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First total synthesis of 11-tellura steroids

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ABSTRACT

The first total synthesis of 11-tellura steroids was achieved via an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes as the key step.

Since the first total synthesis of equilenin and estrone in 1939,[1] many steroids have been prepared using several different strategies. Important progress in steroid synthesis comes from the strategy involving an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes which are mostly generated by thermal ring opening of benzocyclobutenes.[2]

Since it has been proven that the introduction of a heteroatom in the steroidal moiety could have a biological impact, heterosteroids have been known to have a revival of interest.[3] Thus, it has been reported that replacement of the 11-carbon atom of the pregnane skeleton resulted in interesting modifications of the biological activities.[4] For example, anti-bacterial[5] and neuromuscular-blocking activities[6] have been found for some aza steroids.

We have recently reported the first total synthesis of 11-selena steroids.[7] In connection with our ongoing interest in the total synthesis of steroids, we were also interested in the synthesis of 11-tellura steroids. Compounds containing selenium can possess biological properties and have been used as antiviral, antihypertensive, antibacterial or chemopreventive anticancer agents.[8] In the same way, compounds containing tellurium have a great potential for the creation of a new library of molecules important for biological applications.

To the best of our knowledge, there are very few syntheses of tellurasteroids[9] and there is no total synthesis of 11-tellura steroids reported in the literature before.

In this Letter, we wish to report an efficient method for the preparation of 11-tellura steroids using a thermolysis of benzocyclobutenic intermediates as the key step. It is therefore hoped that this reaction occurs with good stereoselectivity to provide the carbocyclic framework of the naturally occurring A-ring aromatic steroids.

Recently, we showed that BISTRO **1** can be obtained by simple acyclic cross metathesis from 1,5-hexadiene and allytrimethysilane, using Grubbs's ruthenium catalyst (5 mol %) $[(Cy_3P)_2Cl_2Ru{=}CHPh]$[10] in CH_2Cl_2 at room temperature under argon atmosphere. BISTRO was obtained as a mixture of (*Z*,*Z*) and (*E*,*E*) isomers in a 60:40 ratio.[7]

The starting compound **3** was easily accessible by a procedure reported by us recently,[7] via a treatment with NaI in acetone of (*d*,*l*)-2,5-divinylcyclopentan-1-ol **2**, prepared by condensation of BISTRO **1** with chloroacetic anhydride (Scheme 1).[11]

We adopted a convergent steroid synthesis, based on the approach A + D→AD→ABCD. The strategy developed in our laboratory to prepare heterosteroids involved an intramolecular cycloaddition of *o*-xylylenes which are generated by thermal ring opening of a benzocyclobutene.[12] This methodology has a remarkable advantage for the formation of the B/C cycle. Thus, iodohydrine **3** was dissolved in dry ethanol containing sodium telluride[13] and heated under reflux for 48 h to give an intermediate which was alkylated in situ with 1-iodo-5-methoxybenzocyclobutene **4**,[14] providing a convenient way to produce **5**.[15] Despite the fair yield, obtaining the key (d,l)-cyclobutene **5** constitutes a very interesting result. Indeed, thermolysis[16] of this latter yielded a 8:2 mixture of two diastereoisomers **6a** and **6b** in a 58% overall yield. These tellura steroids were separated by flash chromatography on silica gel (Scheme 1).

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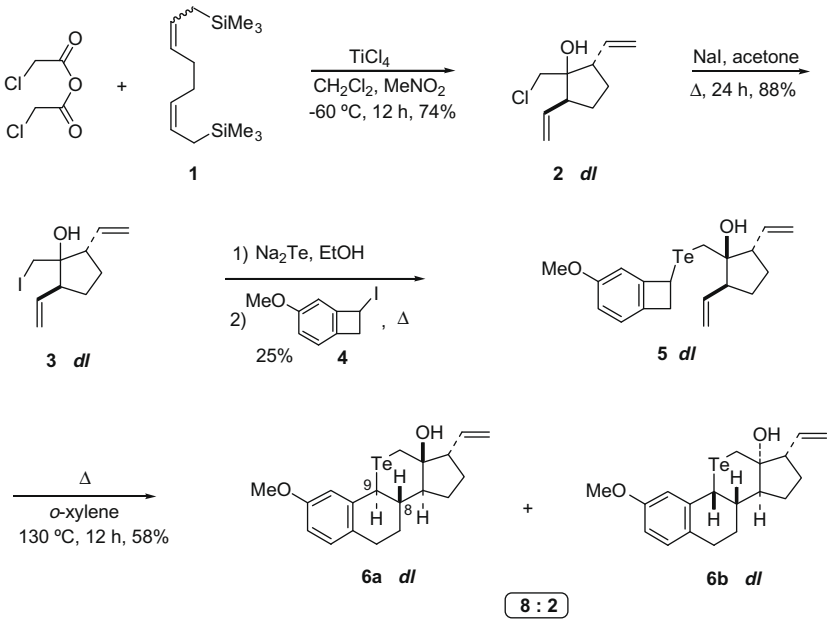
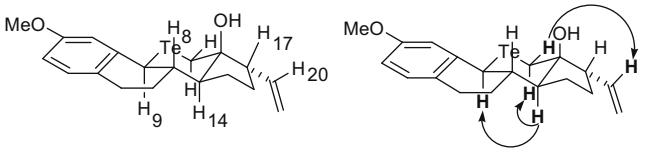


Scheme 1. Synthesis of 11-tellura steroids from BISTRO **1**.



Scheme 2. Stereochemistry of the major isomer **6a**.

The torquoselectivity in the electrocyclic conversion of benzocyclobutenes into *o*-xylylenes has been previously discussed.[17] Generally, a pronounced preference for outward rotation is observed in the case of electron-donating substituents borne by the benzocyclobutene.

The relative stereochemistry of those steroids was determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz). The steroids **6a** and **6b** have, respectively, a *trans-anti-trans* and a *cis-anti-cis* ring fusion.[18] Interestingly, the main product **6a** matches the *trans-anti-trans* ring fusion configuration of natural products (Scheme 2). For **6a**, a NOESY cross peak was observed between H-(9) and H-(14). The *trans* relationship between H-(8) and H-(9) was confirmed by the vicinal coupling constant $J = 10.4$ Hz for **6a** and for **6b** the value is 4.3 Hz corresponding to a *cis* relationship. The presence of tellurium was confirmed by their mass spectra,[18] ^{1}H NMR (δ (H-9) = 2.90 ppm for **6a** and δ (H-9) = 2.65 ppm for **6b**) and ^{13}C NMR (δ (C-9) = 32.2 ppm for **6a** and **6b**; δ (C-12) = 27.2 ppm for **6a** and δ (C-12) = 27.4 ppm for **6b**).

The palladium (II) oxidation of terminal olefins to give methyl ketones (Wacker process) was well established as a synthetic organic reaction.[19] Terminal olefins can be regarded as masked methyl ketones.

First attempts conducted on **6a** with cuprous chloride, oxygen and palladium acetate[20] failed to give the desired ketone. Unfortunately, palladium acetate–benzoquinone oxidation, performed in the presence of perchloric acid,[21] failed also to oxidize compound **6a** [$Pd(OAc)_2$, 10%; benzoquinone; $HClO_4$ (0.3 M); acetonitrile]. In the two cases, starting material was recovered unchanged (Scheme 3). Interesting is to note that this problem[22] of oxidation was also observed with 11-thia and 11-selena steroids but not with 11-oxa[11] and 11-aza[23] steroids reported previously.

In conclusion, we have succeeded in introducing for the first time a tellurium atom onto the steroid skeleton by use of a simple synthetic sequence based on an intramolecular cycloaddition of *o*-xylylene. Moreover, the tellurium atom occupies a position of established biological importance.[4] Studies to extend our strategy to other heterocyclic structures are currently underway and will be reported in due course.

Acknowledgements

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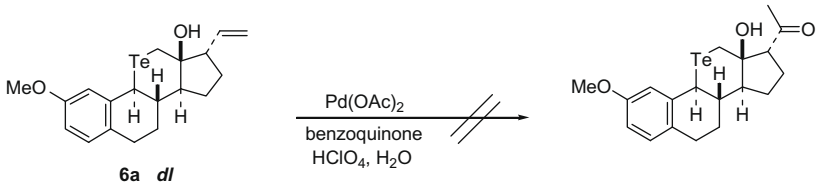

Scheme 3. Attempt of Wacker-type oxidation of **6a**.

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13. (a) Suzuki, H.; Inoue, M. *Chem. Lett.* **1985**, 389; (b) *Sodium telluride was prepared as follows*: a mixture of powdered tellurium (130 mg, 1.02 mmol), rongalite (sodium hydroxymethane sulfinate) (340 mg) and aqueous sodium hydroxide (70 mg in 1 mL of water) was stirred at 60 °C for 2 h under argon, to produce sodium telluride. The wine-colored solution was evaporated to dryness under reduced pressure.
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15. The compound **5** is sensitive to oxygen, and was stored under argon atmosphere. The latter was unstable under the conditions of silica gel chromatography and was used in the following step without further purification.
16. *The typical procedure of thermolysis is as follows*: a solution of **5** (0.5 g, 1.20 mmol) in 20 mL of *o*-xylene was stirred under argon at 130 °C for 12 h. After cooling, the solvent was removed under pressure (1 mmHg). The resulting oil was purified by flash chromatography on silica gel (petroleum ether/diethyl ether 8:2) to afford compound **6a** (0.23 g, 46%) and compound **6b** (0.06 g, 12%). Those compounds are sensitive to oxygen, and were stored under an argon atmosphere.
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18. The configuration of the products was established by analysis of their ^{1}H, ^{13}C, COSY and NOESY NMR 400 MHz spectra. Selected spectral data are as follows. *Compound* **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.50 (m, 6H), 1.60 (d, J = 13.2 Hz, 1H), 1.68 (m, 1H), 2.80 (m, 1H), 1.72 (d, J = 13.2 Hz, 1H), 2.26 (m, 2H), 2.80 (m, 2H), 2.90 (d, J = 10.4 Hz, 1H), 3.70 (s, 3H), 5.03 (m, 2H), 5.64 (m, 1H), 6.72 (dd, J = 2.6 Hz, J = 8.4 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ 23.4, 25.8, 27.2, 28.1, 28.9, 29.6, 32.2, 54.2, 55.6, 57.9, 76.5, 109.7, 112.4, 115.7, 117.4, 129.8, 135.6, 139.6, 157.8. HRMS (EI): m/z: calcd for $C_{19}H_{24}O_2Te$: 414.0839, [M^+]; found: 414.0856. *Compound* **6b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (m, 2H), 1.70 (m, 3H), 1.80 (m, 1H), 1.95 (m, 2H), 2.05 (d, J = 13.2 Hz, 1H), 2.10 (m, 3H), 2.30 (d, J = 13.2 Hz, 1H), 2.35 (m, 1H), 2.65 (d, J = 4.3 Hz, 1H), 3.77 (s, 3H), 5.09 (m, 2H), 5.89 (m, 1H), 6.70 (dd, J = 2.76 Hz, J = 8.4 Hz, 1H), 6.95 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3CN): δ 25.2, 25.8, 27.4, 28.3, 29.1, 29.6, 32.2, 54.6, 56.2, 58.1, 76.8, 110.2, 112.4, 116.2, 117.8, 129.3, 134.2, 139.8, 157.9. HRMS (EI): m/z: calcd for $C_{19}H_{24}O_2Te$: 414.0839, [M^+]; found: 414.0852.
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22. For these three families of heterosteroids (11-thia, -selena and -tellura steroids), we observed an influence of the heteroatom on the Wacker oxidation reagents. In the case of 11-thia steroids, to overcome this problem, the sulfur atom was firstly oxidized before doing the Wacker oxidation. This study on 11-selena and 11-tellura steroids is under progress and will be reported in due course as a full Letter.
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