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A New Approach to the Synthesis of Cortical Steroids

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A new bondset for cortical steroid synthesis is developed from the dual concepts of convergent assembly and multiple construction. A short synthesis on this bondset is presented in which the final bond construction by electrocyclization took an unwanted course. Stereocontrol is discussed separately.

INTRODUCTION

Thousands of organic chemicals are synthesized annually on an industrial scale, and their manufacture can often lead to environmental problems. If alternative syntheses that create fewer hazardous wastes and less pollution could be found, a number of these problems could be solved. The generation of an alternative, environmentally benign,[1] synthesis route depends on having a rigorous and logical protocol for synthesis generation. A particular logic has been developed for the design of organic syntheses, and is implemented in the SYNGEN[2] program, which generates all the shortest synthesis routes to any given input target molecule, using as its source a catalog of available starting materials. The value of such program lies in its ability to offer a number of alternative synthesis routes which in conjuction with environmental assessments will make it possible to locate many possible more benign synthesis routes for compounds currently made by other paths. The following design and synthesis of cortical steroids exploited the same general ideas that went into building SYNGEN. The central idea, of course, is that of deriving the shortest and most efficient synthesis.

The total synthesis of cortical steroids has had a long and vigorous history[3] since Woodward's first synthesis[4] in 1951. His approach embodied a linear sequence of 47 steps to cortisone,[5] and subsequent approaches have improved the efficiency so that the latest synthesis by Stork[6] utilizes only 18 steps in a very ingenious approach to adrenosterone.[7] In an analysis of synthesis efficiency we argued for the importance of convergent sequences in synthesis design and detailed a convergent dissection of the cortical steroid skeleton.[8] We have also argued for the importance of multiple constructions in synthesis design efficiency,[9] and indeed Stork's synthesis, though linear, contains three double constructions, *i.e.*, eleven constructions in eight steps. We present here the initial results of a new and convergent approach to cortical steroids based on these themes of efficiency.

RETRO-SYNTHETIC ANALYSIS

The retro-synthetic sequences are summarized in Fig. 1, in which we took 11-keto-Δ^{16}-progesterone **1** as our goal. This has the advantage that **1** has been converted to cortisone in just two steps.[10] Since a major problem in steroid synthesis has always been the efficient construction of the five-membered D-ring, we elected to construct a model **2** with a six-membered ring convertible to steroid by ozonolysis and aldol cyclization.[11] This has the added advantage that the desired *trans*-C/D ring junction is the more stable one in the 6-6 ring fusion but not in the 6-5 fusion, a central problem in hydrindane syntheses.[12] The first cut in **2**

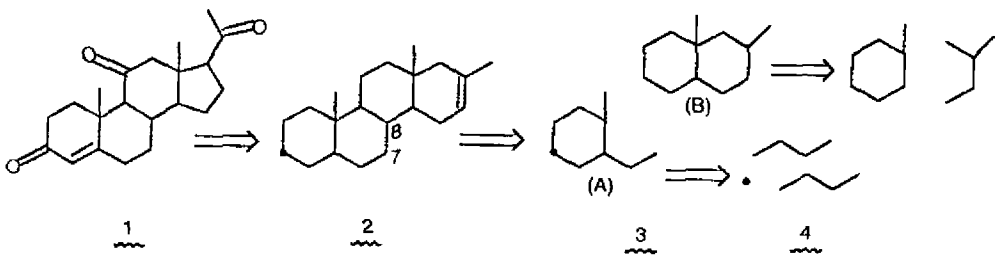

Fig. 1. Retro-Synthetic analysis of cortical steroids.

for a convergent dissection[8] is made in ring B creating skeletal units [A] and [B] of comparable size, which may be joined in an annelation constructing two bonds. In the second cut unit [B] is also conveniently dissected in another annelation to skeletons which might reasonably be starting materials. The unit [A] is uniquely set up for a double affixation of a one-carbon unit to two identical C_4 pieces, followed by cyclization, which potentially allows three skeletal bonds to form at once. The overall analysis afforded the simple convergent plan **2** → **3** → **4** with seven skeletal bonds formation in three multiple-construction steps from simple starting materials.

RESULTS AND DISCUSSIONS

As depicted in Fig. 2, the double affixation/cyclization[9] to the A-ring precursor in **3** followed Spencer's preparation[13] of **5**, with the procedure improved here to one-pot/83% yield, from malonate and methyl vinyl ketone. The proton NMR of compound **5** showed the following characteristics: The ethyl ester groups appeared as quartet at δ 4.15 ppm and triplet at δ 1.2 ppm in the normal way; two methyl group singlets appeared at δ 2.2 ppm (acetyl CH_3) and δ 1.8 ppm (vinyl CH_3); while the rest of the ring protons appeared at δ 2.7 ppm (br, 2H) and δ 2-2.2 ppm (br, 4H). This compound was converted to its pyrrolidine enamine **6** (*71%/TsOH/C₆H₆/-H₂O*), whose proton NMR spectrum showed the disappearance of the acetyl-methyl group at δ 2.2 ppm, and the appearance of a broad peak at δ 3.4 ppm, integrating as two protons, for the two newly formed vinyl protons. The significant up-field shift of the vinyl protons was due to the electronic effect of pyrrolidine. The ester group appeared as usual. The pyrrolidine appeared at δ 3.0 ppm as a broad triplet and δ 1.8 ppm as a multiplet integrating as **4** protons for each. The broad singlet for three protons at δ 1.5 ppm was assigned to the vinyl-methyl group. The CD-ring precursor was forged by a remarkably rigiospecific Diels-Alder reaction between quinone **7** and isoprene,[14] either thermally at 180 °C/5 h or catalytically with $TiCl_4$ at -78 °C/2h. Only the *cis*-adduct **8** (mp 93 °C) is formed. This is an unusual catalysis both in the extent to

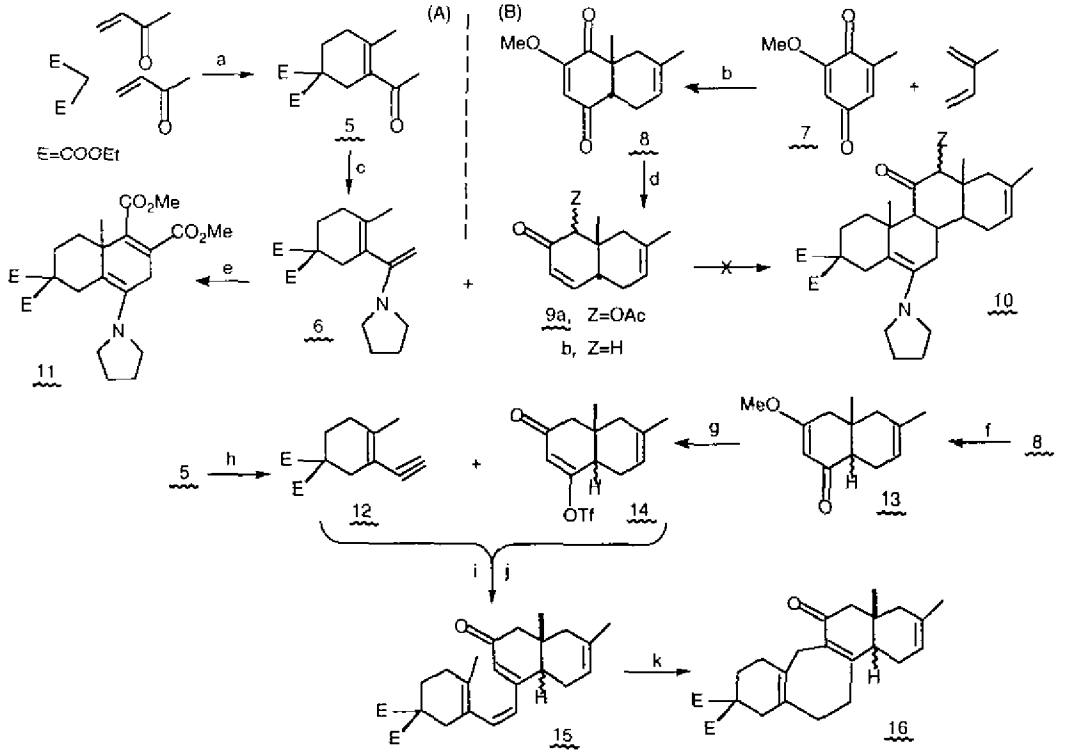

Fig. 2. Convergent assembly of steroids. Reagents and conditions: (a) triton B, dioxane, 14 °C, 2 h, then RT 12 h; TsOH, benzene, reflux 24 h. (b) CH_2Cl_2, $TiCl_4$, -78 °C, 2 h. (c) pyrrolidine, benzene, TsOH, reflux 40 h. (d) $LiAlH_4$, Et_2O, 15 min; Ac_2O, DMAP, 16 h; zinc, reflux 10 min. (e) DMAD, 150 °C, 30 min. (f) $NaBH_4$, glyme, 0 °C, 60 min; Ac_2O, DMAP, 6 h; zinc, reflux 12 h. (g) Tf_2O, CH_2Cl_2, 2,6-di-*t*-Bu-4-Me-pyr, -78 °C, 10 min. (h) LDA, THF, -78 °C, 1 h; $ClPO(OEt)_2$ to RT; LDA, THF, -78 °C, 30 min. (i) DMF, $PdCl_2(PPh_3)_2$, Et_3N, 80 °C, 4 h. (j) H_2, $Pd/BaSO_4$, pyr, RT, 3 h. (k) xylene, reflux, 2 h.

which it moderates the conditions and even more in the fact that the regiochemistry is unchanged. Furthermore, it is unexpected for isoprene to form only one regioisomer, but fortunately compound **8** is the desired isomer here. The structure of adduct **8** was assigned by 500 MHz proton NMR. The spectrum shows two geminally split sharp doublets (δ 1.60 ppm and 2.40 ppm, J = 18 Hz) without further coupling for one methylene, while the two geminally split doublets (δ 2.12 ppm and 2.57 ppm, J = 20 Hz) from the other are multiplets further coupled to the methine proton (δ 2.68 ppm, J = 6, 6 Hz) as well as the isoprene vinyl proton (δ 5.3 ppm, br.), as shown by decoupling of each of the latter signals. The other vinyl proton appeared at δ 5.85 ppm (s), and the two methyls appeared at δ 1.56 ppm (bs.) for the vinyl methyl and δ 1.28 ppm (s) for the quaternary methyl. The quinone **7** (mp 147 °C) was available *via* Fremy salt oxidation of orcinol methyl ether.[15]

Refunctionalization of the adduct **8** to initiate cycloaddition with **6** was achieved by lithium aluminum hydride reduction worked up with acetic anhydride to afford **9a**, which was reduced to **9b** (zinc/Ac_2O/Δ/8 min/60%). Attempts to achieve the Diels-Alder coupling of **6** and **9** to **10** were without success; the components were destroyed above 180 °C and showed no reaction below or with a variety of Lewis acid catalysts. Submitted to 14 kbar pressure (2 days/40 °C)[16] the components were recovered without change. However, the dienamine **6** reacted spontaneously with dimethyl acetylenedicarboxylate to form a yellow crystalline compound (mp 78-81 °C) which was confirmed as a 1:1 adduct and existed as a *Z/E*-pair of two stereoisomers (which could not be separated) in a ratio of 1:2. The mass spectrum (CI analysis) showed a strong M + 1 peak at 478 amu, corresponding to a 1:1 adduct. The proton NMR displayed two pairs of doublets for two vinyl protons. The first pair appeared at δ 6.3 ppm (J = 1.8 Hz) and δ 6.0 ppm (J = 1.8 Hz) integrating into 2/3 H and 1/3 H respectively. The second pair appeared at δ 5.3 ppm (J = 1.8 Hz) and δ 5.05 ppm (J = 1.8 Hz) integrating into 1/3 H and 2/3 H, respectively. The ethoxy group appeared as usual, and the methoxy groups appeared as two pairs of singlets. The first pair appeared at δ 3.72 and 3.68 ppm with a 2:1 ratio, integrating into three protons; the second pair appeared at δ 3.58 and 3.51 ppm with a 1:2 ratio, integrating into three protons. The vinyl-methyl group appeared at δ 1.55 ppm as a broad singlet. The *Z/E* isomers when heated neat to 150 °C were smoothly cyclized to the adduct **11** (mp 90 °C; 80%); this showed that the dienamine **6** was at least capable of uncomplicated cycloaddition. The adduct **11** displayed the following spectral characteristics. The mass spectrum (CI analysis) showed a strong M + 1 peak at 478 amu. The proton NMR showed the ethoxy groups as usual. Two singlets appeared at δ 3.6 and 3.5 ppm, each integrated into three protons, for the two methoxy groups. The rest of the molecule appeared at a range of δ 3.1-1.45 ppm, with a sharp singlet at δ 1.52 for the angular methyl group, integrating for 19 protons.

Our next effort was directed at prior formation of the 7-8 bond (steroid numbering in **2**). The [B] unit was created by partial reduction of **8** to **13**, mp 68 °C ($NaBH_4$; Ac_2O/DMAP; zinc/AcOH successively in one pot, 76%). This vinylogous ester was conveniently transformed into **14** (Tf_2O/2,6-*t*-Bu_2-4-Me-pyr/-78 °C/60%) with a good leaving group at C-8. The triflate **14** formed in this reaction was a 1:1 *cis/trans* mixture on the basis of its proton NMR spectrum, in which the quaternary methyl group appeared as two singlets at δ 1.04 and 0.88 ppm, indicating a 1:1 mixture. It also showed a doublet at δ 5.94 ppm (J = 3 Hz) and a singlet at δ 5.88 ppm, integrating for 1/2 H each, for the vinyl proton on the C-ring (steroid number). The appearance of the doublet must be due to a long range coupling (W-coupling) of the *cis* isomer, and the singlet was assigned to that of the *trans* isomer. However reaction with **6**, or with the enolate or enol silyl ether of **5**, afforded no C-C bond formation; in each case the [A] unit was recovered and the triflate **14** was converted to the corresponding β-diketone.

However, when methyl ketone **5** was dehydrated to the acetylene **12** by elimation of its enol phosphate with LDA,[17] this compound-characterized by a strong band at 3300 cm^{-1} for the C≡C-H absorption, a weak absorption at 2080 cm^{-1} for the C≡C group in IR spectrum, and a singlet at δ 3.15 ppm for the C≡C-H in ^1H NMR-displaced triflate smoothly from **14** ($PdCl_2(PPh_3)_2$/Et_3N/DMF/80 °C/76%). This acetylenic intermediate, in which the two convergent units are joined, was then partially hydrogenated to **15**. Both adducts were confirmed by their spectral characteristics. The mass spectrum of the acetylenic intermediate had the correct parent ion peak at 438 amu, the compound **15** at 440 amu. In the IR spectrum, the acetylenic intermediate had a weak absorption at 2160 cm^{-1} for the C≡C group which disappeared in the compound **15**. The C=O of the ester and the C=C-C=O appeared as usual at 1725, 1650 cm^{-1}, respectively, in both adducts. In the ^1H NMR, two vinyl protons appeared in the δ 6.35-5.9 ppm region and the two vinyl-methyl groups on the A and D-rings collapsed into a broad singlet at δ 1.55 ppm for the compound **15**. The rest of the spectrum showed the same features as their precursors. A very similar, though monocyclic, trienone had been cyclized by pyrolysis into a decalin with an angular methyl by Ramage,[18] and this served as our model. However, heating **15** at 140 °C in xylene smoothly transformed it into a cyclized product which showed the expected parent ion peak at 440 amu in the mass

spectrum. The ^{1}H NMR showed the broad singlets at δ 1.8 and 5.5 ppm for the methyl and vinyl protons on the D-ring and the routine quartet and triplet for the ethoxy groups. Two singlets at δ 1.1 and 0.9 ppm, indicating a 1:1 mixture, were assigned to the angular methy group on the C/D junction as before, but their combined integration was only 3 H. The apparent disappearance of the C-19 methyl group and the lack of any vinyl proton except that on the D-ring clearly indicated that structure **16** was the product of this reaction, presumably caused by a prior [1,7]-hydrogen shift[19] followed by cyclization. This is in contrast both to the Ramage model and to the cyclization of the triene addition product which yielded **11**.

Our focus in this work was the convergent and rapid assembly of the steroid skeleton, yet we have not so far discussed the stereochemistry. Another reason for the choice of a six-membered D-ring was the presumed favorable *trans*-C/D ring fusion which Woodward achieved[4] by equilibration of an initial adduct[20] very similar to **8**; in our case we could never create a more favorable *cis-trans* ratio than about 1:1 in any of the intermediates **8**, **9**, or **13**. The crucial stereocontrol in joining units [A] and [B] is that of *cis*-angular methyl groups. Jung has argued[21] that the Alder *endo*-rule should favor this in the Diels-Alder coupling to **10**. The correct electrocyclization of **15** (or a variant) is stereochemically precedented in vitamin D chemistry[22] and should accordingly form the correct steroid skelton, *i.e.*, with *cis*-angular methyls. Variants on this synthesis plan are currently under investigation.

EXPERIMENTAL SECTION

General

Melting points were taken on a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 683, Model 137 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390, or XL-300 unless indicated otherwise. Mass spectra were recorded on an AEI MS12 or an AEI MS9. The Silica used in chromatography was Kieselgel 60 (0.04-0.06 mm) supplied by EM Reagents; flash techniques were generally used. All thin layer chromatography (TLC) was performed on Anal Tech (GHLF) precoated, 0.25 mm, glass-backed silica gel plates. Tetrahydrofuran (THF) and ether (refers to diethyl ether) were distilled from sodium benzophenone ketyl immediately prior to use. Methylene chloride was distilled from phosphorus pentoxide immediately prior to use. All reactions, unless otherwise specified, were performed under a nitrogen atmosphere.

Preparation of Diethyl 3-Acetyl-4-methylcyclohex-3-en-1,1-dicarboxylate (5): Double Affixation/Dehydration

Diethyl malonate (80 mL, 1 equivalent) and triton B (40% solution in MeOH) (10 mL) were dissolved in 100 mL of dioxane (redistilled). The reaction mixture was kept at 12-14 °C while methyl vinyl ketone (106 mL, 2.5 equivalent) was added dropwise for a period of two hours. After the addition of methyl vinyl ketone was complete, the reaction was kept at 0 °C for two more hours and then warmed up to RT. After being stirred at RT overnight, the reaction mixture was diluted with 250 mL of water and neutralized with concentrated HCl to pH 7-8. The mixture was extracted with ether and dried over $MgSO_4$, then filtered and evaporated to afford 163.8 g of crude yellow oil. The pure colorless liquid was obtained in 85% yield by distillation at bp 135 °C/0.05 mmHg. ^{1}H NMR ($CDCl_3$): δ 4.1 (q, 4H, J = 7 Hz, ester methylene), 3.7 (s, 1H, -OH), 2.6 (dd, 1H, J = 6.2 Hz, J = 2.5 Hz, H next to acetyl), 2.1 (s, 3H, acetyl CH_3), 2.3-1.3 (m, 6H, ring protons), 1.1 (m, 6H, ester methyl), 1.0 (s, 3H, quaternary CH_3). MS *m/z*: 300; IR (CH_2Cl_2): 3500 (s, -OH), 1725 (s, C=O) cm^{-1}.

30 g (10 mmol) of the above liquid in 150 mL of benzene were refluxed, in the presence of 600 mg of *p*-toluenesulfonic acid, with removal of water in a Dean-Stark trap. After 24 h, 1.9 mL of H_2O had been distilled. The reaction mixture was washed first with saturated sodium bicarbonate solution twice and then with water and dried over $MgSO_4$. After removal of the solvent, 23.38 g of brown oil was obtained, which was distilled at bp 115-120 °C/0.75-0.01 mmHg: 15 g (83%) of colorless oil was thus obtained. ^{1}H NMR ($CDCl_3$): δ 4.15 (q, 4H, J = 7 Hz, ester methylene), 2.7 (bs, 2H, ring =C-CH_2-), 2.2 (s, 3H, acetyl CH_3), 2-2.2 (m, 4H, ring protons), 1.8 (bs, 3H, C=C-CH_3), 1.2 (t, 6H, J = 7 Hz, ester methyl). MS *m/z*: 210, 181, 137, 123, 93, 77, 43, 29; IR (CH_2Cl_2): 1725, 1650 cm^{-1}.

Preparation of Diethyl 4-Methyl-3-(1′-pyrrolidinyl-1′-vinyl)cyclohex-3-en-1,1-dicarboxylate (6): Reaction with Pyrrolidine

3.75 g (0.0133 mol) of compound (5) and 1.89 g of pyrrolidine (0.0266 mol) were dissolved in 50 mL of benzene. The mixture was refluxed in the presence of 50 mg of *p*-toluenesulfonic acid, with continuous removal of water. After 40 h, 0.2 mL of water had separated. The reaction mixture was evaporated to remove the solvent, and the dark-red residue was distilled at bp 116-118 °C/0.15 mmHg to give 3.2 g (71%) of pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 4.1

(q, 4H, J = 7 Hz, ester methylene), 3.4 (bs, 2H, vinyl), 3.0 (bt, 4H, pyrrolidine -N-CH_2-), 2.6 (br, 2H, ring =C-CH_2-), 2.0 (br, 4H, pyrrolidine -CH_2-), 1.8 (m, 4H, ring protons), 1.5 (bs, 3H, C=C-CH_3), 1.2 (t, 6H, J = 6 Hz, ester methyl); MS *m/z*: 335.

Preparation of 3-Methoxy-2,5-toluquinone (7): Fremy's Salt Oxidation

Sodium nitrite 69 g (200 mL, 5 M) was placed in a large beaker and cooled in an ice bath, chopped ice (400 g) was added and the solution was stirred steadily during the addition of fresh sodium bisulfite solution (200 mL, 70 g), followed by glacial acetic acid (40 mL). Reaction was complete in 2-3 min., as shown by the momentary darkening in color of the reaction mixture and by its failure to decolorize iodine solution. After addition of concentrated ammonia solution (50 mL), the mixture was again cooled in an ice bath, with fresh ice added whenever necessary to keep some present in the reaction mixture through the next stage. Ice cold 0.2 M potassium permanganate (800 mL) was now added dropwise with continued stirring for one hour. The precipitated manganese dioxide was removed by gravity filtration, using two or more funnels in parallel to reduce the time required, the filtrate was allowed to come to room temperature as filtration proceeded, but any unfiltered suspension was kept in an ice bath. The filtrate was then cooled to 0 °C, and 140 mL of 1/6 M KH_2PO_4 was added. To this solution, a solution containing 10 g of orcinol methyl ether in 60 mL of acetone was added dropwise. The reaction was kept at 0 °C for one hour after the addition was complete. The yellow precipitate was then collected and washed with fresh H_2O and ether. Yellow needles of quinone (7) were obtained in 86% yield after recrystallization from ethyl acetate. mp. 147 °C; ^{1}H NMR ($CDCl_3$): δ 2.1 (bs, 3H, CH_3), 3.85 (s, 3H, -OCH_3), 5.85 (bs, 1H, vinyl), 6.5 (br, 1H, vinyl); MS *m/z*: 152; IR (CH_2Cl_2): 1680, 1650, 1605 cm^{-1}.

Preparation of Adduct *cis*-1,4-Dioxo-2-methoxy-7,9-dimethyl-$\Delta^{2,6}$-hexahydronaphthalene (8): Diels-Alder Reaction

3.04 g of quinone (7) was dissolved in 180 mL of methylene chloride (dry, distilled) and cooled to -78 °C with stirring. To this cold solution, 2.3 mL of $TiCl_4$ was added, and the resultant dark solution was kept at this temperature for 10 min. before 10 mL (0.1 mol) of isoprene was added dropwise. After the addition was complete, the reaction mixture was kept at -78 °C for two hours before quenching with water. The organic compound was then extracted with ether and washed with water and brine. The ether layer, dried with $MgSO_4$, was evaporated to afford 5.31 g of orange gum, which was crystallized from an acetone and hexane mixture. The light orange cyrstals thus obtained were 3.5 g (80%) and could be used for the next reaction. The pure sample was recrystallized from methanol, mp. 93 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.85 (s, 1H, vinyl next to -OCH_3), 5.35 (bs, 1H, vinyl next to CH_3), 3.72 (s, 3H, -OCH_3), 2.68 (overlapping dd, J = 6, 6 Hz, 1H, methine proton), 2.57 (d, J_{gem} = 20 Hz, 1H, axial proton next to methine proton), 2.4 (d, J_{gem} = 18 Hz, 1H, axial proton next to angular CH_3), 2.12 (d, J_{gem} = 20 Hz, 1H, equatorial proton next to methine proton), 1.6 (d, J_{gem} = 18 Hz, 1H, equatorial proton next to angular CH_3), 1.56 (bs, 3H, -C=C-CH_3), 1.28 (s, 3H, angular CH_3); MS *m/z*: 220; IR (CH_2Cl_2): 2970, 1705, 1670, 1605, 1225, 1195, 1065 cm^{-1}.

Preparation of *cis*-1-Acetoxy-2-oxo-7,9-dimethyl-$\Delta^{3,6}$-hexahydronaphthalene (9a): LAH Reduction/Acetylation

To a suspension of LAH (480 mg, 12.6 mmol) in anhydrous ether (60 mL) was added a THF solution (40 mL) of 1.6 g (7.07 mmol) adduct (8) over 10 minutes at RT under nitrogen. During the addition the solution turned slightly green and a viscous sticky precipitate separated, which changed into white powder toward the end of the addition. Stirring was continued for a further five minutes and the excess reagent was decomposed by a careful addition of ethyl acetate until no more reaction was observed. Saturated aqueous sodium sulfate solution was added gradually with vigorous stirring until the precipitate became slightly wet and adhered to the sides of the flask. The reaction mixture was then stirred with anhydrous magnesium sulfate for 10 minutes. The precipitated salts were filtered off and washed well with ether. After evaporation of the combined solutions, a white solid (1.58 g ,98%) remained which was diluted with a small portion of ether and left overnight in the freezer. The white pure diol was collected in 62% yield. mp. 120-130 °C; ^{1}H NMR (d_6, DMSO): δ 5.25 (bs, 1H, vinyl), 4.55 (s, 1H, vinyl), 3.85 (br, 2H, CH-O), 3.5 (s, 3H, -OCH_3), 1.25-2.8 (m, 5H), 1.55 (bs, 3H, -C=C-CH_3), 1.3 (s, 3H, angular CH_3); IR (KBr): 3340 (s, -OH), 2960, 1665 cm^{-1}.

To a solution of 0.39 g of the diol in 25 mL of dioxane was added 5 mL of 2N H_2SO_4. This clear solution was allowed to stand for 24 h at RT and was then poured into an ether/water mixture. The aqueous layer was washed twice more with ether and the combined organic layers were washed with aqueous sodium bicarbonate and water. After drying over $MgSO_4$, the solvent was removed to afford 0.311 g of the ketol as a white solid (92%). The pure sample

was recrystallized from methanol. mp. 57 °C; ^{1}H NMR ($CDCl_3$): δ 6.8 (dd, 1H, J = 10.2 Hz, J = 1.5 Hz, vinyl), 6.09 (dd, 1H, J = 10.2 Hz, J = 2.7 Hz, vinyl), 5.43 (bs, 1H, vinyl D-ring), 4.0 (s, 1H, CH-O), 3.75 (s, 1H, -OH), 2.6-1.7 (m, 5H), 1.6 (bs, 3H, -C=C-CH_3), 1.3 (s, 3H, angular CH_3). MS *m/z*: 192, 177, 159, 131, 96; IR (CH_2Cl_2): 3480 (s, -OH), 2980, 1700 (s, O=C), 1670 cm^{-1}.

20 mL of methylene chloride solution containing a mixture of ketol (998 mg; 5.2 mmol), triethylamine (1 mL; 7.8 mmol), acetic anhydride (0.73 mL; 7.8 mmol), and a catalytic amount of DMAP (50 mg; 0.41 mmol) was allowed to stand 16 h at RT. The reaction mixture was then partitioned between ether and 10% HCl. The organic layer was separated and washed with saturated $NaHCO_3$ twice, and brine once. After drying over $MgSO_4$, the ether was evaporated to afford 1.1 g (90%) of a yellow solid. The pure white solid was obtained by recrystallization from ether/hexane mixture in an overall 80% yield. mp. 130 °C; ^{1}H NMR ($CDCl_3$): δ 6.6 (dd, 1H, J = 10.2 Hz, J = 1.5 Hz, vinyl), 6.0 (dd, 1H, J = 10.2 Hz, J = 2.7 Hz, vinyl), 5.4 (bs, 1H, vinyl D-ring), 5.2 (s, 1H, CH-O), 2.5-1.5 (m, 5H), 2.15 (s, 3H, acetyl CH_3), 1.5 (bs, 3H, -C=C-CH_3), 1.0 (s, 3H, angular CH_3); MS *m/z*: 234, 192, 159, 126, 107, 96, 84, 67, 55, 43; IR (CH_2Cl_2): 2980, 1745, 1690, 1610, 1430, 1370, 1230, 1110, 1080, 1050, 900 cm^{-1}.

Preparation of *cis*-2-Oxo-7,9-dimethyl-$\Delta^{3,6}$-hexahydronaphthalene (9b): Zinc Reduction

The crude acetate, (**9a**) (3.4 g, 1.4 mmol) and redistilled acetic anhydride 30 mL were heated to reflux by immersion in an oil bath kept at 145-150 °C, commercial zinc dust (29 g, activated) was added all at once to the vigorously stirred solution from which moisture was excluded, and the refluxing mixture was stirred further for 8 minutes at this temperature. Cooled to RT, the zinc was filtered off and washed well with ether; the ether and the acetic anhydride were evaporated. The brown residue was diluted with ether and washed with dilute sulfuric acid, sodium bicarbonate solution and water and then dried over $MgSO_4$. The ether was evaporated to afford 2.4 g of a yellow oil. The pure compound (**9b**) was obtained from column chromatography (silica gel, EtOAc/Hexane 1:5) in 60% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.55 (dd, 1H, J = 10.2 Hz, J = 1.5 Hz, vinyl), 5.75 (dd, 1H, J = 10.2 Hz, J = 2.7 Hz, vinyl), 5.25 (bs, 1H, vinyl D-ring), 2.55-1.65 (m, 7H), 1.45 (bs, 3H, -C=C-CH_3), 0.95 (s, 3H, angular CH_3); MS *m/z*: 176; IR (CH_2Cl_2): 2950, 1700, 1650, 1430, 1360, 1235, 1020, 840 cm^{-1}.

Preparation of 3,3-Dicarboethoxy-7,8-dicarbomethoxyl-9-methyl-5-pyrrolidinyl-$\Delta^{5(10),7}$-hexahydronaphthalene (11): Addition/Electrocyclization

1.187 g (5.37 mmol) of dimethyl acetylenedicarboxylate was added slowly to 2.8 g (5.37 mmol) of enamine diene (**6**) with stirring. Upon mixing, an exothermic reaction took place and the reaction mixture turned dark. The resulting dark gum was then passed through a column containing silica gel with EtOAc/Hexane (1:2) mixture as eluent. 2.375 g (60%) of thick yellow gum was obtained after column chromatography, from which yellow crystals were obtained by crystallization from the acetone/hexane mixture. mp. 78-81 °C; ^{1}H NMR ($CDCl_3$): δ 6.3 (d, 2/3H, J = 1.8 Hz, N-C=CH-C=C), 6.0 (d, 1/3H, J = 1.8 Hz, N-C=CH-C=C), 5.3 (d, 1/3H, J = 1.8 Hz, N-C=C-C=CH), 5.05 (d, 2/3H, J = 1.8 Hz, N-C=C-C=CH), 4.15 (m, 4H, -OCH_2-), 3.72 (s, 6/3H, -OCH_3), 3.68 (s, 3/3H, -OCH_3), 3.58 (s, 6/3H, -OCH_3), 3.51 (s, 3/3H, -OCH_3), 3.4-1.7 (m, 14H), 1.55 (bs, 3H, C=C-CH_3), 1.2 (m, 6H, -$OCH_2\underline{CH_3}$); MS (EI) *m/z*: 478 (M^++1).

The mixture of *cis* and *trans* isomers of the above compound was heated neat at 150 °C for half an hour. The yellow crystals melted and turned red upon heating. This dark red gum was then dissolved in ethyl acetate/hexane and passed through a column containing silica gel with ethyl acetate/hexane (1:1) as eluent. 570 mg (80%) of a pale orange gum was obtained after column chromatography, and white crystals were obtained by crystallization from the acetone/hexane mixture. mp. 90 °C; ^{1}H NMR ($CDCl_3$): δ 4.05 (q, 4H, J = 7 Hz, -OCH_2-), 3.6 (s, 3H, -OCH_3), 3.5 (s, 3H, -OCH_3), 3.1-1.45 (m, 16H), 1.53 (s, 3H, angular -CH_3), 1.15 (t, 6H, J = 7 Hz, -$OCH_2\underline{CH_3}$), MS (EI) *m/z*: 478 (M^++1), 446.

Preparation of Diethyl 3-Ethynyl-4-methylcyclohex-3-en-1,1-dicarboxylate (12): Ketone Dehydration to Acetylene

LDA solution was prepared by addition of *n*-butyl lithium (1.31 mL, 1.6 M solution in hexane, 2.1 mmol) to a 3 mL of THF solution containing diisopropyl amine (0.29 mL, 2.1 mmol) at -78 °C.

To the above LDA solution at -78 °C, 564 mg (2 mmol) of the ketone (**5**) dissolved in 1 mL of THF was added dropwise over 5 minutes. The reaction mixture was stirred at -78 °C for one hour before diethyl chlorophosphate (0.32 mL, 2.2 mmol) was added. The resulting mixture was then gradually warmed up to RT and transferred by cannula into a LDA solution (two equivalents, prepared in the same way as stated above) at -78 °C. After stirring at -78 °C for half an hour, the reaction was quenched with water and extracted with ether. The ether layer was washed with 10% HCl,

water and aqueous $NaHCO_3$, dried over $MgSO_4$, then filtered and evaporated to afford a brown oil. This brown oil was finally purified by column chromatography (silica gel, EtOAc/hexane 1:3) and the desired acetylene (**12**) was obtained as a colorless oil (55%). ^{1}H NMR ($CDCl_3$): δ 4.3 (q, 4H, J = 7 Hz, -OCH_2-), 3.15 (s, 1H, C≡CH), 2.8 (bs, 2H, C=C-CH_2-), 2.2 (bs, 4H), 1.9 (bs, 3H, -C=C- CH_3), 1.3 (t, 6H, J = 7Hz, -$OCH_2\underline{CH_3}$); MS *m/z*: 264, 246, 218, 207, 191, 177, 161, 145, 133, 117, 108, 93, 84, 70, 49, 35. IR (CH_2Cl_2): 3300 (s, C≡C-H), 2950, 2080 (w, C≡C), 1725 (s, C=O), 1450, 1360, 1300, 1210, 1170, 1090, 1020, 850, 900, 700 cm^{-1}.

Preparation of *cis*-4-Oxo-2-methoxy-7,9-dimethyl-$\Delta^{2,6}$-hexahydronaphthalene (13) from *cis*-1,4-Dioxo-2-methoxy-7,9-dimethyl-$\Delta^{2,6}$-hexahydronaphthalene (8): One-pot Reduction

660 mg (3 mmol) of adduct (**8**) was dissolved in 10 mL of glyme (1,2-dimethoxyethane) and the solution was placed in an ice bath. To this solution at 0 °C, 114 mg of $NaBH_4$ was added all in one portion, and the reaction mixture was kept at 0 °C for one hour before 1.5 mL of acetic anhydride and 20 mg of DMAP were added. The resulting mixture was then stirred at RT for 6 h. In the same reaction vessel, 9 g of zinc and 30 mL of acetic acid were then added and the mixture was refluxed overnight. The reaction mixture was filtered to remove the inorganic salts, and these zinc residues were washed well with ether. The combined filtrate was evaporated and the residue redissolved in ether and washed twice with saturated $NaHCO_3$, water, and brine. The ether layer was dried over $MgSO_4$, filtered, and evaporated to afford 533 mg of light yellow oil. The pure compound (**13**) was obtained as a colorless oil in 76% yield by column chromatography (silica gel, EtOAc/hexane 1:3). ^{1}H NMR ($CDCl_3$): δ 5.3, 5.15 (bs, s, 2H, vinyl), 3.6 (s, 3H, -OCH_3), 3.5-1.5 (m, 9H), 1.0, 0.8 (two s, 3H, angular -CH_3); MS *m/z*: 206; IR (CH_2Cl_2): 2950, 1650 (MeO-C=C-C=O), 1610, 1455, 1370, 1250, 1225, 1210, 1040, 1025 cm^{-1}.

Preparation of *cis*-2-Oxo-7,9-dimethyl-4-trifluoromethanesulfonyl-$\Delta^{3,6}$-hexahydronaphthalene (14): Triflation

A solution containing 0.23 mL (1 equivalent) of Tf_2O in 1.5 mL of methylene chloride was added to a 5 mL of methylene chloride solution containing 188 mg of compound (**13**) and 200 mg of 2,6-di-*tert*-butyl-4-methylpyridine at -78 °C. The reaction mixture was stirred at -78 °C for 10 minutes and then poured into water. The organic compound was extracted with ether, and the ether layer was further washed with 30% HCl solution three times to remove the pyridine. After the pyridine was completely removed, the ether layer was washed with aqueous $NaHCO_3$, water and brine and dried over $MgSO_4$, filtered and evaporated to afford a colorless oil. The pure compound (**14**) was obtained by column chromatography (silica gel, EtOAC/hexane 1:2) in an overall 60% yield as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.94 (d, 1/2H, J = 3 Hz, vinyl, C-ring), 5.88 (s, 1/2H, vinyl C-ring), 5.25 (bs, 1H, vinyl D-ring), 2.6-1.8 (m, 7H), 1.6 (bs, 3H, -C=C-CH_3), 1.04, 0.88 (two s, 3H, angular -CH_3); MS *m/z*: 324, 309, 295, 191, 174, 159, 149, 132, 107, 91, 79, 69, 53, 41, 27, 18; IR (CH_2Cl_2): 2950, 1675 (O=C-C=C), 1630 (O=C-C=C, 1420 (O-SO_2CF_3), 1390, 1350, 1220 (O-SO_2CF_3), 1140 (O-SO_2CF_3), 1050, 950, 900, 810 cm^{-1}.

Preparation of *cis*-1-[1′(2′-Methyl-5′,5′-dicarboethoxycyclohexenyl)]-2-[4′(2′-oxo-7′,9′-dimethyl-$\Delta^{3'6'}$-hexahydronaphthyl)]ethylene (15): Crossed Coupling of Triflate (14) with Acetylene (12)/Hydrogenation

120 mg (0.45 mmol, 1 equivalent) of acetylene (**12**) and 147 mg (0.45 mmol, 1 equivalent) of triflate (**14**) were mixed in 5 mL of DMF with 20 mg of $PdCl_2(PPh_3)_2$ and 3.4 equivalent (0.2 mL) of triethylamine. The reaction mixture was heated at 80 °C for 4 h and then poured into ether, the ether layer was washed with 10% HCl, aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, then filtered and evaporated to afford 205 mg of brown oil. The desired coupling product was obtained in 76% yield as a light yellow oil after column chromatography (silica gel, EtOAc/Hexane 1:3). ^{1}H NMR ($CDCl_3$): δ 6.35 (d, 1/2H, J = 3 Hz, vinyl C-ring), 6.3 (s, 1/2H, vinyl C-ring), 5.5 (bs, 1H, vinyl D-ring), 4.3 (q, 4H, J = 7 Hz, -OCH_2-), 2.85 (bs, 2H, C=C-CH_2-), 2.6-1.9 (m, 11H), 2.0 (s, 3H, -C=C-CH_3, A-ring), 1.75 (bs, 3H, -C=C-CH_3, D-ring), 1.4 (t, 6H, J = 7 Hz, -$OCH_2\underline{CH_3}$), 1.2, 1.0 (two s, 3H, angular -CH_3); MS *m/z*: 438; IR (CH_2Cl_2): 3020, 2950, 2160 (w, C≡C), 1725 (C=O), 1650 (C=C-C=O), 1560, 1430, 1350, 1250, 1170, 1070, 1020, 850, 700 cm^{-1}.

65 mg of oil obtained above was partially hydrogenated (excess H_2 by balloon) over Pd($BaSO_4$) in pyridine at RT for 3 h. The reaction mixture was filtered to remove the catalyst, and the catalyst was washed well with ether. The combined filtrate was then washed three times with 10% HCl, aqueous $NaHCO_3$, and brine. The ether layer was dried over $MgSO_4$, filtered, and evaporated to afford 65 mg of yellow oil, which was further purified by column chromatography (silica gel, EtOAc/Hexane 1:3) to afford 55 mg (90%) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.36 (bs, 1/2H, vinyl, C-ring), 6.2 (bs, 1/2H, vinyl, C-ring), 5.9 (bs, 2H, vi-

nyl), 5.35 (bs, 1H, vinyl, D-ring), 4.1 (q, 4H, J = 7 Hz, ethoxyl), 2.5 (bs, 2H, C=C-CH_2-), 2.4-1.6 (m, 11H), 1.55 (bs, 6H, -C=C-CH_3), 1.2 (t, J = 7 Hz, 6H, ethoxyl), 1.0 (s, 3/2H, angular -CH_3), 0.95 (s, 3/2H, angular-CH_3); MS *m/z*: 440, 425, 395, 372, 321, 253, 237, 225, 188, 173, 157, 143, 128, 105, 91, 79, 67, 55, 43; IR (CH_2Cl_2): 2950, 1725 (C=O), 1655 (C=C-C=O), 1600, 1450, 1350, 1250, 1170, 1100, 1030 cm^{-1}.

Conversion of *cis*-1-[1′(2′-Methyl-5′,5′-dicarboethoxycyclohexenyl)]-2-[4′(*cis*-2′-oxo-7′,9′-dimethyl-$\Delta^{3'6'}$-hexahydronaphthyl)]ethylene (15) to (16): Intramolecular Cyclization

50 mg of compound (**15**) was dissolved in 1 mL of xylene and refluxed for 2 h at 140 °C. The new product was isolated by column chromatography (silica gel, EtOAc/Hexane 1:3) to afford 30 mg (60%) of colorless oil. ^{1}H NMR ($CDCl_3$): δ 5.5 (bs, 1H, vinyl, D-ring), 4.2 (q, 4H, J = 7 Hz, -OCH_2-), 3.4 (bs, 2H, C=C-CH_2-C=C-), 3.0-1.8 (m, 20H), 1.2 (t, J = 7 Hz, 6H, -OCH_2CH_3), 1.1, 0.9 (s, s, 3H, angular -CH_3); MS *m/z*: 440.

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Key Words

Cortical steroids; Convergent assembly; Multiple construction; Bondset; Electrocyclization; Synthesis; Design efficiency.

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