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A Novel, Versatile D→BCD Steroid Construction Strategy, Illustrated by the Enantioselective Total Synthesis of Estrone

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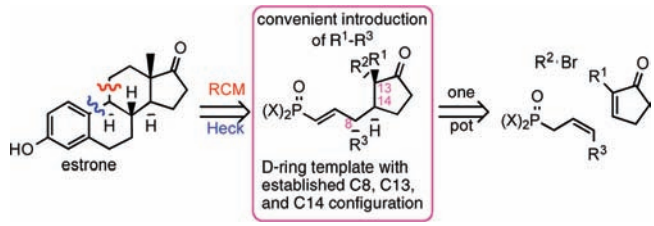
ABSTRACT

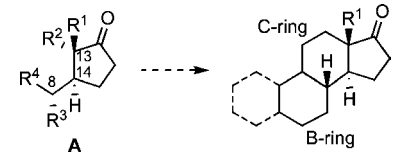


A general steroid synthesis is presented that relies on prior formation of three stereogenic centers (C8, C13, and C14) on a D ring template, followed by C- and B-ring cyclizations. The assembly of the key D ring template, achieved by a 3-component conjugate addition/alkylation process, allows introduction of structural variety as required. The method is illustrated by the total synthesis of estrone via a C-ring closing metathesis and a B-ring Heck cyclization.

Steroids are a very large class of compounds and display a wide range of biological activities. Many steroid derivatives have been synthesized as their biological evaluation is of high interest.[1] While their synthesis most commonly proceeds via a hemisynthetic approach,[2] many ingenious total syntheses continue to be reported.[2,3]

A well-known problem in steroid synthesis is the formation of the *trans*-fused CD ring junction without contamination by the corresponding *cis*-isomer.[4] Apart from employing *trans*-CD ring building blocks, this problem can be circumvented by employing a C ring cyclization strategy that commences from a D ring precursor (or vice versa) already

Scheme 1. Steroid Construction Strategy



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[‡] In memory of Benedetta Guizzardi.
[§] Organon (currently part of Schering-Plough).

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(2) (a) Chapelon, A.-S.; Moraléda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, *63*, 11511–11616. (b) Nising, C. F.; Bräse, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 9389–9391, and refs cited therein.

(3) Selected examples: (a) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc.* **2008**, *130*, 8865–8869. (b) Pattenden, G.; Stoker, D. A.; Thomson, N. M. *Org. Biomol. Chem.* **2007**, *5*, 1776–1788. See also examples in ref 7.

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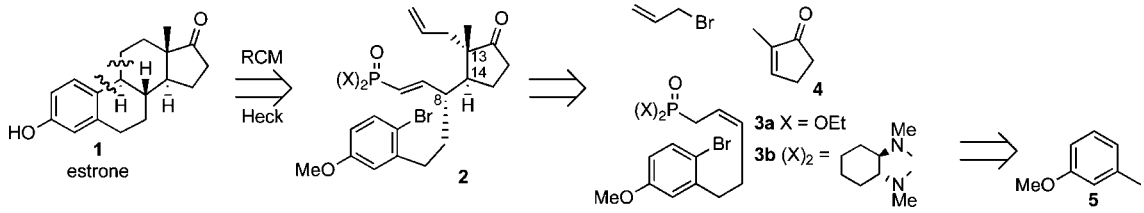
Scheme 2. Retrosynthetic Analysis



containing the correct stereochemistry at the positions of the future CD ring junction (C13 and C14), and this approach has been widely exploited.[2a,4,5]

The extension of this concept, in which *three* stereocenters C8, C13, and C14 would be established prior to C- and B-ring cyclization, as illustrated by the sketch shown in Scheme 1, has hardly been exploited.[6] Hence, we envisioned establishing a general approach to steroid synthesis featuring a one-pot stereoselective assembly of a D-ring intermediate **A**, which would then be subjected to appropriate cyclization reaction groups to give a B−C−D skeleton.

Key requirements for this to be an attractive and versatile synthetic strategy include convenient access to the intermediate **A** in a highly diastereo- and enantioselective fashion, and, crucially, the viability to easily introduce suitable R^1-R^4 groups in order to enable the synthesis of structurally diverse steroid targets via a range of suitable cyclization reactions. In this communication we will showcase our approach toward steroid synthesis by the enantioselective total synthesis of estrone **1**.[7]

Hence, the corresponding retrosynthetic analysis of **1** (Scheme 2) involves a B- and C-ring disconnection to give the key intermediate **2**. This intermediate was envisioned to be directly accessible by a one-pot process involving a conjugate addition of an allylic phosphonate/phosphonamide **3**, to be synthesized from 3-methyl anisole **5**, to 2-methyl-2-cyclopentenone acceptor **4**, followed by diastereoselective alkylation of the resulting enolate with allyl bromide. Conjugate addition reactions of allylic phosphonates are known to be very diastereoselective, with the allylic double bond configuration being translated into the relative configuration of the sp^3-centers of the formed C−C bond.[8] The desired relative C8−C14 configuration requires a *Z*-configuration of the phosphonate double bond. An enantioselective synthesis is possible, eg by using a homochiral phosphonamide auxiliary as described by Hanessian.[9] From **2**, the C-ring of estrone would be obtained via a ring closing metathesis, followed by a B-ring Heck cyclization.[7j]

In general, this approach would allow convenient synthesis of a D-ring intermediate (**A**, Scheme 1) with possible introduction of R^1-R^3 groups by appropriate choice of starting materials. The R^4 group, restricted to an *E*-vinylic phosphonamide/phosphonate, was thought of as a versatile reactive handle to achieve the B and C ring cyclizations.

The synthesis of the substrates **3** for the conjugate addition is shown in Scheme 3. Starting from the known dibromide **6**, accessible in one step from 3-methyl anisole **5**,[10] benzylic displacement with allenyl magnesium bromide[11] followed by one-carbon extension led to the propargylic alcohol **7**. Diastereoselective alkyne reduction (>98% *Z*) was achieved with $Zn/BrCH_2CH_2Br$,[12] which proved consistently reproducible even upon upscaling, unlike more conventional methods using poisoned heterogeneous Pd-catalysts. Conversion to the *Z*-allylic chloride **8** using hexachloroacetone,[13] and final Arbuzov reaction with triethyl phosphite gave **3a** in excellent overall yield. The homochiral phosphonamide **3b** was obtained by reaction of **8** with homochiral phospholane **9**.[14]

The key conjugate addition/allylation sequence was investigated next (Scheme 4). Deprotonation of **3a** with BuLi, followed by addition to 2-methyl-2- cyclopentenone **4** and final alkylation with allyl bromide, gave **2a** as the only observable diastereomer in excellent yield. The conjugate

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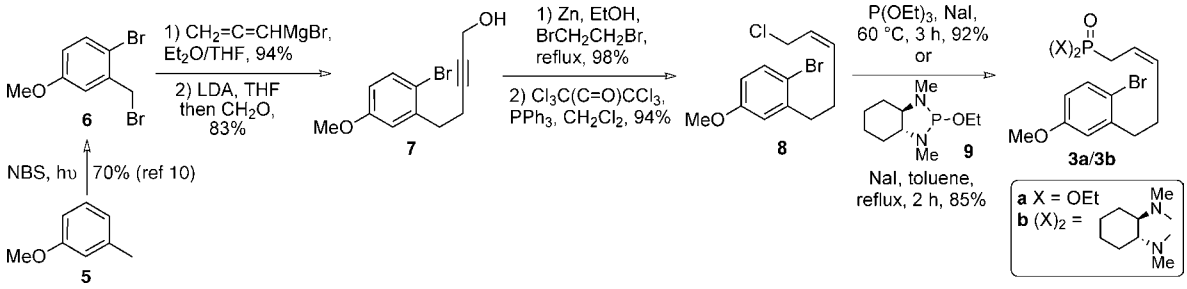
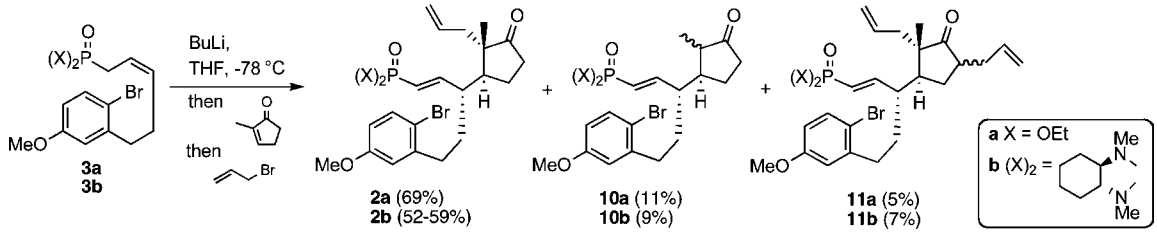
Scheme 3. Synthesis of the Phosphonate/Phosphonamide Conjugate Addition Substrates



Scheme 4. Diastereoselective Conjugate Addition-Alkylation



addition/alkylation process with the homochiral allylic phosphonamide **3b** proceeded in a slightly lower yield, leading to **2b** as the only isolated diastereomer. In both cases, the corresponding nonallylated product **10** was also isolated, as well as, surprisingly, a diallylation product **11**. It is believed that the formation of both byproducts originate from the same process, in that the obtained enolate after conjugate addition reaction deprotonates already formed allylation product **2** to give **10** and a new enolate, which is then allylated to give **11**. Both byproducts are separable by chromatography. It was important to use a limited excess (1.1 equiv) of BuLi to avoid concomitant bromine- lithium exchange, which led to the formation of the corresponding debrominated products (not shown). Fortunately, the relative configuration of **2a** could be unambiguously established by X-ray crystallographic analysis (Figure 1), which confirmed the formation of the desired relative configuration of the C8, C13, and C14 stereogenic centers.

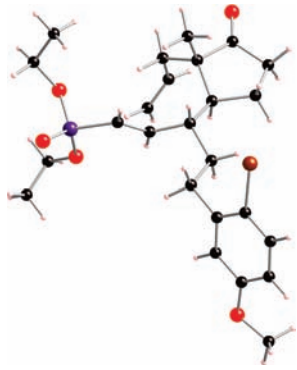


Figure 1. Crystal structure of **2a**.

With the key intermediates **2** in hand, the subsequent cyclization reactions to give estrone were accomplished (Scheme 5). The C-ring closure by ring closing metathesis to the *trans*-hydrindene ring[15] was investigated first using the racemic phosphonate **2a**. RCM reaction using the Hoveyda-Grubbs II catalyst in toluene[16] at 70 °C[17] afforded *trans*-hydrindene ***rac*-12** in good yield. Small amounts (up to 3%) of debrominated product[18]—separable by chromatography—could be observed (NMR) when the Grubbs II catalyst[19] was used. From **rac-12** onward, the estrone synthesis is similar to the Tietze estrone synthesis (in which the C17 ketone was protected as *t*butyl ether).[7j] The Δ9,11 double bond resulting from the RCM reaction is ideally positioned for the subsequent Heck B-ring closure, which proceeded in quantitative yield under conditions developed by Tietze. This led to **13**, with the undesired 9β-configuration. This can be converted to the desired configuration under particular conditions in which the Δ11,12 double bond in **13** is isomerized to its conjugated position, followed by hydrogenation, a process also developed by Tietze. In our case, the isomerization/hydrogenation process from **13** led to a 7:3 mixture of *O*-methyl estrone **14** and its 9β-epimer,

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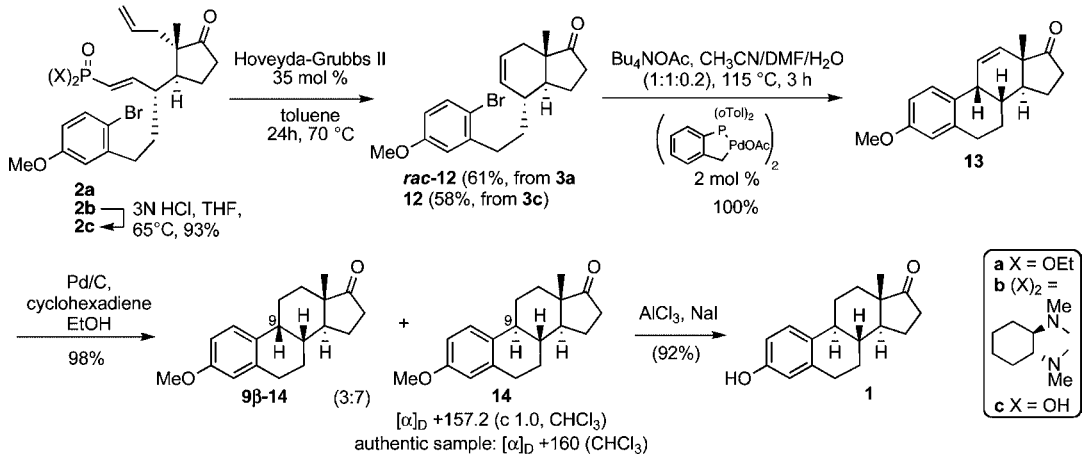
Scheme 5. Successive Cyclizations to Achieve the Estrone Synthesis



in almost quantitative yield. Presumably, the different C17 functionalization is the reason for the difference in stereochemical outcome compared to Tietze's report. Our results are in accord with a literature report in which Δ9,11-*O*-methyl estrone was converted to a 65:35 mixture of **14** and **9*β*−14** using H_2, Pd/C.[20] Estrone methyl ether could be obtained pure by crystallization, and estrone **1** was then obtained by conventional deprotection.[21]

An enantioselective synthesis was achieved from **3b**. Unfortunately, the RCM reaction only proceeded well after prior hydrolysis of the phosphonamide group to the corresponding phosphonic acid **2c**. Starting from **2b**, only 6% of **12** was obtained. The thus synthesized enantioenriched **12** was then taken through to *O*-methyl estrone **14**, of which optical rotation compared well with the reported value for authentic estrone methyl ether.[22]

In conclusion, we have proposed a potentially versatile steroid construction strategy based on the formation of an intermediate that contains the correct C8, C13, and C14 configuration with suitable functionalization to subsequently obtain the desired steroid target by a chosen B and C-ring cyclization event. We have validated this strategy with the synthesis of estrone. Importantly, it was shown that a phosphonate/phosphonamide-based congugate addition/enolate alkylation process led to the desired key intermediate in diastereomerically pure form, and that by using a homochiral auxiliary an enantioselective synthesis is possible. Our work also demonstrated an extension in scope of the Hanessian conjugate addition by using a more complex allylic substituent. We expect that this methodology will be useful for the synthesis of a wide range of unnatural steroids including steroid hybrids,[23] and further work toward this goal is in progress.

Acknowledgment. We thank Organon and the EPSRC for studentships to B.G. and V.F.

Supporting Information Available: Experimental procedures and spectral data, including copies of ^{1}H and ^{13}C NMR spectra, for compounds **1**−**3**, **7**, **8**, **10**−**14**, and the debrominated product arising from the RCM reaction. The crystal information file for compound **2a** is also included. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The starting material **2a** was not contaminated with debrominated side-product.

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