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Stille/Diels–Alder Reaction Sequences: Diversity-Oriented Access to Novel Steroids

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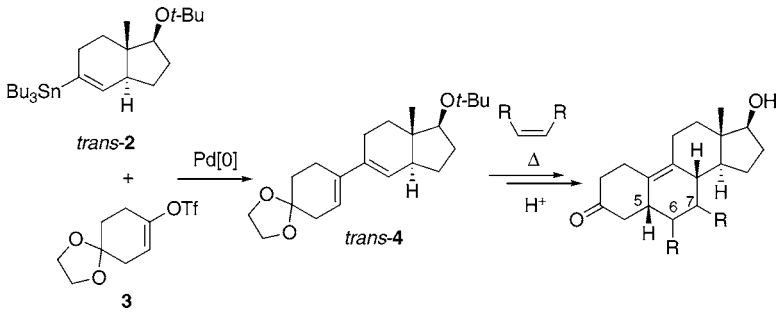
ABSTRACT



An efficient, diversity-oriented approach to novel steroid analogues possessing a C-5*β* configuration begins with the Stille cross-coupling of enantiomerically pure cycloalkenylstannane *trans*-2 and enol triflate 3. The resulting diene *trans*-4 engages in Diels–Alder cycloaddition reactions with a range of dienophiles to give, after removal of protecting groups, biologically interesting 6,7-disubstituted steroid analogues.

Analogues of natural steroids are important compounds that possess a wide spectrum of attractive biological properties. For example, although the use of glucocorticoids as pharmaceuticals can be accompanied by a range of undesirable side effects,[1] certain synthetic variants have been shown to retain the desired biological activities while displaying none of the adverse effects associated with their natural congeners.[2] Despite the consequent and intense interest in synthetic steroids,[3] it is noteworthy that among the large arsenal of established approaches to such compounds,[4] diversity-oriented access to steroidal skeleta capable of delivering large collections of analogues is essentially unknown. Herein, we report a new approach to the tetracyclic steroidal skeleton that follows a convergent A + CD → ACD → ABCD ring-assembling strategy utilizing a simple sequence of Stille cross-coupling and Diels−Alder cycloaddition reactions that achieves rapid increases in molecular complexity. The route involved generates interesting and, thus far, rarely investigated steroids incorporating substituents at C-6 and C-7[5] that have been reported to enhance the biological activities of steroids lacking groups at these positions.[6]

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(1) Refojo, D.; Liberman, A. C.; Holsboer, F.; Arzt, E. *Immunol. Cell Biol.* **2001**, *79*, 385−394.
(2) Fannon, S. A.; Vidaver, R. M.; Marts, S. A. *J. Appl. Physiol.* **2001**, *91*, 1854−1859.
(3) Cepa, M. M. D. S.; Tavares da Silva, E. J.; Correia-da-Silva, G.; Roleira, F. M. F.; Teixeira, N. A. A. *J. Med. Chem.* **2005**, *48*, 6379−6385.
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(5) (a) Rickard, C. E. F.; Le Quesne, P. W. *J. Org. Chem.* **1998**, *63*, 1736. (b) Allevi, P.; Longo, A.; Anastasia, M. *Tetrahedron* **1999**, *55*, 4167−4176. (c) Bondarenko, L.; Lorenc, L.; Bläser, D.; Boese, R. *Eur. J. Org. Chem.* **2004**, 3526−3534.
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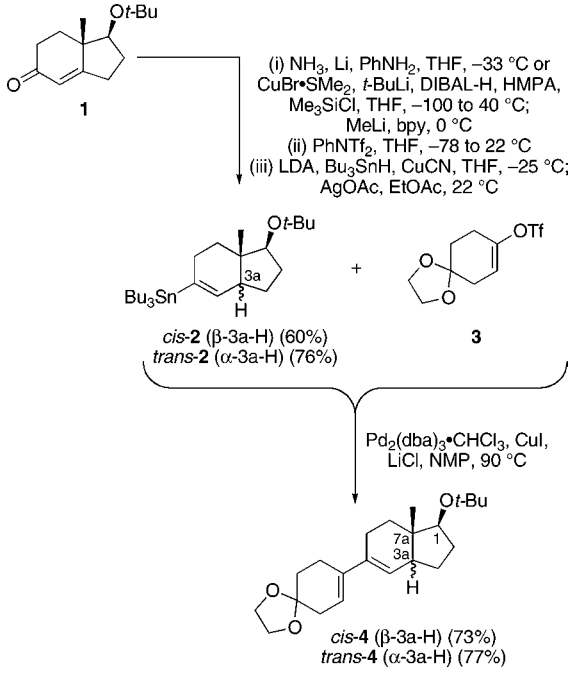
The reaction sequence starts (Scheme 1) with the selective conversion of the readily available and enantiomerically pure bicyclic enone **1**[7] into either the *cis*- or *trans*-ring-fused forms of the hexahydroindenylstannane **2** by subjection of the former compound to appropriate reduction conditions and then trapping of the resulting enolates to generate the corresponding *cis*- or *trans*-configured enol triflate in 71 and 83% yield, respectively.[8−10] These last species were then treated with lithium tri-*n*-butylstannyl cuprate[11] to give *cis*-**2** or *trans*-**2** in 85 and 92% yield, respectively. The other partner required for the foreshadowed Stille cross-coupling reaction[12] was the enol triflate **3**, and this was prepared from the commercially available monoethylene acetal of cyclohexane-1,4-dione by a new protocol employing sodium bistrimethylsilylamide in diethyl ether that allows the conversion of ketones into enol triflates with the relatively inexpensive reagent trifluoromethanesulfonic acid anhydride.[13] The best conditions for carrying out the Stille cross-coupling of stannanes *cis*-**2** and *trans*-**2** with compound **3** involved a procedure employing $Pd_2(dba)_3$ with a copper(I) cocatalyst in the presence of lithium chloride. By such means, the dienes *cis*-**4** and *trans*-**4** were obtained in 73 and 77% yield, respectively.

Scheme 1



The *cis*-**4** and *trans*-**4** diastereomers each appear to be reasonably well set up for participation in Diels−Alder reactions to generate steroid-like adducts, although, in the event, these dienes needed to be treated with rather reactive dienophiles such as maleic acid derivatives so that the desired cycloaddition reaction occurred. For example, upon heating diene *trans*-**4** with 1.5 equiv of fumaronitrile in refluxing toluene (Scheme 2), the steroid analogue *trans*-**5** was formed in 84% yield. The structure of *trans*-**5** follows from a single-crystal X-ray analysis.[14] An analogous reaction conducted in benzene[15] at 95 °C and employing *N*-methylmaleimide as a dienophile afforded the adduct *trans*-**6** in 79% yield. The less reactive dienophile dimethyl acetylenedicarboxylate engaged in the expected cycloaddition reaction with diene *trans*-**4** to give, in 65% yield, the steroidal compound *trans*-**7** incorporating a 1,4-diene residue within the B-ring. The use of unsymmetrically substituted dienophiles such as 2-chloroacrylonitrile in these types of reactions afforded mixtures of two regioisomeric adducts of *trans*-**8** in a combined yield of 67%. Such reactions did not proceed in significantly greater yield when performed under high pressure. The novel heterocyclic steroid analogue *trans*-**9** was obtained in 77% yield when *N*-phenyl-1,2,4-triazoline-3,5-dione was employed as a dienophile. Similarly, reaction of diene *trans*-**4** with maleic anhydride produced, in 80% yield, adduct *trans*-**10** as proven by X-ray crystal structure analysis.[14] Product *trans*-**10** should serve as a precursor to various interesting steroidal diacid derivatives.

All of the abovementioned steroids, viz. *trans*-**5**, *trans*-**6**, *trans*-**7**, *trans*-**8**, *trans*-**9**, and *trans*-**10**, are new compounds and were obtained as single diastereoisomers that must necessarily be formed by *endo*-selective attack of the dienophiles at the face of diene *trans*-**4** opposite to the angular methyl group attached at C-7a. It is important to note that these steroid analogues possess the nonnatural configuration at C-5.[16] Furthermore, polar substituents at C-3 and C-17, which often confer beneficial biological properties on steroids, are conveniently introduced using this Stille/Diels−Alder sequence involving diene *trans*-**4**. Of course, all of the steroidal products described herein are obtained in

(7) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675−681.

(8) (a) Goth, U.; Köhler, T.; Taapken, T. *Tetrahedron* **1991**, *47*, 7583−7592. (b) Knopff, O.; Alexakis, A. *Org. Lett.* **2002**, *4*, 3835−3837.

(9) McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982.

(10) The *trans*-configured enol triflate was prepared by a multistep procedure involving initial reduction of enone **1** with DIBAL-H/*tert*-BuCu and treatment of the resulting diisobutylaluminum enolate with trimethylsilyl chloride. The ensuing trimethylsilyl enol ether was cleaved with MeLi in the presence of catalytic 4,4′-bipyridyl to form the more reactive lithium enolate that was then treated with *N*,*N*-bis(trifluoromethylsulfonyl)aniline.

(11) Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795−4798.

(12) For reviews on the Stille cross-coupling reaction, see: (a) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1−652. (b) Kosugi, M.; Fugami, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-i., de Meijere, A., Eds.; Wiley: New York, 2002; pp 263−284. (c) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; de Meijere, A., Diederich, F., Eds.; Wiley−VCH: Weinheim, 2004; pp 125−161.

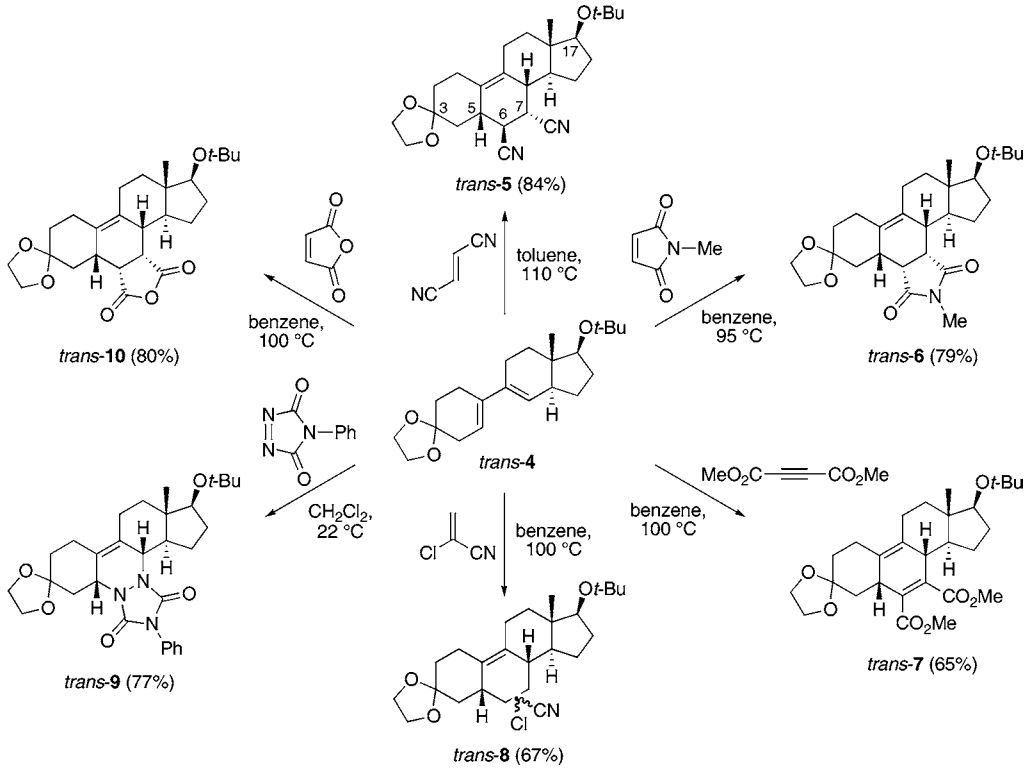
(13) Standard conditions involving the presence of trimethylamine or sodium carbonate failed to provide the desired product in satisfactory yield.

(14) The data relating to the single-crystal X-ray analyses of compounds *trans*-**5** and *trans*-**10** (respectively) are contained in the files CCDC-611592 and CCDC-613303, and these have been deposited at the Cambridge Crystallographic Data Centre. They can be accessed, free of charge, via http://www.ccdc.cam.ac.uk/products/csd/request/.

(15) Using benzene instead of toluene as solvent generally provided the cycloaddition products in significantly higher yields.

(16) For examples of steroids incorporating this configuration and exhibiting interesting biological activities, see: (a) Kaufmann, G.; Schlegel, J.; Eychenne, B.; Schubert, K. *Exp. Clin. Endocrinol.* **1983**, *81*, 222−227. (b) Oettel, M.; Kaufmann, G.; Kurischko, A. *Pharmazie* **1993**, *48*, 541−545.

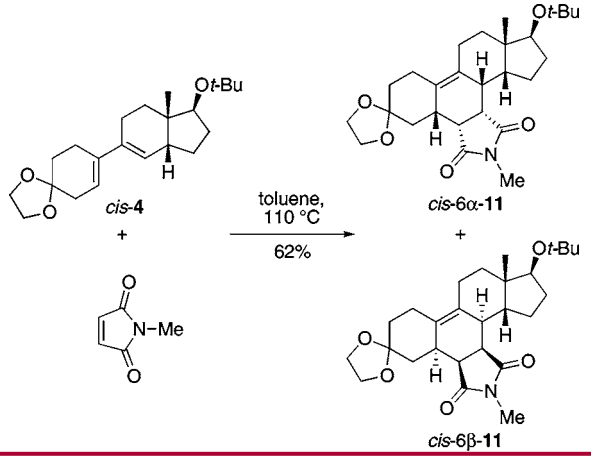
Scheme 2



enantiomerically pure form by virtue of the analogous nature of the starting materials and the fact that there is no possibility for racemization of preset stereogenic centers during the course of the reaction sequences being employed.

The diastereoselectivity observed in the Diels−Alder reaction between *N*-methylmaleimide and diene *cis*-**4** (Scheme 3) was not as high as that associated with the analogous

Scheme 3

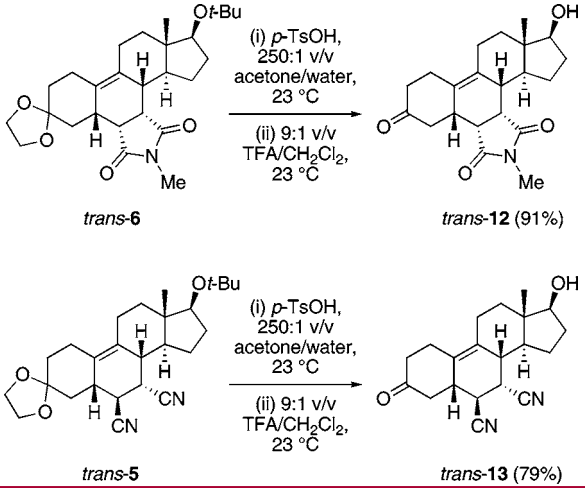


process involving isomer *trans*-**4**. Thus, a 3:2 mixture of the two possible adducts, *cis*-6α-**11** and *cis*-6*β*-**11**, was obtained in 62% combined yield. This outcome is attributed to the more highly curved molecular architecture of the former

diene and the reduced capacity, therefore, of the angular methyl and *tert*-butoxy groups to exert directing effects in the cycloaddition process.

To generate compounds suitable for biological testing, the capacity to effect cleavage of the ethylene acetal and *tert*-butyl ether moieties within certain of the abovementioned Diels−Alder adducts was examined (Scheme 4). In particu-

Scheme 4

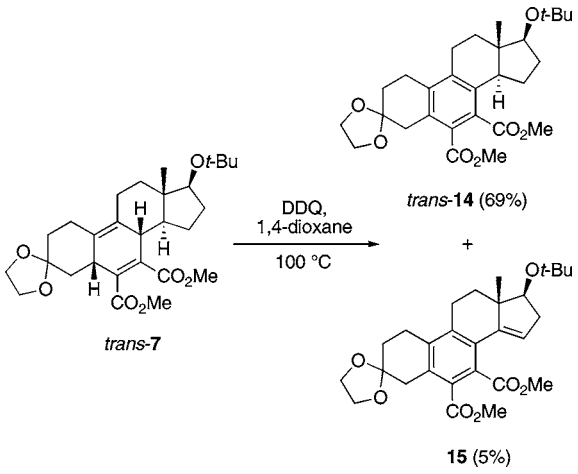


lar, the 1,3-dioxolane moieties within compounds *trans*-**5** and *trans*-**6** were efficiently removed (95−99%) in aqueous acetone using *p*-toluenesulfonic acid as a catalyst, and the

tert-butyl ether residues within the resulting 3-oxo compounds were best cleaved with trifluoroacetic acid in dichloromethane.[17] By such means, the steroids *trans*-**12** and *trans*-**13** were obtained in yields of 91 and 79%, respectively.

Dehydrogenation of the steroidal diene *trans*-**7** can generate new and interesting steroid analogues incorporating an aromatic B-ring.[18] Thus, treatment of *trans*-**7** with DDQ (Scheme 5) under previously reported conditions[19] afforded a chromatographically separable mixture of compound *trans*-**14** (69% yield) and congener **15** (5%) incorporating a double bond in the D-ring.[20]

Scheme 5



(17) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999.

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Supporting Information Available: Preparation and characterization of selected compounds; ^{1}H and ^{13}C NMR spectra of compounds **3**, *cis*-**4**, *trans*-**4**, *trans*-**5**, *trans*-**6**, *trans*-**7**, *trans*-**8**, *trans*-**9**, *trans*-**10**, a mixture of *cis*-6α-**11** and *cis*-6*β*-**11**, *trans*-**12**, *trans*-**13**, the monodeprotected derivative of *trans*-**6**, the monodeprotected derivative of *trans*-**5**, *trans*-**14**, and **15**; and atomic displacement ellipsoid plots for compounds *trans*-**5** and *trans*-**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) When an excess of DDQ and extended reaction times were employed, compound **15** became the major product of reaction.