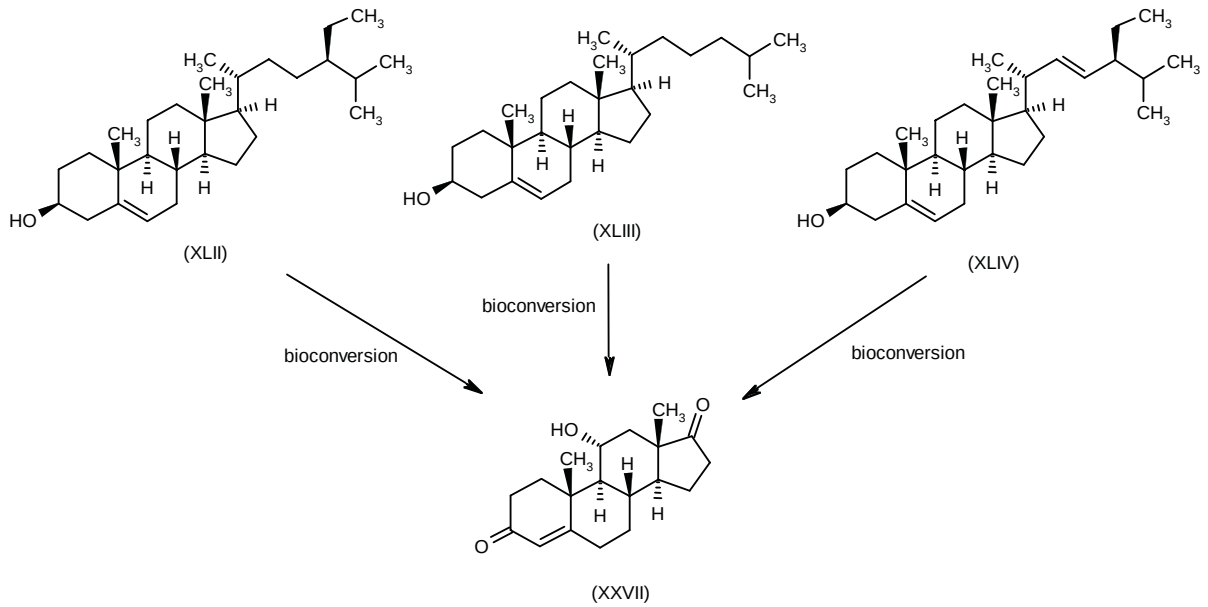
7) Microbiological conversion of β-sitosterol (XLII), cholesterol (XLIII) or stigmasterol (XLIV) also yielded the 11α-hydroxy compound (XXVII), already reported, which was worked up to afford eplerenone as described in Scheme 5 (1, 2). Scheme 7.

8) The hydrolysis of enol ether (XIV) with acetic acid gave androstenedione (XLV), which was dehydrogenated with DDQ or chloranil to androstadienedione (XLVI). The reaction of (XLVI) with KCN and acetic acid yielded the 7α-cyano compound (XLVII), which was treated with

Scheme 6: Synthesis of Eplerenone



Scheme 7: Synthesis of Intermediate (XXVII)



triethyl orthoformate, affording lactone (XLVIII). This compound (XLVIII), by a reaction sequence analogous to Scheme 3, provided epoxide (XLIX), lactone-carboxylic acid ester (L), decarboxylated lactone (LI) and finally enone (LII). The reaction of (LII) with methyl iodide in basic medium afforded the already reported dienone (VIII), which was epoxidized to eplerenone as before (2). Scheme 8.

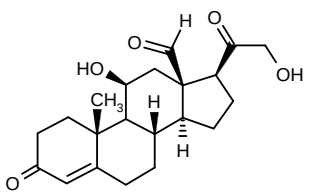
9) Alternatively, the already reported 7α-cyanoandrosta-4,9(11)-diene-3,17-dione (XLVII) was treated with triethyl orthoformate to give the triethoxy derivative (LIII), which was reduced with DIBAL to the corresponding aldehyde (LIV). The selective hydrolysis of (LIV) with dilute acid yielded the keto-lactol (LV), which by alkylation with ethanol and a Lewis acid provided intermediate (LVI). Compound (LVI) was submitted to a reaction sequence analogous to Scheme 3, yielding epoxide (LVII), lactone-carboxylic acid ester (LVIII) and finally decarboxylated lactone (LIX). The hydrolysis of (LIX) in an acid medium gave the unsaturated keto-lactol (LX), which was epoxidized as usual, yielding the epoxy-lactol (LXI). The oxidation of (LXI) provided the epoxy-lactone (LXII), which was finally treated with methyl iodide in basic medium, affording eplerenone (2). Scheme 9.

10) The already reported trienone (XIX) was treated with HCN and triethylaluminum to yield the 7α-cyano derivative (LXIII), which was reduced to the corresponding hydroxy-aldehyde (LXIV) with DIBAL. The oxidation of (LXIV) with CrO_3 afforded the keto-acid (LXV), which was methylated with diazomethane to the already reported dienone (VIII). Finally, this compound was epoxidized to eplerenone with H_2O_2 as described (3) or by means of *m*-chloroperbenzoic acid (4). Scheme 10.

Introduction

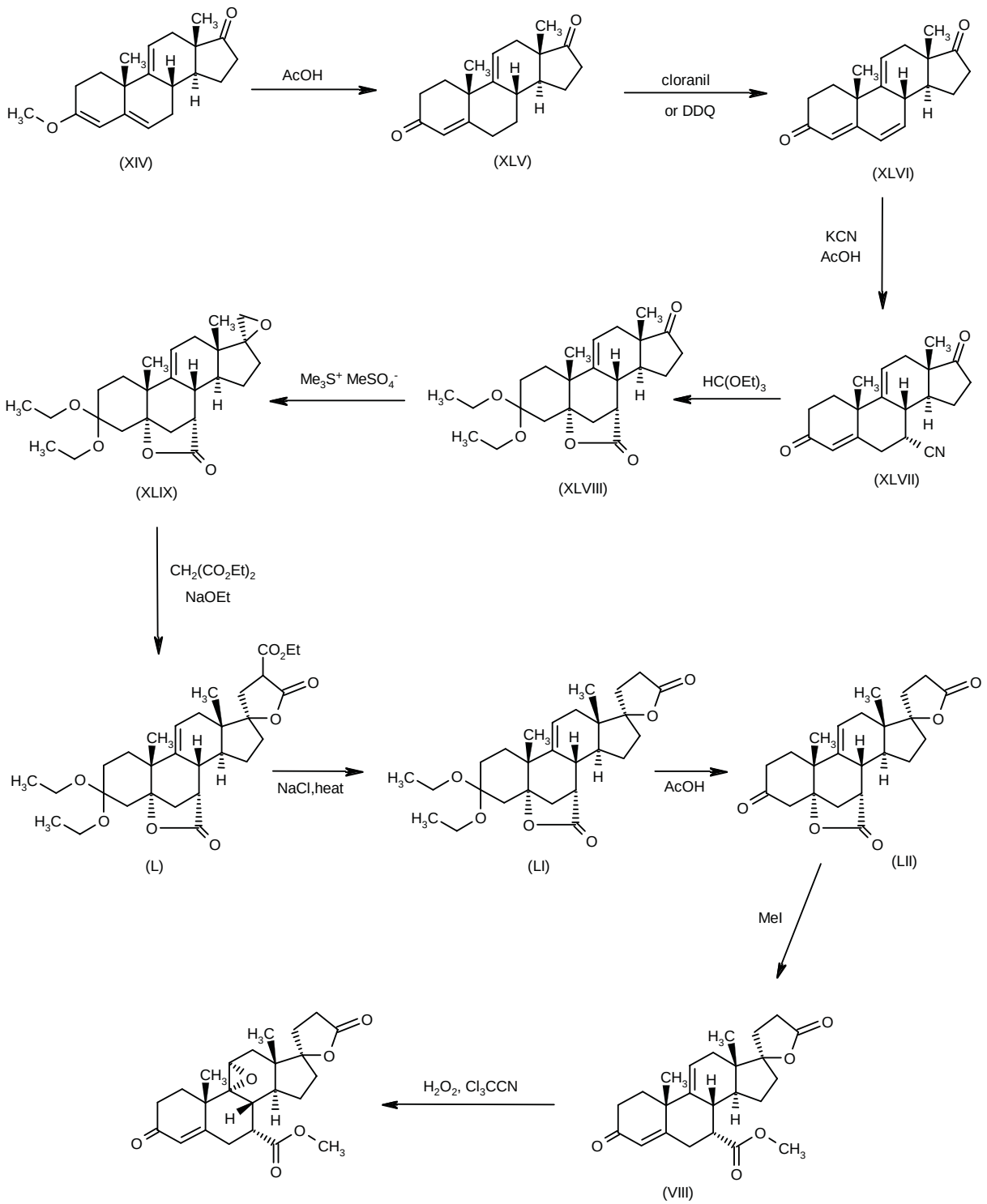
Aldosterone [I] is the most potent natural mineralocorticoid. Its secretion is controlled primarily by the renin-angiotensin system (to such an extent that it is frequently called the renin-angiotensin-aldosterone system or RAAS) and by serum potassium concentrations.

Aldosterone plays an important role in regulating electrolyte composition by promoting sodium retention and potassium excretion. The main renal effect of aldosterone is to stimulate sodium/potassium transport in the distal tubules, thus enhancing sodium reuptake and potassium excretion. Aldosterone has several adverse effects on the cardiovascular system, including myocardial fibrosis, left ventricular hypertrophy, fluid retention, potassium and magnesium excretion, which in chronic states of hyperaldosteronism can lead to significant morbidity and mortality. Elevated aldosterone levels have been observed in

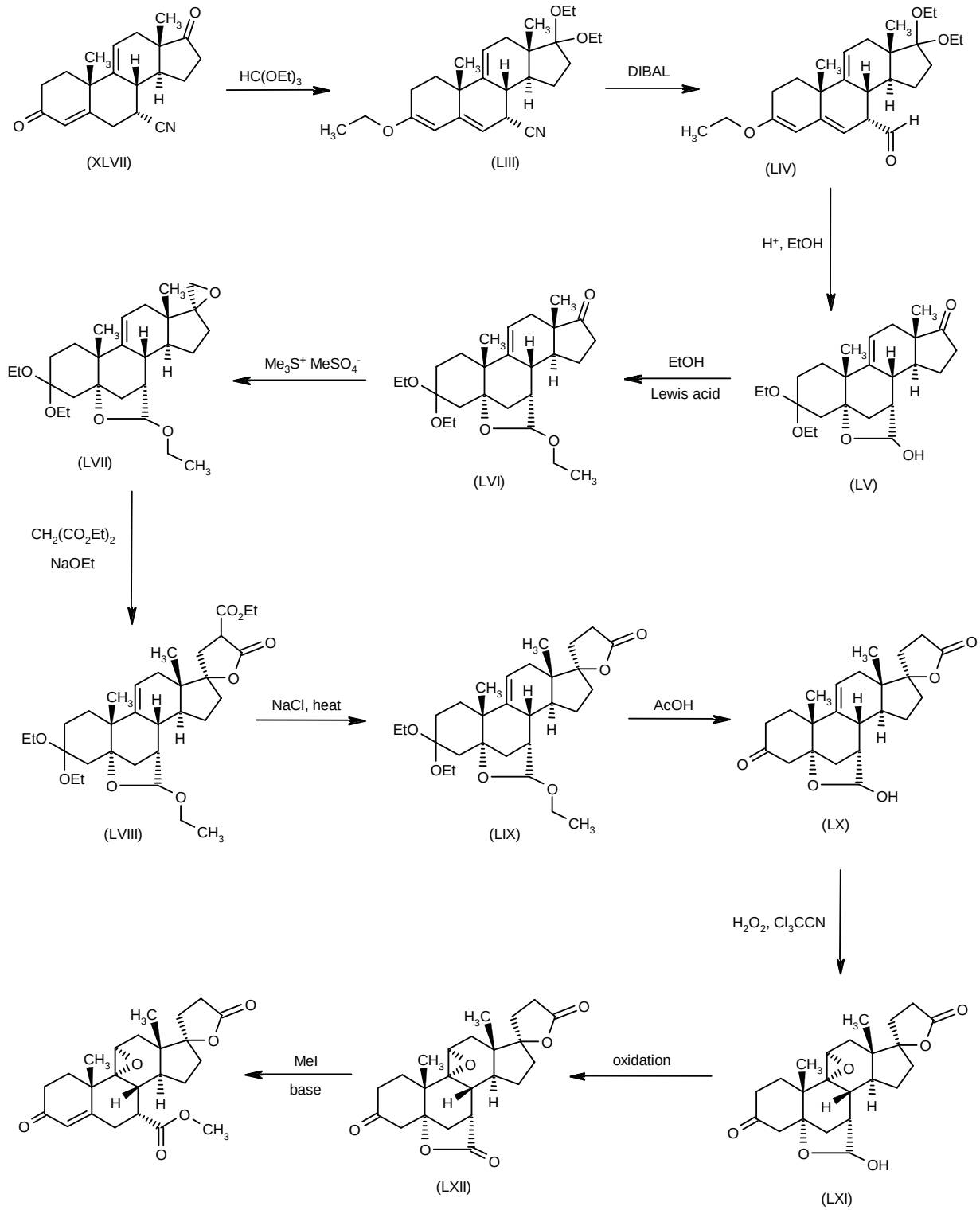


[I]

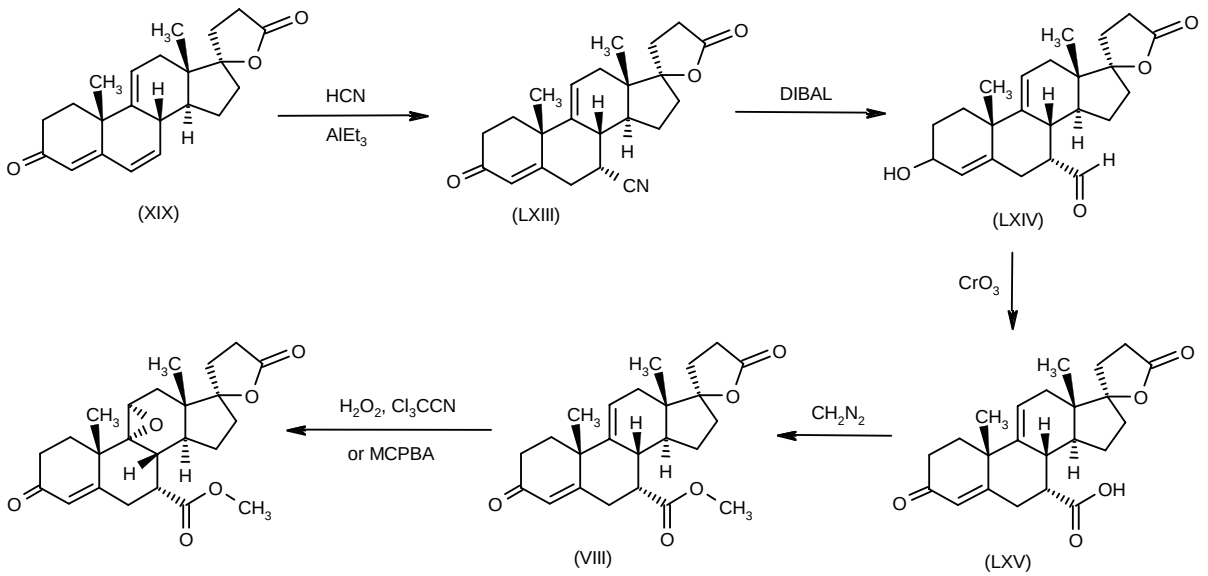
Scheme 8: Synthesis of Eplerenone



Scheme 9: Synthesis of Eplerenone



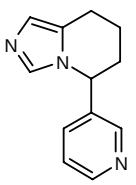
Scheme 10: Synthesis of Eplerenone



conditions such as edema, congestive heart failure, essential hypertension and complications of kidney disease and hepatic cirrhosis. In the CONSENSUS trial, for example, significant relationships were observed between aldosterone and angiotensin II levels and mortality (5).

Aldosterone has been shown to exert its principal pathophysiological effects, including hypertension, cardiac hypertrophy and cardiac fibrosis, by binding to mineralocorticoid receptors in the kidneys, heart and nervous system. Aldosterone receptors have been found in the heart and main vessels (6, 7), which may be important in mediating aldosterone-induced myocardial fibrosis (8). One study noted a direct relationship between left ventricular mass and aldosterone levels in hypertensive patients (9). It has been hypothesized that the interaction of aldosterone with cardiac receptors induces collagen synthesis and deposition from cardiac fibroblasts, which may lead to interstitial myocardial fibrosis. This results in left ventricular stiffness and dysfunction that may cause congestive heart failure (10, 11).

In order to block the pathological effects of hyperaldosteronism, spironolactone (Aldactone®, Searle), a competitive aldosterone antagonist, was introduced in 1959 and has been used as a therapeutic agent for the treatment of congestive heart failure, hepatic cirrhosis, malignant ascites, nephrotic syndrome and primary aldosteronism. Spironolactone has been shown to prevent aldosterone-induced myocardial fibrosis (12), and the Randomized Aldactone Evaluation Study (RALES) suggests that the addition of spironolactone to an angiotensin-converting enzyme (ACE) inhibitor-based regimen in patients with heart failure causes marked



[II]

diuresis and symptomatic improvement (13). Metyrapone (Metopirone®, Novartis) is another aldosterone antagonist that has been in clinical use since 1966. Other aldosterone antagonists currently under investigation are shown in Table I.

The search for novel aldosterone antagonists continues with the aim of identifying compounds devoid of the unwanted progestational and antiandrogenic side effects of currently available drugs. Scientists at Novartis synthesized a series of 9α,11-epoxysteroids, with the most interesting compounds being epoxyspironolactone, epoxyprorenone and epoxymexrenone (3). More recently, Yamanouchi synthesized bicyclic condensed imidazoles (JP 97071586 [II]) as aldosterone antagonists.

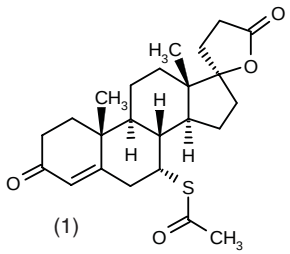
Epoxymexrenone (eplerenone), originally synthesized and described by Novartis, was selected for further development and is under clinical evaluation by Searle.

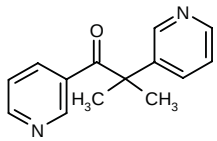
Pharmacological Actions

Spironolactone has been reported to act at the mineralocorticoid receptor level by competitively inhibiting

Table I: Chemical structures of aldosterone antagonists.

1. Spironolactone (*Aldactone*®; Searle)
2. Metyrapone (*Metopirone*®; Novartis)
3. Eplerenone (Epoxymexrenone; Searle)
4. CGP-33033 (Epoxyspironolactone; Novartis)
5. CGP-29245 (Epoxyprorenone; Novartis)


(1)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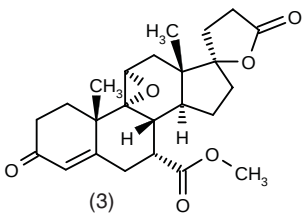
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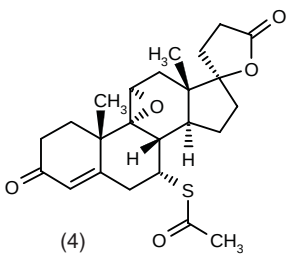
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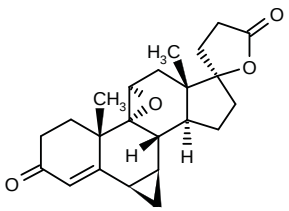
(5)

aldosterone binding. Eplerenone is a highly selective aldosterone antagonist (14). In *in vitro* radioreceptor binding studies, the affinity of eplerenone for aldosterone receptor was approximately 3% that for rat colonic mineralocorticoid receptors, which is substantially less than spironolactone (15).

However, chronic treatment with spironolactone has been associated with endocrine disturbances (loss of libido, menstrual irregularities, gynecomastia, impotence) that are largely due to the strong affinity of the drug for androgen and progesterone receptors. Eplerenone, in contrast to spironolactone, shows little affinity for other steroid receptors (Table II), which results in a much higher selectivity for the mineralocorticoid receptor (14).

Furthermore, on the Kagawa test (which measures the ability of aldosterone receptor antagonists to increase Na excretion and plasma Na/K ratio in comparison with aldosterone or an aldosterone receptor agonist) the antimineralocorticoid activity of eplerenone was twice that of spironolactone (ED_{50} = 2.5 *vs.* 5 mg/kg p.o., respectively) (1-DrP), which shows the high *in vivo* potency of the new compound. However, spironolactone displayed a wide arrange of endocrine effects, whereas eplerenone lacked any significant effects on testicular function, ovulation or target organ weight (14).

The *in vivo* aldosterone-antagonist activity of eplerenone was evaluated in a model of aldosterone-induced hypertension and cardiac fibrosis in rats. In uninephrectomized rats treated with 0.75 μg/min aldosterone, both spironolactone and eplerenone reduced atrial natriuretic

Table II: Mineralocorticoid and glucocorticoid receptor binding affinities of selected aldosterone antagonists launched or under clinical development (from Prous Science MFLine database).

Compound	Mineralcorticoid Receptor (RBA, aldosterone)	Glucocorticoid Receptor (RBA, dexamethasone)	Progesterone Receptor (RBA, progesterone)	Androgen Receptor (RBA, dihydrotestosterone)	AMC Activity (spirolactone)
Canrenone	0.01[a] (21)	<0.001[a] (21)	0.27 (22)	0.011 (22)	0.3 (22)
Eplerenone	0.0051 (14)	0.00018 (14)	<0.00005 (14)	0.0000076[c] (14)	3-10[f] (14)
CGP-29245	0.12 (14)	0.0005 (14)	0.0083 (14)	0.00024[c] (14)	3-10[f] (14)
CGP-33033	0.075 (14)	0.0075 (14)	0.00074 (14)	0.000011[c] (14)	10[f] (14)
Mespirenone	0.21[a] (21)	<0.001[a] (21)	0.03 (22)	0.01 (22)	2.7 (22)
Spironolactone	0.04[a] (21) 0.11 (14)	<0.001[a] (21) 0.0018 (14)	0.048 (22) 0.007 (14)	0.11 (22) 0.0091[c] (14)	1.0 (22)
Spirorenone	0.73[b] (23)	——-	0.15 (22)	0.007 (22)	8.6 (22)
ZK-91587	0.71[d] (24)	——-	0.04 (22)	0.009 (22)	2.1 (22)

[a]Receptors of adrenalectomized male rabbit kidney. [b]RBA to spironolactone and [c]methyltrienolone used as standard control compounds determined from concentrations needed to obtain 50% displacement. Binding of [^{3}H]-aldosterone, [^{3}H]-dexamethasone, [^{3}H]-progesterone and [^{3}H]-dihydrotestosterone except where otherwise indicated: [b][^{3}H]-spironolactone, [c][^{3}H]-methyltrienolone. RBA=IC_{50} control standard/IC_{50} test compound. [d]RBA to aldosterone for displacement of [^{3}H]-ZK-91587 binding in adrenalectomized male rat hippocampus. AMC = antimineralocorticoid activity in adrenalectomized male rats compared to spironolactone i.v. [f]Dose range or single dose (mg/kg p.o.) required to obtain an AMC comparable to that for spironolactone (10 m/kg p.o.). References are given in parentheses.

Box 1: Efficacy of eplerenone in patients with hypertension (18, 19) [from Prous Science CSLine database].

Design	Parallel, double-blind, placebo-controlled, randomized clinical study
Population	Patients with mild to moderate hypertension (n = 417)
Treatments	Eplerenone (E), 50, 100 or 400 mg/day Spironolactone (S), 50 mg b.i.d. Placebo (P)
Adverse events	E was well tolerated with a profile similar to P
Results	Diastolic blood pressure change (mmHg): E* (-4 to -9) = S* (-8.7) > P [*p <0.001 *vs.* P] Systolic blood pressure change (mmHg): E* (-6.2 to -16.1) = S* (-15.8) > P [*p <0.001 *vs.* P] Trough sitting DBP and SBP were similar in all E groups
Conclusions	Eplerenone reduced blood pressure, with significant effects on systolic blood pressure, and had a peak-to-trough ratio of 1

Box 2: Efficacy of eplerenone in patients with heart failure (20) [from Prous Science CSLine database].

Design	Dose-finding, placebo-controlled, randomized clinical study
Population	Patients with stable heart failure (NYHA Class II-IV, LVEF $\leq$ 40%)
Treatments	Eplerenone (E), 25 mg/d, E25 mg b.i.d., E50 mg/d or E100 mg/d x 12 wk[+] Spironolactone (S), 25 mg/d x 12 wk Placebo (P)
Results	BNP decreased in patients on E and S; urinary aldosterone and renin increased [E50, E100 and S *vs.* P, p <0.05] Hyperkalemia (K^+ > 6.0 mEq/l): E100 (12.0%) $\geq$ S (8.7%) Total testosterone increased in male patients on S [S *vs.* E, p <0.02]
Conclusions	Eplerenone was pharmacologically similar to spironolactone but did not affect total testosterone; a dose of 50 mg/d seemed safe and effective

[+]Eplerenone dose was doubled at wk 12 and patients were followed an additional 4 wk

peptide and hydroxyproline content with similar potency, but eplerenone was more potent in the prevention of collagen scars. Drug-treated animals had significantly less cardiac and perivascular fibrosis than the vehicle-treated controls (16).

In a further set of experiments in aldosterone- and angiotensin II-treated stroke-prone spontaneous hypertensive rats (SHRSP), eplerenone did not prevent severe hypertension but did reduce proteinuria and the development of renal lesions. Severe hypertension developed even in animals treated with captopril, but the ACE inhibitor did not prevent proteinuria and renal damage, whereas eplerenone attenuated both, despite angiotensin II infusion (17).

Clinical Studies

Due to the adverse effects of aldosterone on cardiovascular structures and the ineffectiveness of angiotensin II blockers and ACE inhibitors to control its effects, the selective aldosterone antagonist eplerenone is expected to be a valuable treatment option for hypertension and congestive heart failure, targeting organ damage as well as hypertension. Eplerenone is currently being evaluated in phase III trials as a treatment for hypertension and congestive heart failure. It appears to be effective and safe in patients with heart failure maintained on standard therapy, with efficacy similar to that of spironolactone but with better tolerability as regards testosterone levels.

The efficacy, safety and tolerability of eplerenone was evaluated in 417 patients with mild to moderate hypertension in a parallel, double-blind, placebo-controlled study. Following a 4-week run-in period of placebo treatment, subjects were randomized to 8 weeks of active therapy with eplerenone (50, 100 or 400 mg/day), spironolactone (50 mg b.i.d.) or placebo. Blood pressure response with both active drugs was significantly better than with placebo. Ambulatory diastolic and systolic blood pressure decreased by a mean of 4-9 mmHg and 6-16 mmHg, respectively, among eplerenone-treated patients, compared with respective mean decreases of 8.7 and 15.8 mmHg among spironolactone-treated patients. Trough sitting diastolic and systolic blood pressure readings were similar regardless of whether eplerenone was administered on a twice-daily or once-daily basis. Eplerenone was well tolerated, with an incidence of adverse events similar to that seen with placebo (18, 19) (Box 1).

In a dose-finding, randomized, placebo-controlled efficacy and safety study in 321 patients with heart failure (NYHA class II-IV) maintained on standard therapy (including an ACE inhibitor, diuretic and/or digoxin), eplerenone (25 mg b.i.d. or 50 or 100 mg o.d.) was compared to spironolactone (25 mg o.d.) or placebo for 12 weeks, after which the eplerenone dose was doubled and treatment continued for another 4 weeks. Blood natriuretic peptide decreased significantly after the first 12 weeks of treatment with either active treatment. Urinary aldosterone and renin increased compared to placebo in patients receiving eplerenone at doses of 50 mg/day or higher. The incidence of hyperkalemia was significantly greater with 100 mg/day eplerenone than with spironolactone (12.0% *vs.* 8.7%), but testosterone in male patients increased significantly more with spironolactone than with eplerenone, probably as a result of positive feedback in response to androgen receptor blockade with spironolactone (20) (Box 2).

Manufacturer

G.D. Searle & Co. (US).

References

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