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Segment-Coupling Prins Cyclizations

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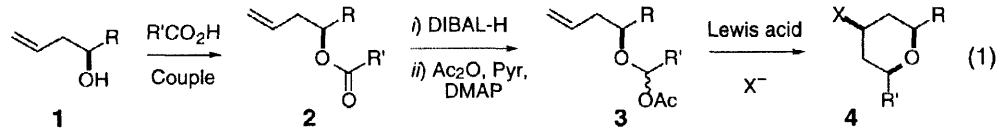
Abstract: A segment-coupling Prins cyclization was developed involving (1) esterification, (2) reductive acetylation and (3) Lewis acid promoted cyclization. A model for the bis-tetrahydropyran segment of phorboxazole was successful assembled using this new method.

The Prins cyclization is one of the most effective reactions for the synthesis of tetrahydropyrans.[1] Most Prins cyclizations involve the coupling of homoallylic alcohols with several equivalents of simple aldehydes under acid catalysis.[1,2] Simple or mixed acetals can be used in the place of the aldehyde,[3] and the use of allylsilane analogs of the homoallylic alcohols facilitate the cyclizations.[4] The most intriguing Prins cyclizations involve couplings of two complex pieces to form new rings. Overman's group has used this strategy very effectively to assemble medium rings in the convergent syntheses of natural products derived from the genus *Laurencia*.[5] One of the principle limitations of this segment-coupling strategy is the lack of effective methods to prepare the complex mixed acetal precursors for the cyclization. Recently, we developed an efficient method for converting esters to α-acetoxy ethers.[6] The α-acetoxy ethers are useful Prins cyclization substrates, and we now report an efficient new segment-coupling Prins cyclization based on these intermediates.

The segment-coupling strategy is outlined in eq 1. The two complex fragments will be coupled by esterification, one of the most reliable reactions in organic synthesis. Reduction with DIBAL-H and *in situ* acetylation of the intermediate aluminum hemiacetal will produce the α-acetoxy ether **3**. In general, this transformation is effective when the aluminum hemiacetal is stable (i.e. when DIBAL-H reduction of the ester gives an aldehyde.) Treatment with a Lewis acid will generate an intermediate oxonium ion, and subsequent Prins cyclization will give the all-cis tetrahydropyran **4**.



(1)

The strategy is effective. Convergent syntheses of a number of simple tetrahydropyrans using this strategy are outlined in Table 1. The esters were prepared from the acid chlorides or anhydrides. Reductive acetylation worked very well, producing the α-acetoxy ethers in good yield. Cyclization using $TiCl_4$ as a

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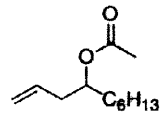
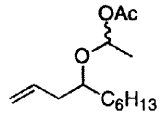
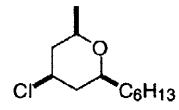
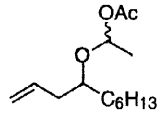
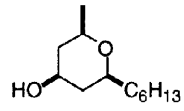
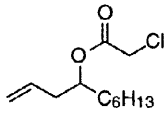
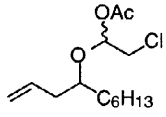
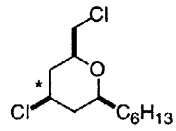
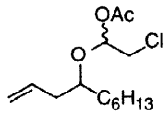
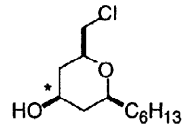
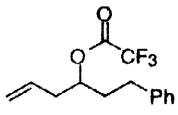
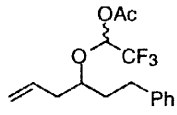
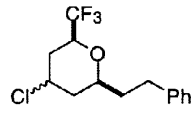
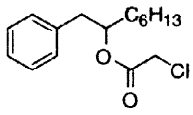
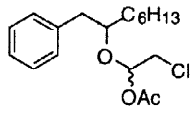
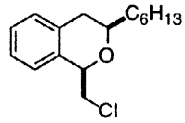
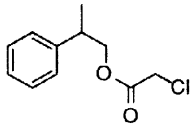
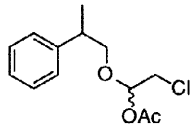
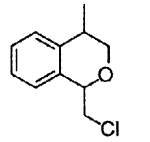
Table 1. Prins Reaction of Hemiacetal Acetates

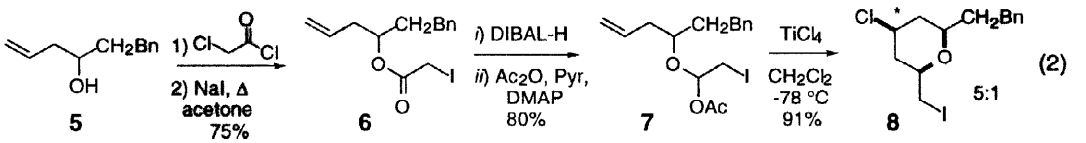
Entry	Ester	Condition	Hemiacetal	Condition	Rearrangement Product	Yield
1		A (87%)		B		80%
2				C		79%
3		A (94%)		B		95% (7:1)
4				C		80% (8:1)
5		A (86%)		B		65% (1:1.5)
6		A (91%)		B		90%
7		A (96%)		B		97% (3:1)

A: *i.* DIBAL-H, –78°C; *ii.* pyridine, DMAP, Ac_2O, –78°C to 0°C.
B: $TiCl_4$, CH_2Cl_2, –78°C.
C: *i.* TFAA, HOAc, CH_2Cl_2, 0°C to r.t ; *ii.* K_2CO_3, MeOH

Lewis acid lead to tetrahydrofurans in good to excellent yields. The trifluoromethyl substituent lead to a mixture of equatorial and axial 4-chloro products (entry 5), but otherwise the all-cis selectivity was good to excellent.[7] Although many of these tetrahydrofurans could be prepared from the appropriate aldehydes, these highly reactive aldehydes are noxious and unpleasant to handle.

Alkyl iodides are effective substrates for convergent synthesis. They are particularly easy to alkylate, and is often the leaving group of choice for carbon-carbon bond forming alkylations.[8] Eq 2 shows

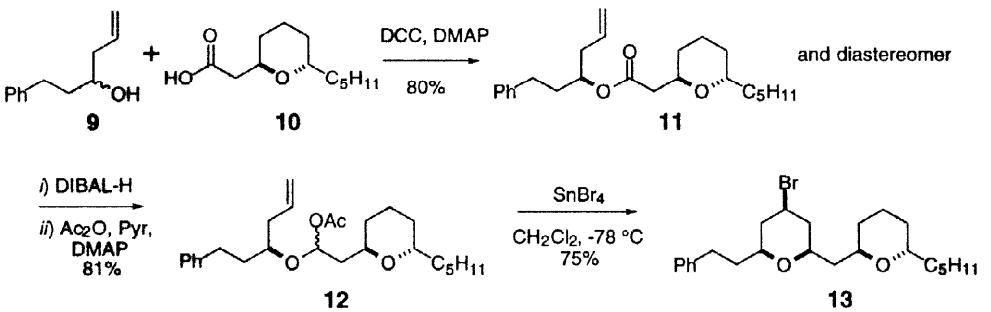
the introduction of an iodomethyl substituent in the Prins cyclization. Esterification of alcohol **5** with chloroacetyl chloride was more effective than with iodoacetic acid. Finkelstein reaction gave the iodo ester **6**, and reductive acetylation gave the α-acetoxy ether **7** in good yield. The α-acetoxy ether intermediates were invariably produced as a mixture of diastereomers, which had no effect on the subsequent cyclization. Prins cyclization with $TiCl_4$ generated the all-cis tetrahydropyran **8** as a 5:1 mixture favoring the equatorial isomer. The iodomethyl functionality will facilitate further coupling reactions.



(2)

Phorboxazoles A and B are remarkably potent anticancer agents with a complex structure that includes several tetrahydropyran rings.[9] They have attracted the interest of synthetic chemists,[10] and the first total synthesis was recently reported by Forsyth.[11] An efficient segment-coupling reaction would facilitate the assembly to the C1-C15 bis-tetrahydropyran fragment, and a model for this coupling is shown in Scheme 1. Esterification of the *trans*-tetrahydropyran **10** with the homoallylic alcohol **9** gave **11**. In this model system, both segments were racemic and so two diastereomers of the ester **11** were isolated. Reductive acetylation lead to a diastereomeric mixture α-acetoxy ethers **12**. Cyclization with $SnBr_4$ gave the all-cis tetrahydropyran **13** in good overall yield. This model coupling illustrates the power of a segment-coupling Prins cyclization for natural products synthesis.

Scheme 1



Sample Prins cyclization of an α-acetoxy ether:
(*2S*,4S*,6R**)-2-Hexyl-4-hydroxy-6-methyl-tetrahydropyran (entry 2): To a solution of the α-acetoxy ether (89.8 mg, 0.37 mmol) in 3.7 mL dry methylene chloride under N_2 at 0 °C, was added HOAc (0.21 mL, 3.70 mmol) and trifluoroacetic anhydride (0.52 mL, 3.70 mmol). The reaction was warmed to room temperature and stirred for 2 h until no starting material was observed by TLC. The reaction was quenched with saturated $NaHCO_3$, and the mixture extracted with CH_2Cl_2, dried, filtered and concentrated. The resulting residue was treated with K_2CO_3 in 5 mL methanol at room temperature for 3 h. The methanol was removed under reduced pressure. Water was added and the mixture was extracted with ethyl acetate (× 3). The organic layer was dried, filtered and concentrated. Chromatography on silica gel (20–25% ethyl acetate/hexanes) gave the product (58.6 mg, 0.29 mmol, 79%) as a colorless oil. ^1H NMR ($CDCl_3$, 300

MHz) δ 3.75 (tt, J = 11.0, 4.7 Hz, 1 H); 3.40 (qdd, J = 6.9, 1.6, 11.1 Hz, 1 H); 3.21–3.28 (m, 1 H); 1.88–1.94 (m, 3 H); 1.55–1.57 (m, 1 H); 1.03–1.43 (m, 15 H); 0.86 (t, J = 6.9 Hz, 3 H). **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 75.6, 71.5, 68.2, 43.0, 40.9, 36.1, 31.8, 29.3, 25.5, 22.6, 21.7, 14.0. **IR (neat, cm^{-1})** 3358 (br), 2933, 2857, 1456; **MS (HREI)** Calcd for $C_{12}H_{24}O_2$, 200.1776 (M); Obsd, 200.1770 (M). Anal. Calcd for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.15; H, 11.86.

Acknowledgments. Financial support was provided by the University of California, Irvine.

References and Notes

1 Snider, B. B. in *Comprehensive Organic Synthesis*, ; Trost, B. M., Fleming, I. and Heathcock, C. H., Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 527–61.

2 (a) Stapp, P. R. *J. Org. Chem.* **1969**, *34*, 479–85. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661-72.

3 (a) Winstead, R. C.; Simpson, T. H.; Lock, G. A.; Schiavelli, M. D.; Thompson, D. W. *J. Org. Chem.* **1986**, *51*, 275–7. (b) Nikolic, N. A.; Gonda, E.; Longford, C. P. D.; Lane, N. T.; Thompson, D. W. *J. Org. Chem.* **1989**, *54*, 2748–51. (c) Blumenkopf, T. A.; Bratz, M.; Castaneda, A.; Look, G. C.; Overman, L. E.; Rodriguez, D.; Thompson, A. S. *J. Am. Chem. Soc.* **1990**, *112*, 4386–99.

4 (a) Marko, I. E.; Mekhalfia, A.; Bayston, D. J.; Adams, H. *J. Org. Chem.* **1992**, *57*, 2211–3. (b) Mohr, P. *Tetrahedron Lett.* **1993**, *34*, 6251–4. (c) Marko, I. E.; Bayston, D. J. *Tetrahedron Lett.* **1993**, *34*, 6595–8.

5 Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248–56. (b) Berger, D.; Overman, L. E.; Renhowe, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 9305–6. (c) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958–66.

6 Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, 8317–20.

7 Configurations of the products were assigned from coupling constant analysis and NOE measurements.

8 For example, see Richardson, T. I.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1997**, *119*, 12360-1.

9 (a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126–31. (b) Molinski, T. F. *Tetrahedron Lett.* **1996**, *37*, 7879–80. (c) Searle, P. A.; Molinski, T. F.; Brzezinski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422–3.

10 (a) Lee, C. S.; Forsyth, C. J. *Tetrahedron Lett.* **1996**, *37*, 6449–52. (b) Cink, R. D.; Forsyth, C. J. *J. Org. Chem.* **1997**, *62*, 5672-3. (c) Ahmed, F.; Forsyth, C. J. *Tetrahedron Letters* **1998**, *39*, 183-6. (d) Ye, T.; Pattenden, G. *Tetrahedron Letters* **1998**, *39*, 319-22.

11 Forsyth, C. J.; Ahmed, F.; Cink, R. D.; Lee, C. S. *J. Am. Chem. Soc.* **1998**, *19*, 5597-8.