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First total synthesis of 11-selena steroids

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ABSTRACT

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

Steroids represent an important class of natural products due to their high ability to penetrate cells and bind to nuclear and membrane receptors. The steroid system, selected by the evolutionary process to perform some of the most fundamental biological functions, has not only inspired biochemists and endocrinologists, but has also become the basis of many important discoveries in organic chemistry.

The fact that minor changes in steroid structures can cause extensive changes in biological activity has long intrigued medicinal chemists. Naturally occurring steroid nuclei have been modified in several ways with the aim of finding more active compounds, free from undesirable or harmful side effects, and of recognizing the structural and stereochemical features required for the display of specific, selective physiological activity. Among the many known analogues of steroids, compounds containing either heterocyclic rings condensed with the cyclopentaneperhydrophenanthrene nucleus or heteroatoms within the steroid nucleus itself, have received much attention in view of their different and interesting biological activities.[1] The replacement of one or more carbon atoms of a steroid molecule by a heteroatom affects the chemical properties of a steroid and often results in useful alterations to its biological activity.

We described previously the first total synthesis of 11-thia[2] and 11-oxa[3] steroids based on our general strategy for elaborating the steroid skeleton.[4] We are now interested by the synthesis of selena derivatives of steroid, in which the selenium atom occupies a position of established biological importance. To the best of our knowledge, no total synthesis of 11-selena steroid structures has been reported in the literature.

All steroids previously described[5] were prepared from 1,8-bis(trimethylsilyl)-2,6-octadiene BISTRO. BISTRO[6] **1** was obtained from 1,3-butadiene by reduction with lithium in the presence of chlorotrimethylsilane. The material formed is a mixture of the (*Z*,*Z*) isomer (ca. 50%), the (*Z*,*E*) isomer (ca. 40%) and the (*E*,*E*) isomer (4%), contaminated with about 6% of 1,6-bis(trimethylsilyl)-2,7-octadiene. We disclosed in this Letter a novel method to prepare BISTRO easier to implement. Indeed, we show that BISTRO **1** can be obtained by simple acyclic cross metathesis from 1,5-hexadiene and allytrimethysilane, using Grubbs's ruthenium catalyst. The CM reaction of 1,5-hexadiene and allyltrimethysilane was accomplished by treatment with a catalytic amount of Grubbs's catalyst (10 mol %) $[(Cy_3P)_2Cl_2Ru{=}CHPh]$[7] in CH_2Cl_2 at room temperature under argon atmosphere. After stirring for 12 h, BISTRO was isolated as the sole product in a fair yield of 45%. Moreover, we found that 5 mol % of catalyst was sufficient to complete this reaction in the same time. Otherwise, BISTRO was here obtained as a mixture of (*Z*,*Z*) and (*E*,*E*) isomers in a 60:40 ratio (Scheme 1).

We turned then our attention to synthesize 11-selena steroids from BISTRO. Indeed, the reaction of BISTRO revealed reliable high levels of diastereocontrol in spite of being a mixture of isomers.[8] The key reactions leading to these new hetero steroids are depicted in Scheme 2. We adopted a convergent steroid synthesis, based on the approach A + D → AD → ABCD. This strategy involves the use of intramolecular cycloaddition of *o*-xylylenes to generate the BC ring system, which was developed by Oppolzer[9] and Kametani et al.[10] The condensation of BISTRO **1** with chloroacetic anhydride led to

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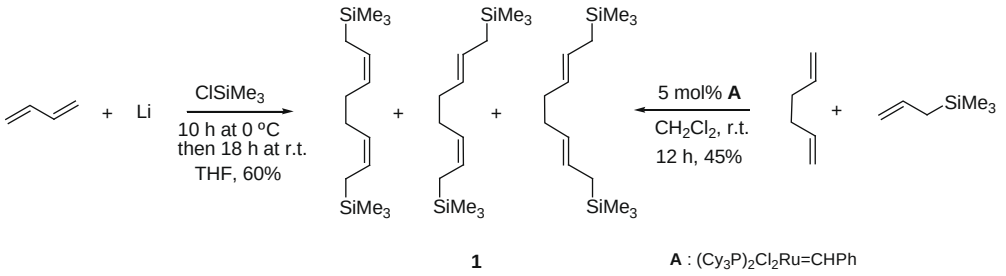
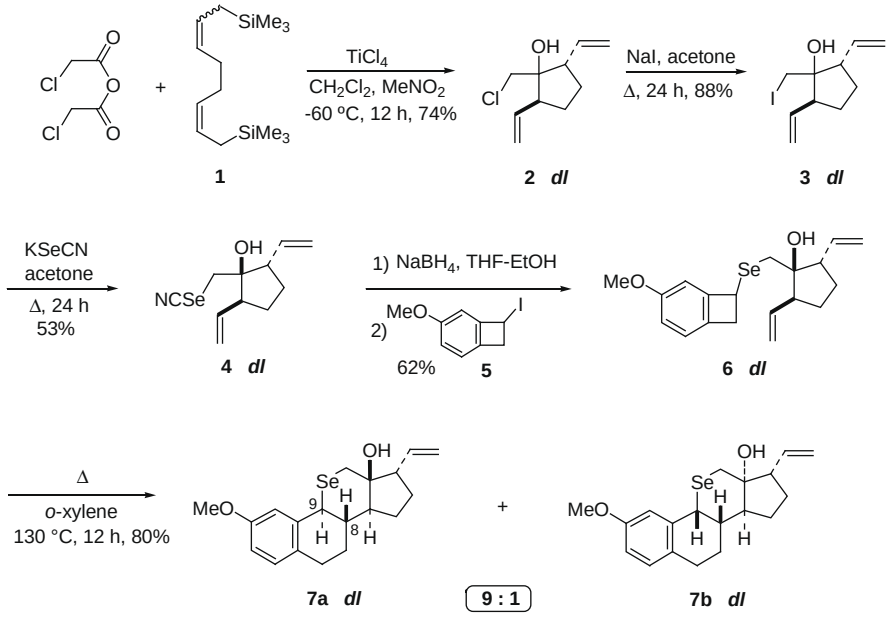


Scheme 1. Preparation of BISTRO **1**.



Scheme 2. Synthesis of 11-selena steroids through a five-step sequence.

(*d,l*)-2,5-divinylcyclopentan-1-ol **2** which was heated with NaI in acetone to give **3** in good yield. Iodhydrine **3** was dissolved in acetone containing potassium selenocyanate[11] and was heated under reflux for 48 h, to give the selenocyanate **4** in 53% yield. The latter, dissolved in tetrahydrofuran-ethanol, was treated with $NaBH_4$ at rt for 24 h, then the reductive product generated in this manner has been alkylated in situ with 1-iodo-5-methoxybenzocyclobutene[12] **5**, providing a convenient way to produce **6**. Thermolysis[13] of (*d,l*)-cyclobutene **6** afforded a mixture of two selena steroids **7a** and **7b** in 80% yield and a 9:1 ratio, which were easily separable by flash chromatography on silica gel.

The relative stereochemistry of these steroids was determined by a series of 1D NMR, COSY and NOESY experiments (400 MHz). The steroids **7a** and **7b** have, respectively, a *trans–anti–trans* and a *cis–anti–cis* ring fusion.[14] Interestingly, the main product **7a** matches the *trans–anti–trans* ring fusion configuration of natural products. The *trans* relationship between H-(8) and H-(9) was confirmed by the vicinal coupling constant J = 10.2 Hz for **7a** and for **7b** the value is 3.9 Hz corresponding to a *cis* relationship (δ(H-9) = 3.10 ppm for **7a** and δ (H-9) = 2.85 ppm for **7b**).

In conclusion, we have described the first short and efficient synthesis of 11-selena steroids through a five-step sequence from BISTRO and chloroacetic anhydride. Moreover, we show that BISTRO can also be obtained by simple acyclic cross metathesis from 1,5-hexadiene and allyltrimethylsilane. Application of this strategy to the obtention of 11-tellura steroids is in progress.

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13. *The typical procedure of thermolysis is as follows*: A solution of **6** (0.6 g, 1.65 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 **7a** (0.43 g, 71.5%) and compound **7b** (0.05 g, 8.5%).
14. 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* **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50–2.00 (m, 8H), 2.20 (m, 1H), 2.65 (d, J = 13.4 Hz, 1H), 2.80 (m, 1H), 2.95 (d, J = 13.4 Hz, 1H), 3.10 (d, J = 10.2 Hz, 1H), 3.25 (s, 1H), 5.00 (m, 2H), 5.60 (m, 1H), 7.40 (d, J = 5.1 Hz, 1H), 8.29 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.3, 26.7, 27.3, 28.1, 40.2, 42.8, 47.8, 51.2, 53.6, 76.8, 116.0, 122.4, 132.5, 139.6, 144.0, 147.6, 150.8. *Compound* **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.34 (m, 1H), 1.57 (m, 1H), 1.87 (m, 1H), 1.92 (m, 1H), 2.03 (m, 1H), 2.12 (m, 1H), 2.32 (d, J = 13.5 Hz, 1H), 2.37 (d, J = 13.5 Hz, 1H), 2.46 (m, 1H), 2.65 (td, J = 2.9, J = 9.0 Hz, 1H), 2.76 (m, 2H), 2.85 (d, J = 3.9 Hz, 1H), 4.83 (dd, J = 1.5, J = 9.1 Hz, 1H), 4.92 (m, 1H), 5.29 (dt, J = 1.5, J = 9.8 Hz, J = 16.9 Hz, 1H), 7.85 (d, J = 5.2 Hz, 1H), 8.31 (br s, 1H), 8.39 (d, J = 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 26.2, 26.7, 27.3, 35.2, 27.2, 41.8, 42.1, 53.6, 76.7, 115.5, 123.1, 133.1, 139.1, 144.4, 147.5, 150.2.