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Access to Functionalized Steroid Side Chains via Modified Julia Olefination

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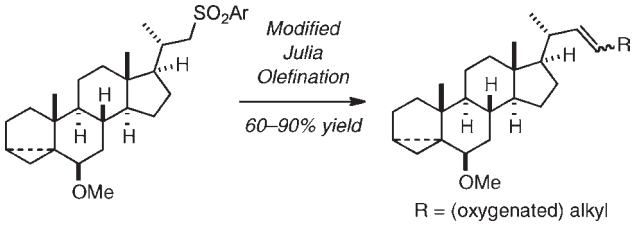
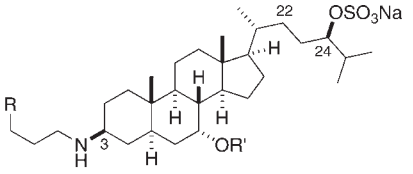
ABSTRACT



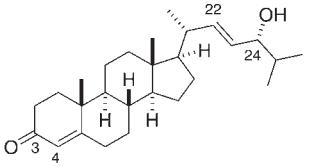
Various functionalized steroidal side chains were conveniently accessed by a modified Julia olefination strategy using a common sulfone donor and an appropriate α-branched aldehyde acceptor. For the coupling of these hindered classes of reaction partners (and in contrast to typically observed trends), the benzothiazolyl(BT)-sulfone anion gave superior outcomes compared to the phenyltetrazolyl(PT)-sulfone anion.

Steroids with oxidatively modified side chains comprise an important family of compounds, largely because of their biological properties (e.g., **1**−**4**, Figure 1). Our interest in the preparation of analogs of sea lamprey pheromone components (e.g., **3**[1d]) drove a need for a flexible strategy in which a common intermediate could be used in a conjunctive fashion to attach an array of structurally diverse side chains. In this regard, we have studied the use of the modified Julia olefination[2] involving C22-sulfonyl steroids as the anionic donor partner, and our results are described here.

Previously, steroidal aldehydes **5** have been used as the electrophilic acceptor component in Horner−Wadsworth−Emmons (HWE, **6a**),[3a−e] modified Julia (**6b**),[3f] and Wittig (with stabilized ylides, **6c**)[3g−m] olefination reactions to forge the C22−C23 alkene in products **9**. Alternatively, steroidal phosphonium ylide (**7a**) and phenylsulfonyl (**7b**)



1 squalamine; R = –NH(CH$_2$)$_4$NH$_2$, R' = H
2 MSI-1436; R = –NH(CH$_2$)$_4$NH(CH$_2$)$_3$NH$_2$, R' = H
3 petromyzonamine disulfate (PADS); R = pyrrolidin-2-onyl, R' = SO$_3$Na



4 (22*E*,24*R*)-24-Hydroxycholest-4,22-dien-3-one

Figure 1. Some of the related highly potent C24-functionalized steroids (**1**,[1a,b] **2**,[1c] **3**,[1d] and **4**[1e]).

(1) (a) Moore, K. S.; Wehrli, S.; Roder, H.; Rogers, M.; Forrest, J. N., Jr.; McCrimmon, D.; Zasloff, M. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 1354–1358. (b) Wehrli, S. L.; Moore, K. S.; Roder, H.; Durell, S.; Zasloff, M. *Steroids* **1993**, *58*, 370–378. (c) Rao, M. N.; Shinnar, A. E.; Noecker, L. A.; Chao, T. L.; Feibush, B.; Snyder, B.; Sharkansky, I.; Sarkahian, A.; Zhang, X.; Jones, S. R.; Kinney, W. A.; Zasloff, M. *J. Nat. Prod.* **2000**, *63*, 631–635. (d) Sorensen, P. W.; Fine, J. M.; Dvornikovs, V.; Jeffrey, C. S.; Shao, F.; Wang, J.; Vrieze, L. A.; Anderson, K. R.; Hoye, T. R. *Nat. Chem. Biol.* **2005**, *1*, 324–328. (e) Mellado, G. G.; Zubia, E.; Ortega, M. J.; Lòpez-Gonzàlez, P. J. *Steroids* **2004**, *69*, 291–299.

(2) (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. A. *Tetrahedron Lett.* **1991**, *32*, 1175–1178. (b) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.

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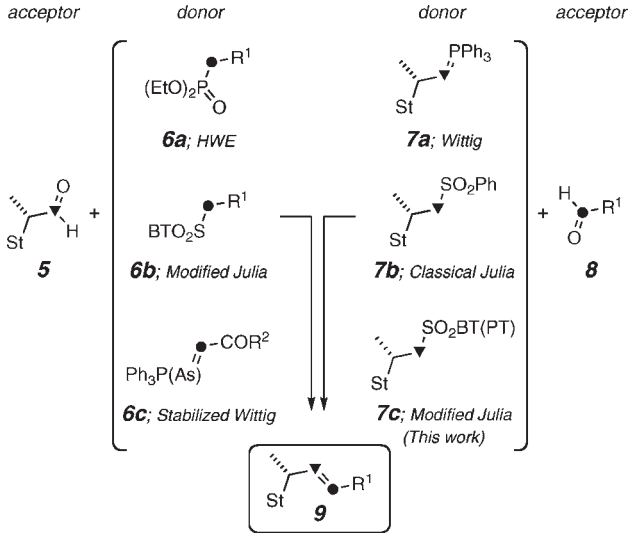
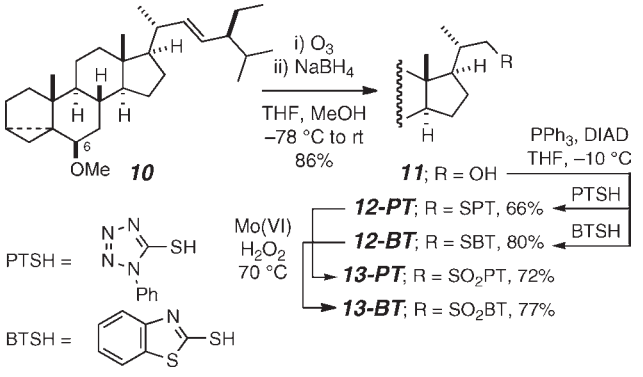
Scheme 1. Overview of the Coupling Strategies To Construct Oxygenated Steroidal Side Chains[a]



[a] St = generic steroid nucleus; BT = benzothiazolyl; PT = 1-phenyl-1*H*-tetrazol-5-yl.

donors were coupled with aldehyde acceptors **8** via Wittig[3n] and classical Julia[3o] olefination reactions, respectively (Scheme 1). In this study, we have established the modified Julia coupling with donors **7c**, primarily with the benzothiazolyl (BT) sulfone [although we have also compared the use of the 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone] and a variety of acceptor aldehydes **8**.

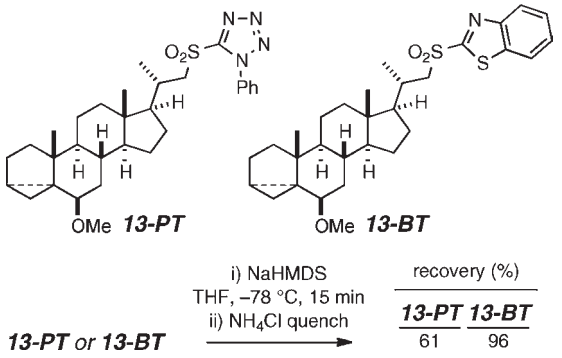
Scheme 2. Synthesis of the Key Sulfones **13-PT** and **13-BT**



To test the feasibility, both the PT and BT sulfones **13-PT** and **13-BT**, respectively, were prepared as outlined in Scheme 2 from *i*-stigmasteryl methyl ether (**10**, two steps, 74% yield from stigmasterol).[4] Ozonolysis (and reductive workup with $NaBH_4$) of the disubstituted olefin smoothly provided the primary alcohol **11** [and (*S*)-2-ethyl-3-methylbutan-1-ol]. It is worth noting that a major problem associated with the ozonolysis of *i*-steroids, namely the undesired oxidation of the methine C−H bond at the C6-ether,[5] is avoided by using the unconventional solvent tetrahydrofuran as a component of the reaction medium (THF/MeOH; 10:1). The resulting alcohol **11** was formed in high yield (86%), and butyrolactone was isolated as a byproduct, its amount increasing with increased reaction time. We believe that THF effectively buffers the ozonolysis reaction by acting as a sacrificial reductant, preventing overoxidation of **10** and its derived products. The thioethers **12-PT** and **12-BT** were then prepared from **11** using the Mitsunobu protocol (PTSH or BTSH, DIAD, PPh_3). Each was subsequently oxidized to the sulfone **13-PT** or **13-BT** (ammonium paramolybdate, H_2O_2).

We first attempted olefination using the *potassium* anion of **13-PT** and **13-BT**. Preforming the anion (KHMDS, THF, −78 °C) and addition of propionaldehyde provided none of the expected olefination product, nor was the starting sulfone recovered. When a solution of KHDMS was added at −78 °C to a THF solution containing both the sulfone **13-BT** and propionaldehyde, the desired propylidene coupling product was isolated in low yield with the cis isomer predominating.

Scheme 3. Recovery/Stability of Sulfone Anions[a]



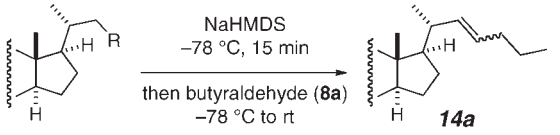
[a] Stoichiometric ratio of sulfone/NaHMDS was 1:1.2.

We then turned our attention to the *sodium* anions derived from **13-PT** and **13-BT** by studying the relative stability of the sulfones upon metalation with NaHMDS in THF at −78 °C

(3) (a) Giroux, S.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 9866–9867. (b) Yamamoto, S.; Watanabe, B.; Otsuki, J.; Nakagawa, Y.; Akamatsu, M.; Miyagawa, H. *Bio. Med. Chem.* **2006**, *14*, 1761–1770. (c) Tochtrop, G. P.; DeKoster, G. T.; Cistola, D. P.; Covey, D. F. *Bio. Med. Chem. Lett.* **2002**, *12*, 433–435. (d) Kinney, W. A.; Zhang, X.; Williams, J. I.; Johnston, S.; Michalak, R. S.; Deshpande, M.; Dostal, L.; Rosazza, J. P. N. *Org. Lett.* **2000**, *2*, 2921–2922. (e) Jones, S. R.; Selinsky, B. S.; Rao, M. N.; Zhang, X.; Kinney, W. A.; Tham, F. S. *J. Org. Chem.* **1998**, *63*, 3786–3789. (f) Jiang, B.; Shi, H.; Xu, M.; Wang, W.; Zhou, W. *Tetrahedron* **2008**, *64*, 9738–9744. (g) Shingate, B. B.; Hazra, B. G.; Pore, V. S.; Gonnade, R. G.; Bhadbhade, M. M. *Tetrahedron* **2007**, *65*, 5622–5635. (h) Shu, Y.; Jones, S. R.; Kinney, W. A.; Selinsky, B. S. *Steroids* **2002**, *67*, 291–304. (i) Rao, M. N.; McGuigan, M. A.; Zhang, X.; Shaked, Z.; Kinney, W. A.; Bulliard, M.; Laboue, B.; Lee, N. E. *J. Org. Chem.* **1997**, *62*, 4541–4545. (j) Okamoto, M.; Tabe, M.; Fuji, T.; Tanaka, T. *Tetrahedron: Asymmetry* **1995**, *6*, 767–768. (k) Wei-Shan, Z.; Hui-Qiang, Z.; Zhi-Qin, W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2281–2286. (l) Zhou, W.; Jiang, B.; Pan, X. *Tetrahedron* **1990**, *46*, 3173–3188. (m) Zheng-Wu, S.; Wei-Shan, Z. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1765–1767. (n) Harney, D. W.; Macrides, T. A. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1353–1356. (o) D'Ambra, T. E.; Javitt, N. B.; Lacy, J.; Srinivasan, P.; Warchol, T. *Steroids* **2000**, *65*, 401–407.

(Scheme 3). Each anion was quenched with saturated NH_4Cl solution 15 min after the addition of base. The starting sulfones were reisolated by SiO_2 chromatography (MPLC) with 61 vs 96% recovery efficiency, respectively. This shows that the **13-BT** anion was more stable than that of **13-PT**.

Scheme 4. Olefination of Sulfones **13-PT** or **13-BT** with **8a**[a]



sulfone donor	solvent	yield (%)	E:Z
13-PT, R = SO_2PT	THF	39	50:50
13-BT, R = SO_2BT	THF	61	64:36
13-BT	THF/HMPA (4:1)	65	80:20

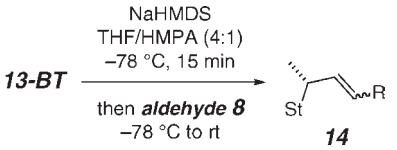
[a] Stoichiometric ratio of sulfone/**8a**/NaHMDS was 1:1:1.2.

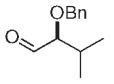
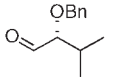
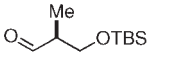
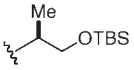
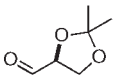
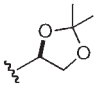
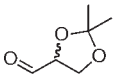
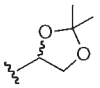
We next tested the relative efficiency of each of the donor sulfones **13** to effect olefination using butyraldehyde (**8a**) as a simple acceptor substrate and NaHMDS as the base (Scheme 4). The behavior mirrored that seen in the above stability studies; namely, the yield of alkene **14a** was higher when the benzothiazolyl sulfone **13-BT** was used. Moreover (and as described elsewhere[6]), the use of HMPA as an additive improved the **14a-*E***:**14a-*Z*** product ratio.

We then studied the olefination reactions of a series of aldehydes **8** with **13-BT** as the sulfone donor (Table 1). The aldehydes contain α-methyl or α-alkoxy branching. Aldehyde **(*S*)-8b** provided **14b** both in high yield and with excellent *E*/*Z*-selectivity (entry 1). Use of the enantiomeric aldehyde **(*R*)-8b** gave the C24-epimer in 80% yield and with an *E*/*Z*-ratio of 82:18 (entry 2). Entries 3−5 demonstrate the additional scope of the method. Aldehyde **(*S*)-8e** showed a high *E*/*Z*-selectivity. Use of the racemate ***rac*-8e** (2 equiv, entry 6) produced similar amounts of C24-epimers. While the *E*/*Z*-ratio of product **14e-(24*R*)** was essentially the same as that observed in entry 5 (i.e., 90:10), the epimeric mixture of alkenes **14e-(24*S*)** was formed with reduced selectivity for alkene geometry (i.e., 65:35). Thus, the degree of matching/mismatching for the substrates in either entry 1 vs 2 or 5 vs 6 is small.

In conclusion, this study demonstrates the utility of a modified Julia olefination strategy for providing easy access to steroidal products containing a variety of functionalized side chains. The steric demand of both α-branched coupling partners that participate in this transformation is noteworthy. Contrary to the general trend observed for the modified Julia reaction using less hindered pairs of substrates, the olefination efficiency and alkene diastereoselectivity of the steroidal BT-sulfonyl donor was found here to be superior to the PT-sulfonyl version.[7] This is likely a result of the greater lability of the metalated PT-sulfone anion (Scheme 3). An ancillary observation of note is the use of THF as the bulk solvent to improve the ozonolysis of cyclopropyl-contianing substrate **10**. This protocol may be useful for chemoselective transformation of other complex substrates bearing functionality sensitive to oxidation.

Table 1. Alkenes **14** via the Modified Julia Olefination



entry	aldehyde	R	yield (%)	E/Z[a]
1	 ***(S)-8b***	 ***14b***	82	94:6
2	 ***(R)-8b***	 ***epi-14b***	80	82:18
3	 ***8c***	 ***14c***	90	75:25
4	 ***(S)-8d***	 ***14d***	60	85:15
5	 ***(S)-8e***	 ***14e-(24R)***	81	90:10
6	 ***rac-8e***	 ***14e-(24S) + 14e-(24R)***	60	ca. 65:35 from ***14e-(24S)***

[a] *E*/*Z* ratios determined by ^{1}H NMR analysis of product mixtures.

Acknowledgment. These studies were supported by the National Institute of General Medical Sciences (GM-65597) and the National Cancer Institute (CA-76497) of the United States National Institutes of Health.

Supporting Information Available. Experimental procedures and spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(4) Fernholz, E.; Ruigh, W. L. *J. Am. Chem. Soc.* **1940**, *62*, 3346–3348.
(5) Spencer, T. A.; Li, D.; Russel, J. S.; Tomkinson, N. C. O.; Willson, T. M. *J. Org. Chem.* **2000**, *65*, 1919–1923.
(6) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772–10773.
(7) (a) Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563–2585. (b) Aissa, C. *Eur. J. Org. Chem.* **2009**, 1831–1844.