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First total synthesis of (±)-3-aza-11-oxa-1,3,5(10)-trieno steroids

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ABSTRACT

We set out to describe a new and versatile method for preparing 3-aza-11-oxa-1,3,5(10)-trieno steroids *via* an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes as the key step. The characteristic ^{1}H and ^{13}C NMR spectroscopic features of the synthesized compounds are reported.

1. Introduction

It was soon realized that steroids alone were important in respect of the endocrine aspects of the cancer problem, since the implication of steroids in the carcinogenesis and the treatment of tumours seemed to be clearer than that of other endocrine factors [1–3]. In particular, it has been stressed the interest of hetero steroids in which the hetero atom takes the place of a carbon atom in a position of high biological importance [4–7]. The C-11 position of the steroid ring has a major effect on biological properties, such as corticoid activities [8,9]. An increasing number of compounds containing oxygen in the nucleus of the steroidal skeleton have been prepared in the last two decades and their activities studies [10–13]. Several oxa analogues of biologically active steroids have been found to retain their activity partially [14].

We recently described the first total synthesis of *N*-oxido-3-aza-1,3,5(10)-trieno steroids [15]. We were now interested by the synthesis of 11-oxa steroids possessing a pyridine as an A ring, using our general approach for elaborating the steroidal skeleton [16–21]. To the best of our knowledge and much to our surprise, there is no total synthesis described in the literature though their biological potential. In this paper, we are relating a total synthesis of 3-aza-11-oxa-1,3,5(10)-trieno steroids, the significance of which is apparent if one considers the biological importance of 11-oxygenated steroid hormones. We show that our method may be applicable not only to the synthesis of 3-aza-11-thia-1,3,5(10)-trieno steroids [22], we can also put an oxygen atom in place of the sulfur atom at the position 11. Moreover, in this paper, we give the experimental details of the steroids reported by us recently [15,22], and possessing a pyridine as an A ring. Furthermore, we make a comparative study

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on the selectivity of the key thermolysis reaction between 11-hetero and 3,11-dihetero steroids, and on the NMR values of their corresponding spectra.

2. Experimental

All reactions were run under argon in oven-dried glassware. ^{1}H and ^{13}C NMR spectra are recorded at 200 or 400 and 50 and 100 MHz, respectively, in $CDCl_3$ solutions. Chemical shifts (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 F_{254}) and TLC on silica gel. Dichloromethane was distilled from P_2O_5 and tetrahydrofuran (THF) over sodium/benzophenone.

Compounds **6**, **13** and **18** were prepared according to the previously described procedures [18], [26] and [30]. The nomenclature used for the steroids is not the nomenclature used by chemical abstracts [31].

2.1. 4-Azabenzocyclobuten-1-one (2)

A mixture of 3-bromopyridine (1 equiv.), lithium hexamethyl disilazide (LiHMDS) (2 equiv.), and 2-methylen-1,3-dioxepane (2 equiv.) in THF (approximatively 3 mL/mmol of bromopyridine) was stirred at reflux. The reaction was monitored by TLC. The reaction mixture was allowed to cool to room temperature and poured carefully onto crushed ice. The product was extracted with ether and the combined ether extracts were then washed with water and brine and dried with anhydrous $MgSO_4$. Removal of the solvent left a brown oil. Hydrolysis of the ketal was effected by stirring the brown oil in a THF/water/HCl mixture (89:10:1) until completion of the reaction (TLC). The residue was diluted and extracted with CH_2Cl_2. The combined extracts were then washed with water and brine and dried with anhydrous $MgSO_4$. Removal of the solvent and purification by flash chromatography (petroleum ether/ethyl acetate: 5/5) afforded the pure azabenzocyclobutenone (55% yield for the two steps). IR (neat) 2965, 1732, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.89 (1H, s), 8.72 (1H, d, J = 4.7 Hz), 7.15 (1H, d, J = 4.7 Hz), 4.11 (2H, s); ^{13}C NMR ($CDCl_3$) 187.7, 155.7, 149.3, 145.9, 144.9, 113.5, 53.5. HRMS Calcd for C_7H_5NO 119.0371, found 119.0374.

2.2. 4-Azabenzocyclobuten-1-ol (3)

A flask equipped with a magnetic stirring bar and an argon outlet was charged with $NaBH_4$ (1.27 g, 33.6 mmol) and absolute ethanol. The solution was cooled at −20 °C and then the azabenzocyclobutenone **2** (4 g, 26 mmol) was added. After completion of the reaction (TLC), it was quenched by addition of aqueous saturated NH_4Cl and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered and then concentrated under vacuum. The residue was chromatographed on silica gel (diethyl ether: 100%) to give pure alcohol **3** (3.6 g, 90% yield) as an oil.

IR (neat) 3385, 2923, 1604, 1470 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.28 (1H, d, J = 4.5 Hz), 8.14 (1H, s), 7.08 (1H, dd, J = 4.5 Hz, J = 1.2 Hz), 5.28 (1H, dd, J = 4.7 Hz, J = 1.9 Hz), 3.62 (1H, dd, J = 14.5 Hz, J = 4.7 Hz), 3.11 (1H, d, J = 14.5 Hz); ^{13}C NMR ($CDCl_3$) 158.3, 147.3, 143.5, 138.8, 117.6, 70.8, 41.7. HRMS Calcd for C_7H_7NO 121.0528, found 121.0530.

2.3. Mesylate of 4-azabenzocyclobuten-1-yle (4)

A solution of **3** (0.56 g, 4.62 mmol) in anhydrous CH_2Cl_2 (10 mL) was cooled to −10 °C and NEt_3 freshly distilled (1.3 mL, 9.24 mmol) and mesyl chloride (0.54 mL, 6.93 mmol) were added. After stirring 1 h, the mixture was hydrolysed with water and extracted with CH_2Cl_2. The organic layer was washed with a saturated solution of NaCl, dried over $MgSO_4$ and then concentrated under vacuum. The residue was chromatographed on silica gel (AcOEt: 100%) to afford 0.71 g (77% yield) of **4**. mp = 110 °C; IR (neat) 2931, 1601, 1476 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.62 (1H, d, J = 4.7 Hz), 8.47 (1H, s), 7.26 (1H, dd, J = 4.7 Hz, J = 1.3 Hz), 5.91 (1H, dd, J = 4.5 Hz, J = 1.9 Hz), 3.84 (1H, dd, J = 14.9 Hz, J = 4.5 Hz), 3.55 (1H, d, J = 14.9 Hz); ^{13}C NMR ($CDCl_3$) 151.3, 148.8, 144.5, 138.1, 118.4, 73.8, 39.3, 38.5. HRMS Calcd for $C_8H_9NO_3S$ 199.0303, found 199.0307.

2.4. 1-Iodo-4-azabenzocyclobutene (5)

To a stirred solution of mesylate **4** (1.36 g, 6.82 mmol) in anhydrous acetone (30 mL) under argon was added NaI (2.04 g, 13.64 mmol). The mixture was stirred 24 h at reflux then cooled to room temperature, filtered over celite and concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (diethyl ether: 100%) to give **5** (1.27 g, 81% yield). mp = 62 °C; IR (neat) 2925, 1607, 1586 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.57 (1H, d, J = 4.8 Hz), 8.28 (1H, s), 7.02 (1H, d, J = 4.8 Hz), 5.46 (1H, dd, J = 4.7 Hz, J = 2.1 Hz), 4.00 (1H, dd, J = 15.0 Hz, J = 4.7 Hz), 3.56 (1H, d, J = 15.0 Hz); ^{13}C NMR ($CDCl_3$) 156.4, 149.1, 143.8, 138.3, 117.5, 44.7, 11.1. HRMS Calcd for C_7H_6IN 230.9545, found 230.9548.

2.5. 3-(4-Azabenzocyclobuten-1-yl)-3-methoxycarbonyl-6,9-divinyl-1-oxaspiro[4,4]nonan-2-one (7)

To a stirred solution of the spirolactone **6** (5 g, 20 mmol) in anhydrous acetone (100 mL) (5 mL/mmol) under argon was added successively $CsCO_3$ (20 mmol, 6.5 g) and a solution of the mesylate **4** (2.65 g, 13.3 mmol) in anhydrous acetone (10 mL). The mixture was stirred 5 days at reflux then cooled to room temperature, filtered over celite and concentrated under *vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/diethyl ether: 8/2) to give **7** (3.85 g, 82% yield) as an inseparable diastereoisomeric mixture (2.5:1). Data are given for the major isomer. IR (neat) 2961, 1774, 1728, 1630 cm^{-1}; ^{1}H NMR ($CDCl_3$) 8.42 (1H, s), 8.21 (1H, d, J = 8.3 Hz), 6.95 (1H, d, J = 8.3 Hz), 5.57 (2H, m), 5.05 (4H, m), 4.14 (1H, dd, J = 5.3 Hz, J = 2.7 Hz), 3.67 (3H, s), 3.40 (1H, dd, J = 15.1 Hz, J = 4.9 Hz), 3.02 (1H, dd, J = 15.1 Hz, J = 2.6 Hz), 2.31 (2H, m), 1.78 (6H, m); ^{13}C NMR ($CDCl_3$) 172.7, 169.8, 152.4, 148.1, 143.2, 137.0, 136.7, 135.1, 118.0, 117.7, 117.5, 93.9, 56.6, 53.3, 52.9, 52.7, 47.2, 33.0, 30.9, 28.1, 27.7. HRMS Calcd for $C_{21}H_{23}NO_4$ 353.1627, found 353.1630.