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Substituted Pyrroles via Olefin Cross-Metathesis

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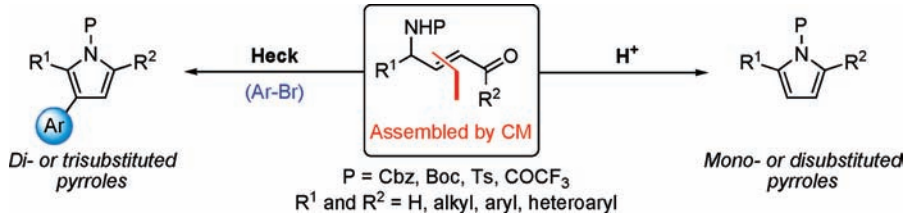
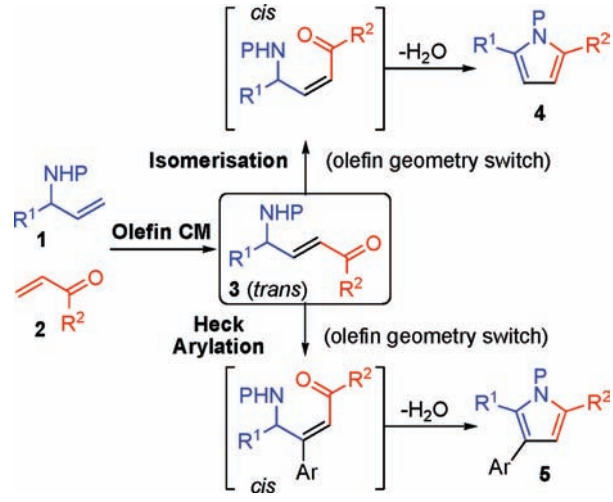
ABSTRACT



Olefin cross-metathesis (CM) provides a short and convenient entry to diverse *trans*-γ-aminoenones. When exposed to either acid or Heck arylation conditions, these intermediates are converted to mono-, di-, or trisubstituted pyrroles. The value of this chemistry is demonstrated by its application to the tetrasubstituted pyrrole subunit of Atorvastatin.

Recently, we have reported highly efficient and convergent methods for the synthesis of di- and trisubstituted furans.[1] This chemistry is reliant upon the generation of *trans*-γ-hydroxyenones via olefin cross-metathesis (CM) of an enone and allylic alcohol. *Trans*- to *cis*-isomerization and subsequent cycloaromatization to the furan target are then promoted by either an acid cocatalyst or separate Heck arylation step. This latter process also serves to introduce a substituent onto the enone β-position to afford ultimately trisubstituted furans. Herein, we report that an analogous strategy is applicable to the synthesis of mono-, di-, and trisubstituted pyrrole derivatives (**4** and **5**) (Scheme 1). In these cases, the key aspect is the synthesis and manipulation of a *trans*-γ-aminoenone intermediate **3** which is accessible via the CM of readily available allylic amine **1** and enone **2** components. These studies further add to the notion that olefin CM can provide a general and enabling basis for the regiocontrolled synthesis of diverse aromatic and heteroaromatic targets.[2,3]

Scheme 1. Olefin CM-Based Approach to Pyrroles



Our initial studies focused upon evaluating the CM of a representative range of allylic amine derivatives **1a**−**h** with enone partners **2a**−**d** (Scheme 2).[4−6] Here, we found that,

[†] Author to whom correspondence regarding X-ray crystallography should be addressed.

(1) Donohoe, T. J.; Bower, J. F. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 3373–3376. These studies represent the first systematic investigations into the use of olefin CM for aryl synthesis.

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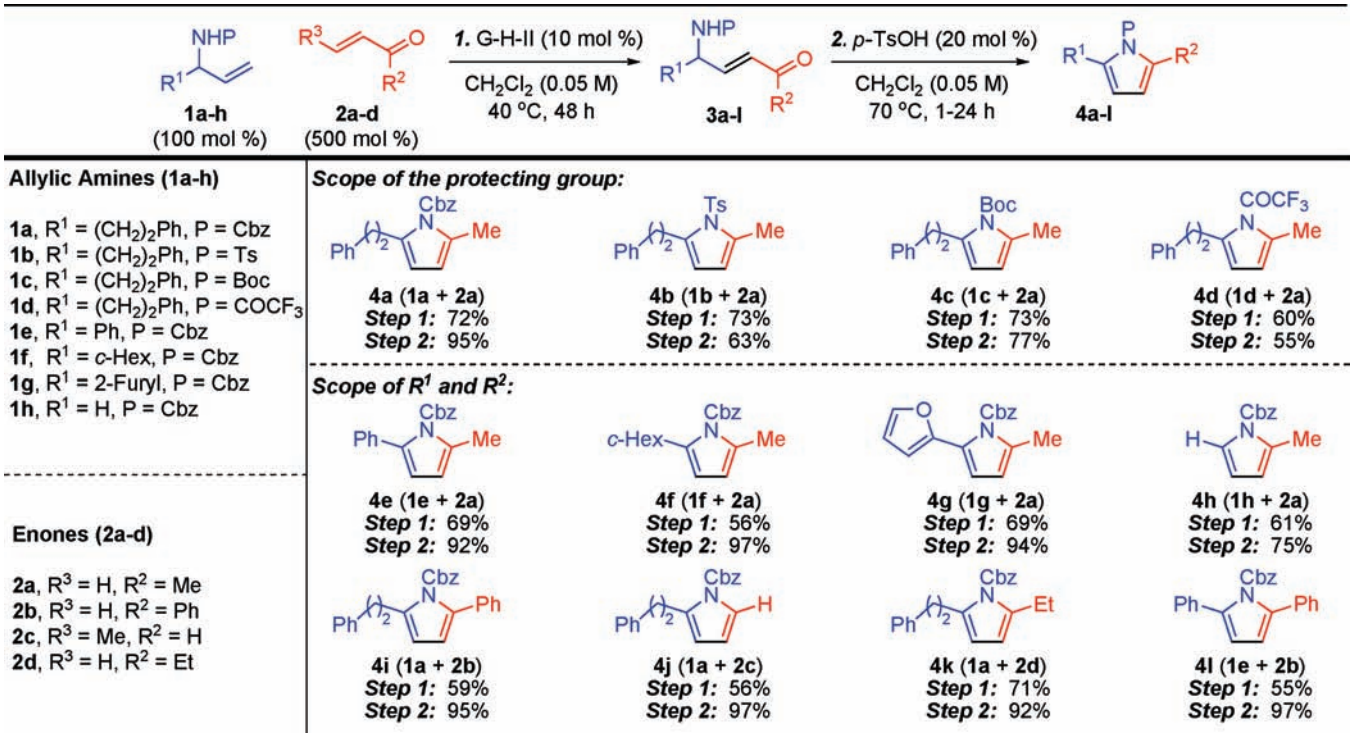
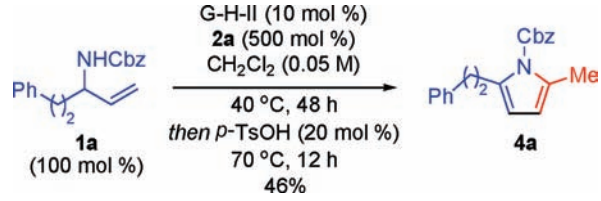
Scheme 2. Mono- and Disubstituted Pyrroles via a CM−Isomerization Tandem[a]



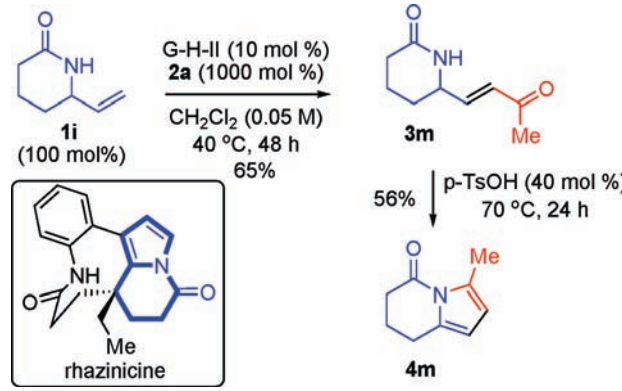
[a] The R^1 and R^2 substituent definitions for **3a**−**l** are the same as for **4a**−**l**.

using 10 mol % Grubbs−Hoveyda second-generation catalyst (G-H-II)[7] in combination with 500 mol % of the enone partner,[8] a series of *trans*-γ-aminoenone intermediates **3a**−**l** were accessible in good yields (55−73%). These species were then converted smoothly to the mono- or 2,5-disubstituted pyrrole targets **4a**−**l** upon exposure to catalytic *p*-TsOH at 70 °C.[9] This sequence tolerates a range of protecting groups on nitrogen (e.g., Cbz, Ts, $COCF_3$) although carbamates were found to be the most effective. Exemplification using a range of Cbz-protected allylic amines (**1a**,**e**−**h**) shows

Scheme 3. One-Pot Pyrrole Formation



Scheme 4. Dihydroindolizinone Synthesis



(2) For reviews on the use of olefin metathesis in the synthesis of aromatic compounds, see: (a) van Otterlo, W. A. L.; de Koning, C. B. *Chem. Rev.* **2009**, *109*, 3743–3782. (b) Donohoe, T. J.; Fishlock, L. P.; Procopiou, P. A. *Chem.—Eur. J.* **2008**, *14*, 5716–5726. (c) Donohoe, T. J.; Orr, A. J.; Bingham, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2664–2670.

(3) β-Alkyl enones prepared by CM have been employed previously for pyrrole synthesis: Poulard, C.; Cornet, J.; Legoupy, S.; Dujardin, G.; Dhal, R.; Huet, F. *Lett. Org. Chem.* **2009**, *6*, 359–361.

(4) CM between N-protected allylic amines and enones has previously been reported on limited substrate ranges. For examples, see: (a) Dewi-Wülfing, P.; Blechert, S. *Eur. J. Org. Chem.* **2006**, 1852–1856. (b) Gebauer, J.; Dewi, P.; Blechert, S. *Tetrahedron Lett.* **2005**, *46*, 43–46. For Lewis acid enhancement, see: (c) Vedrenne, E.; Dupont, H.; Oualef, S.; Elkaïm, L.; Grimaud, L. *Synlett* **2005**, 670–672. For microwave enhancement, see: (d) Ettari, R.; Micale, N.; Schirmeister, T.; Gelhaus, C.; Leippe, M.; Nizi, E.; Di Francesco, M. E.; Grasso, S.; Zappalà, M. *J. Med. Chem.* **2009**, *52*, 2157–2160.

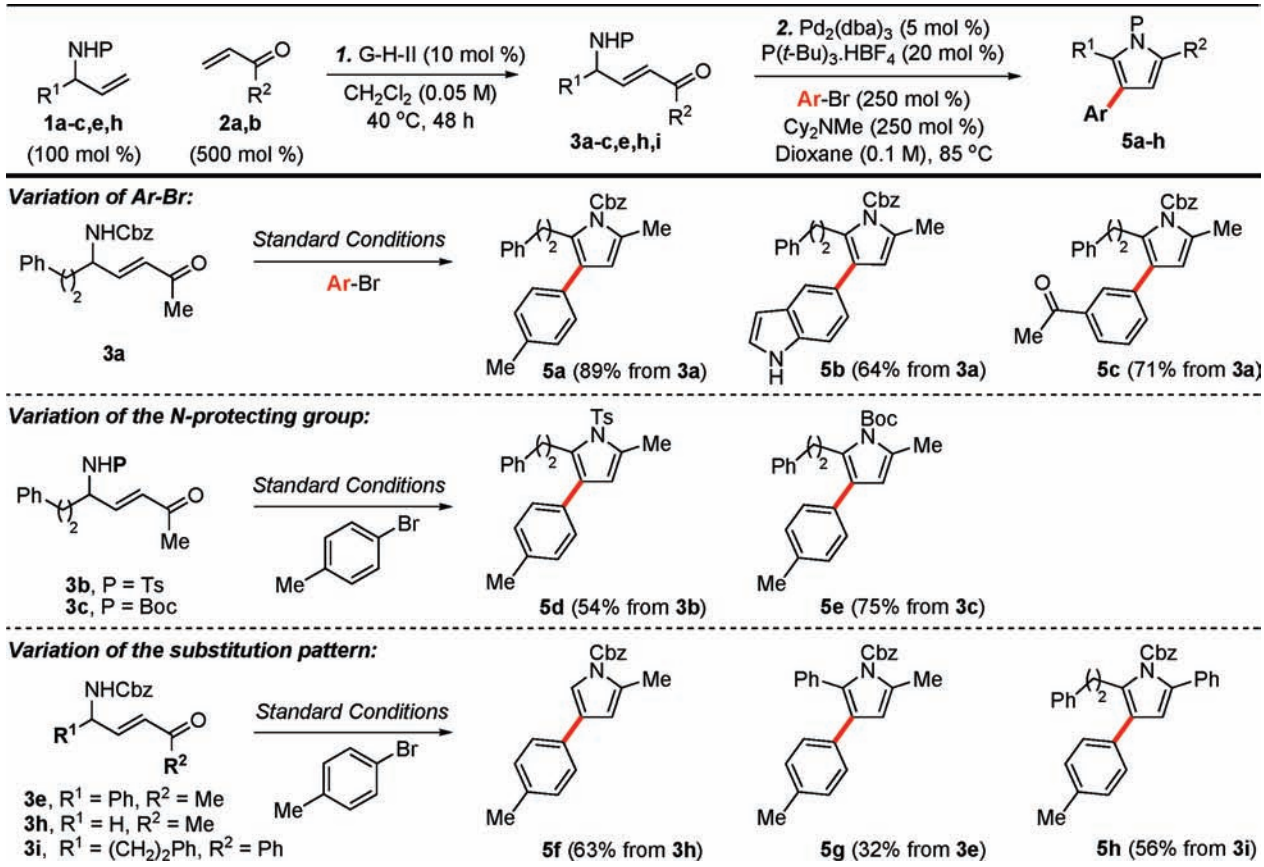
(5) The efficiency of this process may be enhanced by hydrogen bonding between the allylic amine N−H and the chloride ligands associated with G-H-II: Hoveyda, A. H.; Lombardi, P. J.; O'Brien, R. V.; Zhugralin, A. R. *J. Am. Chem. Soc.* **2009**, *131*, 8378–8379.

(6) The Supporting Information gives details for the preparation of the allylic amine derivatives employed here. In general, these were prepared via the corresponding α-amido sulfone. See: Mecozzi, T.; Petrini, M. *J. Org. Chem.* **1999**, *64*, 8970–8972.

(7) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

(8) Lower catalyst or enone loadings result in diminished yields of the CM product (e.g. 5 mol % of G-H-II affords **3a** in ca. 55% yield).

Scheme 5. Di- and Trisubstituted Pyrroles via a CM−Heck Tandem[a]



[a] For the yields of **3a**−**c**,**e**,**h**,**i**, see Scheme 2.

that the process is amenable to the introduction of diverse alkyl or aryl substituents at either R^1 or R^2.

As both the CM and acid-catalyzed cycloaromatization steps are conducted efficiently in CH_2Cl_2, and by analogy with our earlier work on furans,[1] we considered whether a one-pot pyrrole synthesis could be developed. However, using **1a** and **2a** as test substrates, simultaneous employment of both the acid catalyst and G-H-II was not efficient, and only very low conversions (<15%) to pyrrole **4a** were observed. A sequential one-pot protocol, involving addition of *p*-TsOH after completion of the metathesis step, was more promising, and after extensive optimization, pyrrole **4a** was accessible in 46% yield (Scheme 3). Nevertheless, this sequence is still less efficient than the two-step method presented in Scheme 2 (68% yield for **4a**) and so was not exemplified further.

Extension of this chemistry provides access to bicyclic pyrrole derivatives. For example, CM of allylic amide **1i**[10] with methyl vinyl ketone **2a** afforded *trans*-γ-aminoenone **3m** in good yield (Scheme 4). Cyclization of this species was slow,[11] but reasonably efficient, and afforded dihydroindolizinone **4m** in 56% yield. Substructures of this type are common motifs in a range of natural products such as rhazinicine.[12]

Access to trisubstituted pyrrole derivatives is potentially achieved via either (i) CM employing 1,1-disubstituted allylic amine or enone components or (ii) modifying the *trans*-γ-aminoenone intermediates **3a**−**l**. While CM of 1,1-disubstituted derivatives was not effective, Heck arylation of the *trans*-γ-aminoenone intermediates does provide an efficient entry to tri- or disubstituted pyrrole derivatives (Scheme 5). For example, Heck arylation of aminoenone **3a** with bromotoluene, under the conditions reported by Fu,[13] resulted in the isolation of pyrrole **5a** in 89% yield. Extension to the introduction of other aryl groups was readily achieved, and pyrroles **5b** and **5c** were also formed in good yield. This sequence is also able to generate efficiently a variety of differentially protected pyrroles such as **5d** and **5e**. Appropriate choice of aminoenone precursor enables the

(9) Acid-catalyzed cycloaromatization of isolable *trans*-γ-aminoenals/enones has been reported previously: (a) Haidounne, M.; Mornet, R.; Laloue, M. *Tetrahedron Lett.* **1990**, *31*, 1419–1422. (b) Paulus, O.; Alcaraz, G.; Vaultier, M. *Eur. J. Org. Chem.* **2002**, 2565–2572, and references cited therein.

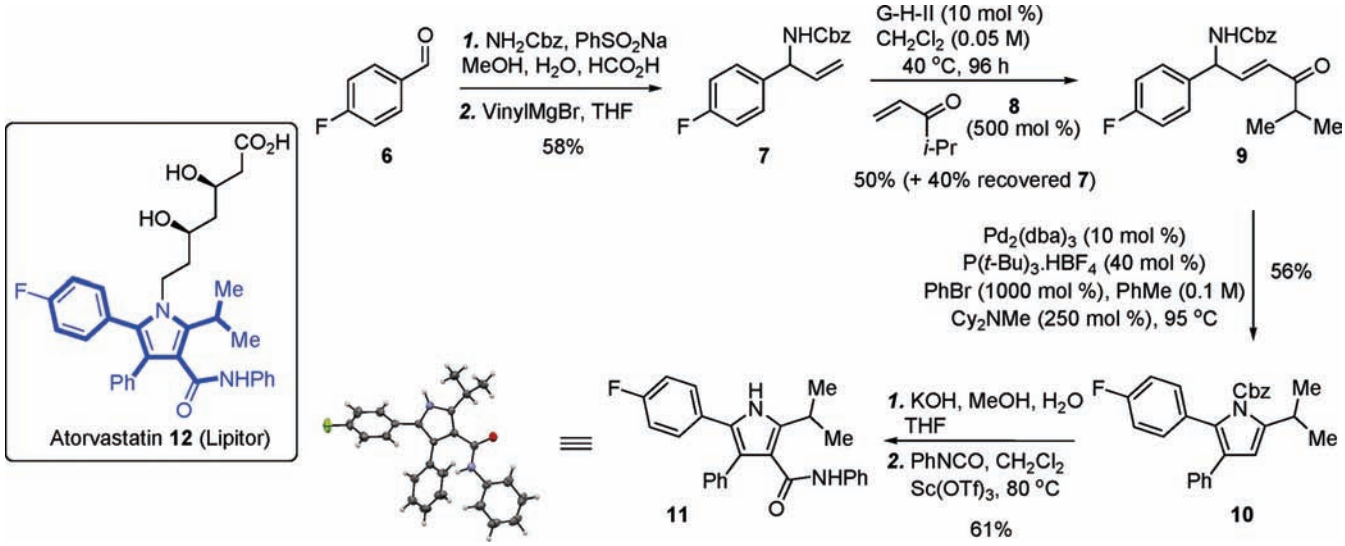
(10) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867–8878.

(11) Cycloaromatization, which requires *trans*- to *cis*-isomerisation of the enone moiety, may proceed via an aziridine intermediate. For **3m**, this would invoke the intermediacy of a strained 6,3-fused ring system which may account for the slow rate of cyclization observed in this case.

(12) Gerasimenko, I.; Sheludko, Y.; Stöckigt, J. *J. Nat. Prod.* **2001**, *64*, 114–116.

(13) Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.

Scheme 6. CM-Based Approach to the Pyrrole Subunit of Atorvastatin



synthesis of 2,4-disubstituted pyrroles (as in **5f**). Finally, as the regiochemistry of the final target is dictated by the nature of the aminoenone precursor, programmable access to various different substitution patterns is readily achieved (cf. alkyl/aryl substitution in **5g** and **5h**).

The *direct* formation of pyrroles from the Heck step is most likely due to mechanistic requirements that were delineated previously in our furan studies.[1] Carbopalladation (*syn*) of the enone moiety is followed by β-hydride elimination (*syn*), and these processes should enforce *trans* to *cis* isomerization of the alkene. The resulting adduct is then perfectly set up for in situ aminal formation and dehydration to the target pyrrole (see Scheme 1, bottom).[14]

The relatively high reactivity of the pyrrole nucleus detracts from applications of this substructure in medicinal chemistry. However, this belies the value of highly substituted derivatives where reactivity is often attenuated. Indeed, such polysubstituted pyrroles have potentially profound medicinal impact, as evidenced by Atorvastatin **12** (Lipitor), the world's largest selling pharmaceutical (Scheme 6).[15] This compound provides a suitable testbed for our CM-based synthetic methodology and also acts as a vehicle to demonstrate that tetrasubstituted pyrroles are available via C−H functionalization of the trisubstituted variants reported here. Accordingly, conversion of aldehyde **6** to allylic amine derivative **7** was readily achieved via the corresponding sulfone.[6] Next, CM of **7** with enone **8**[16] delivered aminoenone **9** in 50% yield. Heck reaction of this species (with bromobenzene) was demanding (cf. pyrrole **5g**), but after optimization, pyrrole **10** was generated in 56% yield. Hydrolytic Cbz deprotection (KOH) was followed by $Sc(OTf)_3$-promoted Friedel−Crafts type acylation with phenylisocyanate to deliver the key tetrasubstituted pyrrole subunit **11** in good yield; the structure of **11** was confirmed by X-ray crystallography (see Supporting Information).[17,18]

In summary, olefin CM provides an efficient and general entry to *trans*-γ-aminoenones which then function as versatile precursors to mono-, di-, and trisubstituted pyrrole derivatives. Tetrasubstituted variants are accessible via functionalization of the remaining pyrrole C−H bond, as demonstrated by a synthesis of the core of Atorvastatin. The methodologies presented here combine readily available precursors in a direct, convergent, and regiocontrolled manner to provide a powerful entry to polysubstituted pyrroles.

Acknowledgment. We thank the EPSRC for financial support and the Oxford Chemical Crystallography Service for use of instrumentation.

Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra and experimental procedures are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) For a related aminal dehydration to afford a pyrrole, see: Mori, M.; Hashimoto, A.; Shibasaki, M. *J. Org. Chem.* **1993**, *58*, 6503–6504.

(15) Roth, B. D. US Patent 5,273,995.

(16) Fujieda, S.; Tomita, M.; Fuhshuku, K.-i.; Ohba, S.; Nishiyama, S.; Sugai, T. *Adv. Synth. Catal.* **2005**, *347*, 1099–1109.

(17) The synthesis of pyrrole **11** has been reported previously: Pandey, P. S.; Rao, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129–131. However, the ^{13}C NMR data obtained for our material are not consistent with that reported earlier. For this reason structural confirmation of **11** was undertaken by X-ray crystallography. This, in conjunction with 2D NMR and nOe data, also underpins the structural assignment of the other pyrroles presented in this paper (see Supporting Information).

(18) Selective (but low yielding; < 20%) N-alkylation of **11** with 2-(2-bromoethyl)-1,3-dioxolane (see Supporting Information) affords an intermediate which has been converted previously to **12** in 4 steps: Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Stratton, C. D.; Wilson, M. W. *J. Med. Chem.* **1991**, *34*, 357–366. We are currently investigating strategies for the efficient and direct installation of a fully functionalized side chain.