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Furanosteroid studies. Improved synthesis of the A,B,C,E-ring core of viridin

Kristen C. Mascall, Peter A. Jacobi *

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

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ABSTRACT

The tetracyclic core skeleton of the furanosteroid viridin is prepared in nine steps from readily available materials. The key step in the synthesis is a facile acid-promoted cyclodehydration of an aryloxyketone to prepare the benzofuran moiety. From this intermediate, the known target skeleton is prepared in four steps. This new synthesis is a six-step improvement over the previously reported one.

The furanosteroids make up a small class of natural products known for their novel pentacyclic skeleton—in addition to the usual steroidal scaffold, there is a furan ring fused at the C4 and C6 positions. This ring introduces considerable strain in the skeleton, and is the site of biological activity of these compounds. The parent members of the furanosteroid class of natural products are viridin (**1**) and wortmannin (**2**) (Fig. 1).[1]

Isolated in 1945 and 1957, respectively,[2a] these natural products were long known for their high antifungal and anti-inflammatory activity.[2b] More recently, wortmannin (**2**) was recognized as a potent bimodal inhibitor of phosphoinositide-3 kinases (PI-3K),[2c,d] a family of enzymes involved in the intracellular signaling pathway essential for the growth and development of cells. Wortmannin (**2**) has a strong affinity for the ATP-pocket of the enzyme, and binds tightly through a series of hydrogen bonds. Although this interaction is sufficient to inhibit enzymatic activity, the structure–activity studies have shown that C20 of the furan ring in **2** binds irreversibly to a lysine residue of the PI-3 kinase, rendering the inhibition irreversible (Fig. 2).[2e,f] This position on the furan ring is made highly electrophilic due to the flanking carbonyl groups. It is believed that inhibitors of PI-3Ks related to **2** can be developed into remedial agents for diseases characterized by rapid cell proliferation, such as cancer.

However, **2** is unselective and interacts with many other biological targets, and the enhanced electrophilicity of the furan ring makes **2** very susceptible to hydrolysis.[1b] These toxicity and instability issues make the natural products unsuitable for clinical use. Thus, structural analogs of the furanosteroids are attractive

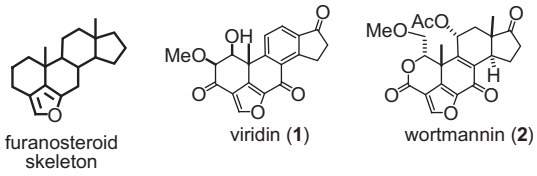

Figure 1. Parent members of furanosteroid class, viridin (**1**) and wortmannin (**2**).

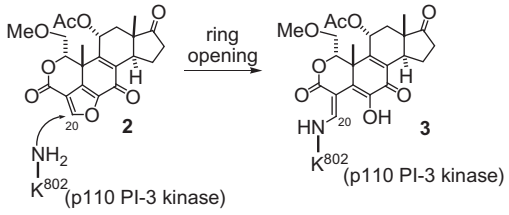

Figure 2. Covalent PI-3K inhibition of wortmannin (**2**).

synthetic targets in the ongoing discovery and development of anti-cancer drugs.[3] Although viridin (**1**) and wortmannin (**2**) have been known for over half a century, only one synthesis of **1** has been reported,[4] and two syntheses of **2** (one de novo).[5] In other noteworthy work, the pentacyclic skeleton of viridin has been prepared in nine steps via an *ortho*-quinone Diels–Alder reaction.[6] Indeed, the furanosteroid skeleton itself is a synthetic challenge.[7] Previously, the viridin core skeleton **4** has been prepared in 15 steps from commercially available materials, utilizing an intramolecular Diels–Alder/*retro* Diels–Alder (DA) reaction between a

* Corresponding author. Tel.: +1 603 646 3495; fax: +1 603 646 3946.
E-mail address: peter.jacobi@dartmouth.edu (P.A. Jacobi).

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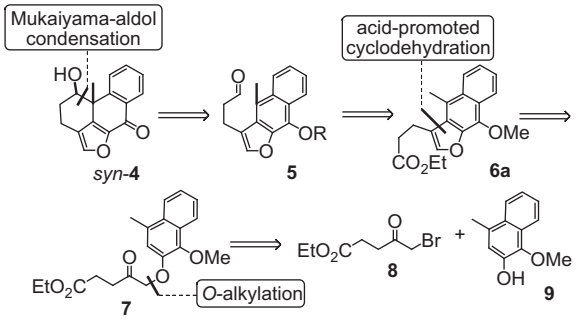


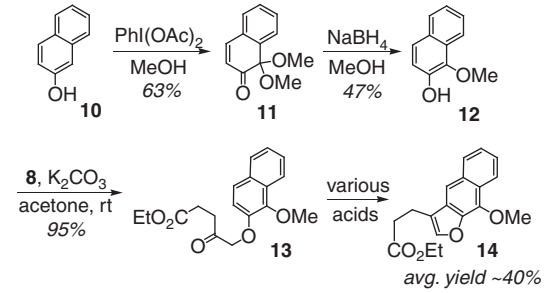
Scheme 1. Synthetic analysis of viridin model **4**.

tethered alkyne and oxazole as the key step.[8] The final step of the synthesis was a Mukaiyama-aldol cyclization which gave tetracycle **4**, with the desired *syn*-isomer predominating under kinetic control due to a more favorable Burgi–Dunitz angle.[9]

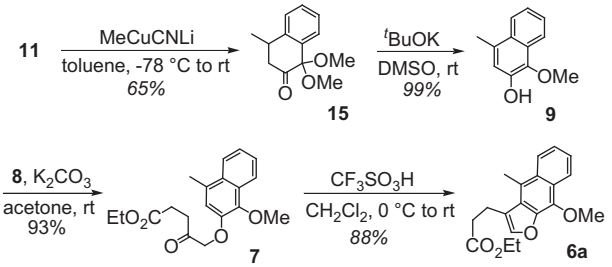
In this letter, a new approach to the viridin core skeleton is described, which utilizes an acid-promoted cyclodehydration of an aryloxyketone to form the benzofuran.[10] Our synthetic analysis for **4** is outlined in Scheme 1. We envisioned that the final C1–C10 bond connection would be made via an intramolecular aldol condensation of **5**, a transformation that was previously used in the synthesis of **4**.[8] Aldehyde **5** would be derived in a sequence of steps from **6a**, which would be prepared via the cyclodehydration of aryloxyketone **7**.[11] Finally, the cyclodehydration precursor **7** would be prepared by O-alkylation of an appropriately functionalized naphthol.

In the first synthetic approach to **4**, we chose naphthol **12** as the starting point, since this material could easily be prepared in two steps from 2-naphthol (**10**) as reported in the literature.[12] We proposed that the necessary C4 methyl group could be installed at a later stage. Alkylation of **12** with α-bromoketone **8**[13] proceeded under standard conditions to give aryloxyketone **13**. Cyclodehydration of **13** was studied extensively using various acids and reaction conditions, but it became apparent that **13** was a poor substrate for cyclization. Of the acids tested,[14] only PPA and CF_3SO_3H induced cyclodehydration of **13**, but benzofuran **14** was consistently obtained in unsatisfactory yield (Scheme 2). Optimization studies were performed with these acids but there was no improvement in yield.

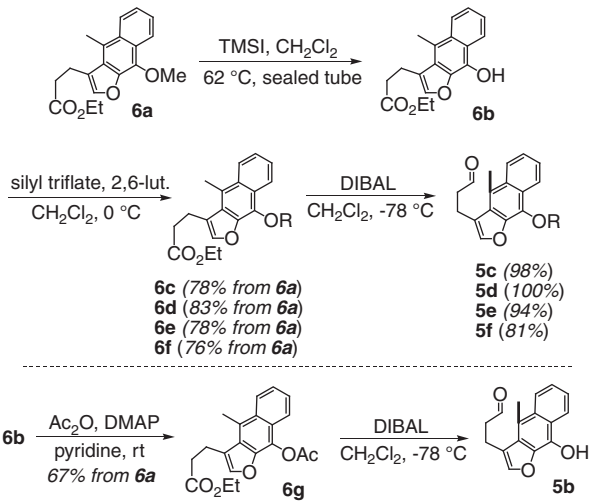
We postulated that the cyclodehydration reaction could be improved by starting the synthesis with a more electron-rich naphthol such as **9**, where the C4 methyl group was already in place. A search of the literature revealed that naphthols with the required substitution pattern of **9** were relatively uncommon. Despite this apparent lack of precedent, the focus shifted to the preparation of **9**. After some synthetic studies, we were pleased to find that this compound could be prepared in three steps from 2-naphthol (**10**). As before, oxidative dearomatization of **10** gave **11** (cf. Scheme 2),[12a] and by exploiting the imbedded enone functionality, the C4 methyl group was introduced via conjugate addition of MeCuCNLi to give ketone **15**. This intermediate is on the same oxidation level as the target naphthol, and a simple keto-enol tautomerization followed by the elimination of a molecule of MeOH would give **9**. This transformation was serendipitously achieved in quantitative yield using ^{t}BuOK in DMSO. Thus, **9** can be prepared efficiently on gram scale in good overall yield (41% from **10**). Alkylation with **8** gave the key aryloxyketone **7**, and gratifyingly, when **7** was treated with CF_3SO_3H (5 equiv), benzofuran **6a** was obtained in high yield (Scheme 3).



Scheme 2. First generation cyclodehydration approach.



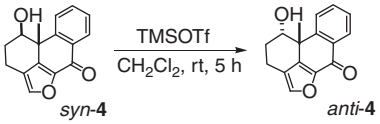
Scheme 3. Second generation cyclodehydration approach.



a) R = Me. **b**) R = H. **c**) R = TMS. **d**) R = TES. **e**) R = TBS. **f**) R = TIPS. **g**) R = Ac

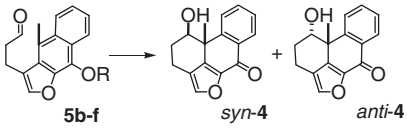
Scheme 4. Synthesis of aldol cyclization precursors.

Next, the focus of the synthesis turned to the Mukaiyama-aldol cyclization to form the final C1–C10 bond as shown in the retrosynthetic scheme (**54**). This key step was well-precedented, since it was successfully used to prepare *syn*- and *anti*-**4** in a favorable 4:1 ratio from aldehyde **5e** (R = TBS). For this particular transformation, many reagents and conditions were screened, and it was found that $TiCl_4$ in CH_2Cl_2 at rt gave the best result.[15] As an extension of this study, we chose to investigate the substrate effect in the reaction by varying the protecting group 'R' on the phenol. In addition to the usual class of Mukaiyama-aldol reactants, where



Scheme 5. Isomerization of *syn*-**4** with TMSOTf.

Table 1
Intramolecular Mukaiyama-aldol cyclization studies of **5b–f**

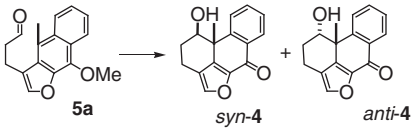


b) R = H. **c**) R = TMS. **d**) R = TES. **e**) R = TBS. **f**) R = TIPS.

	Substrate	% Conversion[a]	*syn*-**4**[b]	*anti*-**4**[b]	**5b**[b]
1	**5b**	0	—	—	100
2	**5c**	100	21	7	72
3	**5d**	100	55 (40)	11 (10)	34
4	**5e**	100	80 (46)	20 (11)	—
5	**5f**	100	89 (55)	11 (11)	—
6[c]	**5c**	100	—	—	100
7[c]	**5d**	100	—	—	100
8[c]	**5e**	90	40	10	40
9[d]	**5b**	100	(11)	(22)	—
10[d]	**5e**	100	—	100	—

Reagents and conditions: $TiCl_4$, CH_2Cl_2, rt; reaction progress monitored by TLC.
[a] % conversion based on unreacted starting material.
[b] Ratios determined by ^1H NMR integrations; isolated yields in parentheses. Low isolated yields are due to the instability of *syn*-**4** and *anti*-**4** at room temperature.
[c] Reaction run at −78 °C.
[d] TMSOTf instead of $TiCl_4$.

Table 2
Cyclization studies of aldehyde **5a**



	Reagent	% Conversion[a]	*syn*-**4**[b]	*anti*-**4**[b]	**5b**[b]
1	$TiCl_4$	0	—	—	—
2[c]	BBr_3	—[d]	—	—	—
3	TMSI	—[d]	—	—	—
4	TMSOTf	15[d]	—	15	—
5	$TiCl_4$/NaI	29	—	29	—
6	$TiCl_4$/LiI	20	—	20	—
7	BBr_3/NaI	16	—	8	8
8[e]	$TiCl_4$/TMSI	75	50 (30)	25 (20)	—
9[f]	$TiCl_4$/TMSI	0	—	—	—
10[g]	$TiCl_4$/TMSI	50	17 (8)	33	(12)

Reagents and conditions: reagent, CH_2Cl_2, rt; reaction progress monitored by TLC.
[a] % conversion based on unreacted starting material.
[b] Ratios determined by ^1H NMR integrations; isolated yield in parentheses.
[c] Reaction run at −78 °C.
[d] Predominant decomposition.
[e] $TiCl_4$ was added one minute after adding TMSI.
[f] $TiCl_4$ and **5a** were stirred together at rt for 35 min before adding TMSI.
[g] TMSI and **5a** were stirred together at rt for 35 min before adding $TiCl_4$.

R = silyl, we were interested in the cyclization potential of methyl ether aldehyde **5a** and phenol aldehyde **5b**. With ample quantities of **6a** readily available, a small library of cyclization substrates was prepared as outlined in Scheme 4. The silyl-protected phenol aldehydes **5c–f** were prepared by demethylating **6a** with TMSI,[16] then protecting the unstable phenol as the appropriate silyl ether under standard conditions. Facile DIBAL reduction of the ester group gave the desired aldehydes. By maintaining a low reaction temperature and quenching at −78 °C, no over-reduction of the ester was observed, even in the presence of excess DIBAL reagent.

Phenol aldehyde **5b** is susceptible to air oxidation, and it had to be synthesized and used directly without purification. We found it expedient to demethylate **6a**, and then convert it to the corresponding acetate **6g**. In the subsequent step, treatment with DIBAL reduced the ester cleanly and removed the acyl-protecting group in the same pot to give **5b**. Attempts to reduce the ester in **6b** directly resulted in either incomplete conversion at −78 °C, or over-reduction at higher temperature. Furthermore, demethylation of **5a** was unsuccessful, resulting in decomposition.

Using the conditions developed for **5e**, the Mukaiyama-aldol reaction of **5b–f** was studied (Table 1). We were pleased to find that the ring closure occurred in every case (entries 2–5), except for **5b**, which gave no reaction (entry 1). Furthermore, the size of the silyl group did affect the product ratios. In general, desilylation was predominant with substrates bearing smaller silyl protecting groups (**5c, d**), while more favorable results were achieved with the larger groups. Thus, **5f** (R = TIPS) gave an improved ratio of *syn*/*anti*-**4** (89:11; entry 5),[17] compared to **5e** (80:20; entry 4). Finally, lowering the reaction temperature was detrimental, giving either complete desilylation (entries 6 and 7), or sluggish cyclization (entry 8).

Since **5b** was unreactive toward $TiCl_4$, other Lewis acids were screened, and the only one that induced ring closure was TMSOTf (entry 9). However, the product distribution was unfavorable (*syn*/*anti* = 1:2), and the isolated yield was poor (33%). Although these results were not synthetically useful, we were satisfied to know that **5b** was able to undergo cyclization.

The last substrate to be tested in the Mukaiyama-aldol cyclization was **5a** (Table 2). Cyclization of this aldehyde would provide the shortest route to tetracycle **4**, since protecting group manipulation would be avoided. Under the standard cyclization conditions, no reaction was observed (entry 1). Other reagents resulted in decomposition. When $TiCl_4$ was combined with NaI or LiI, a trace of *anti*-**4** was detected by NMR (entries 5 and 6). The combination of $TiCl_4$ and TMSI gave an encouraging *syn*- to *anti*-**4** ratio of 50:25 (entry 8). No reaction was observed when $TiCl_4$ and **5a** were allowed to stir together for 35 min before adding TMSI (entry 9). Conversely, when TMSI and **5a** were stirred together for 35 min before adding $TiCl_4$ (entry 10), some cyclization was observed, but the ratio of desired to undesired isomer was worse than that observed in entry 8. To date, cyclization of **5a** with TMSI/$TiCl_4$ as shown in entry 8 gives the best ratio of *syn*- to *anti*-**4**.

The isomerization of *syn*-**4** to its *anti*-isomer was also briefly investigated. It was already shown that the ratio obtained from cyclization of **5e** was a kinetic one, and subjecting either isomer to the standard reaction conditions ($TiCl_4$, CH_2Cl_2, rt) resulted in no equilibration.[8] However, we noticed that cyclizations of **5b**, **5c**, and **5e** with TMSOTf appeared to favor the formation of the *anti*-isomer, and it was hypothesized that this reagent was promoting equilibration of *syn*-**4** and *anti*-**4**, presumably through **5b**. This hypothesis is supported by DFT calculations, which predict that *anti*-**4** is more stable in CH_2Cl_2 than *syn*-**4** by approximately 2 kcal/mol, mainly due to differences in solvation energy.[18] In the event, when *syn*-**4** was treated with TMSOTf at ambient temperature, the *anti*-isomer was almost immediately detectable by TLC (Scheme 5). After 5 h, TLC and proton NMR analysis indicated that all of the *syn*-isomer was converted to *anti*-**4**, although the conversion was not quantitative (decomposition poses a problem in these systems after prolonged reaction times). Nevertheless, we have shown that we can equilibrate *syn*-**4** to its thermodynamic isomer with TMSOTf, supporting our hypothesis.

In conclusion, tetracycle **4** has been successfully prepared by the new cyclodehydration approach, with an improvement in product ratio. This synthesis is more efficient than the previous route, and provides us with larger quantities of material in order

to study these tetracyclic systems in greater detail. Further transformations of **4** and its derivatives are currently under investigation, and will be reported in due course.

Acknowledgments

Financial support of this work by the National Science Foundation, CHE-0646876, and Dartmouth College is gratefully acknowledged. We are grateful to Professor Russell Hughes of the Dartmouth College Chemistry Department for carrying out DFT calculations on compounds *syn*-**4** and *anti*-**4**.[18]

Supplementary data

Supplementary data (experimental and NMR spectra for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.01.070.

References and notes

1. For reviews, see: (a) Hanson, J. R. *Nat. Prod. Rep.* **1995**, *12*, 381; (b) Wipf, P.; Halter, R. J. *Org. Biomol. Chem.* **2005**, *3*, 2053.
2. (a) Brian, P. W.; McGowan, J. C. *Nature (London)* **1945**, *156*, 144; (b) Vischer, E. B.; Howland, S. R.; Raudnitz, H. *Nature* **1950**, *165*, 528; (c) Powis, G.; Bonjouklian, R.; Berggren, M. M.; Gallegos, A.; Abraham, R.; Ashendel, C.; Zalkow, L.; Matter, W. F.; Dodge, J.; Grindey, G.; Vlahos, C. J. *Cancer Res.* **1994**, *54*, 2419; (d) Wymann, M. P.; Bulgarelli-Leva, G.; Zvelebil, M. J.; Pirola, L.; VanHaese-Broeck, B.; Waterfield, M. D.; Panayotou, G. *Mol. Cell. Biol.* **1996**, *16*, 1722; (e) Norman, B. H.; Paschal, J.; Vlahos, C. J. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1183; (f) Norman, B. H.; Shih, C.; Toth, J. E.; Ray, J. E.; Dodge, J. A.; Johnson, D. W.; Rutherford, P. G.; Schultz, R. M.; Worzalla, J. F.; Vlahos, C. J. *J. Med. Chem.* **1996**, *39*, 1106.
3. Wipf, P.; Minion, D. J.; Halter, R. J.; Berggren, M. I.; Ho, C. B.; Chiang, G. G.; Kirkpatrick, L.; Abraham, R.; Powis, G. *Org. Biomol. Chem.* **1911**, *2004*, 2.
4. Anderson, E. A.; Alexanian, E. J.; Sorensen, E. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 1998.
5. (a) Sato, S.; Nakada, M.; Shibasaki, M. *Tetrahedron Lett.* **1996**, *37*, 6141; (b) Mizutani, T.; Honzawa, S.; Tosaki, S.-Y.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4680.
6. (a) Souza, F. E. S.; Rodrigo, R. *Chem. Commun.* **1947**, *1999*, 19; (b) Lang, Y.; Souza, F. E. S.; Xu, X.; Taylor, N. J.; Assoud, A. Rodrigo, R *J. Org. Chem.* **2009**, *74*, 5429.
7. For synthetic studies toward the furanosteroid class of compounds, see: (a) Moffatt, J. S. *J. Chem. Soc. (C)* **1966**, *734*; (b) Yasuchika, Y.; Kenji, H.; Kanematsu, K. *Chem. Commun.* **1987**, 515; (c) Broka, C. A.; Ruhland, B. *J. Org. Chem.* **1992**, *57*, 4888; (d) Carlina, R.; Higgs, K.; Older, C.; Randhawa, S.; Rodrigo, R. *J. Org. Chem.* **1997**, *62*, 2330; (e) Boynton, J.; Hanson, J. R.; Kiran, I. *J. Chem. Res. (S)* **1999**, *638*; (f) Wright, D. L.; Robotham, C. V.; Aboud, K. *Tetrahedron Lett.* **2002**, *43*, 943; (g) Sessions, E. H.; O'Connor, R. T.; Jacobi, P. A. *Org. Lett.* **2007**, *9*, 3221; (h) Muller, K. M.; Keay, B. A. *Synlett* **2008**, 1236; (i) Sundstrom, T. J.; Wright, D. L. *Synlett* **2010**, 2875.
8. Sessions, E. H.; Jacobi, P. A. *Org. Lett.* **2006**, *8*, 4125.
9. Burgi, H. B.; Dunitz, J. D. *Acc. Chem. Res.* **1983**, *16*, 153.
10. Cagniant, P.; Cagniant, D. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1975; Vol. 18, pp 337–473.
11. Representative examples of cyclodehydration of aryloxyketones in synthesis: (a) Hirai, Y.; Doe, M.; Kinoshita, T.; Morimoto, Y. *Chem. Lett.* **2004**, *33*, 136; (b) Marugán, J. J.; Manthey, C.; Anaclerio, B.; LaFrance, L.; Lu, T.; Markotan, T.; Leonard, K. A.; Crysler, C.; Eisennagel, S.; Dasgupta, M.; Tomczuk, B. *J. Med. Chem.* **2005**, *48*, 926; (c) Kedrowski, B. L.; Hoppe, R. W. *J. Org. Chem.* **2008**, *73*, 5177; (d) Davydenko, I. G.; Slominskii, Y. L.; Kalchenko, O. I.; Gutov, A. V.; Chernega, A. N.; Tolmachev, A. I. *Russ. Chem., Bull. Int. Ed* **2008**, *57*, 159; (e) Kim, I.; Choi, J. *Org. Biomol. Chem.* **2009**, *7*, 2788; (f) Kim, K.; Kim, I. *Org. Lett.* **2010**, *12*, 5314.
12. (a) Mal, D.; Roy, H. N.; Hazra, N. K.; Adhikari, S. *Tetrahedron* **1997**, *53*, 2177; (b) Dolson, M. G.; Jackson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun* **1979**, *327*.
13. Stearns, B. A.; Clark, R. WO 2010/085820 A2, 2010.
14. Representative examples of acids tested include: $TiCl_4$, $AlCl_3$, $BF_3{\cdot}OMe_2$, BCl_3, $Ga(OTf)_3$, $Bi(OTf)_3$, CF_3CO_2H, CF_3SO_3H, *p*-TsOH, H_2SO_4, PPA, P_2O_5-CH_3SO_3H (Eaton's reagent). Except for CF_3SO_3H and PPA, these acids resulted in either dealkylation of **13**, decomposition, or no reaction.
15. Sessions, E. H. Ph.D. Dissertation, Dartmouth College, 2006.
16. We found that commercially available TMSI worked best in this reaction. Other reagents such as BBr_3 (McOmie, J. F. W.; Watts, M. L.; West, D. E. *Tetrahedron*, **1968**, *24*, 2289) and in-situ generated TMSI (Olah, G. A.; Narang, S. C.; Balaram Gupta, B. G.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247) did not work as well. For a review of ether cleavage, see: Bhatt, M. V.; Kulkarni, S. U. *Synthesis*, **1983**, 249.
17. Representative procedure for the Mukaiyama-aldol cyclization of **5f**–**4**. Aldehyde **5f** (0.20 mmol, 1.0 equiv) is dissolved in dry CH_2Cl_2 (21 mL) at rt under nitrogen, and $TiCl_4$ (0.42 mmol of a 1.0 M solution in CH_2Cl_2, 2.1 equiv) is added dropwise. The resulting dark–green reaction mixture is stirred at rt for 45–50 min (prolonged reaction times cause decomposition), then diluted with CH_2Cl_2 and washed with water. The aqueous layer is extracted twice with CH_2Cl_2 and the combined organic layers are washed with brine and dried over $MgSO_4$. After concentration, the crude product mixture is purified by flash chromatography to give *syn*-**4** and *anti*-**4** as unstable brown oils.
18. Calculations were carried out using Jaguar 7.7 (B3LYP/LACV3P** + +); Poisson-Boltzmann solvation method.