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Conversion of Weinreb Amides into Benzene Rings Incorporating the Amide Carbonyl Carbon

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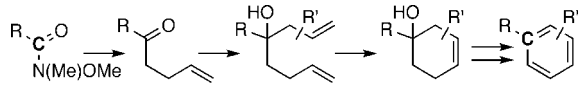
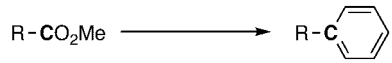


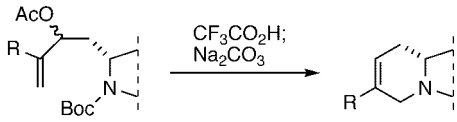
Esters, acids and acid chlorides can be converted via the intermediacy of their corresponding Weinreb amides into benzene derivatives that incorporate the original carbonyl carbon as part of the benzene ring. The process involves treatment of the derived Weinreb amides with 3-butenylmagnesium bromide and an allylic Grignard reagent, followed by ring-closing metathesis, dehydration and dehydrogenation. The dehydration−dehydrogenation can be done under acidic conditions with a mixture of $TsOH \cdot H_2O$ and DDQ or in two steps with $SOCl_2$/pyridine, followed by treatment with DDQ. Application of the method to carbohydrates provides a convenient route to C-5 aryl pyranosides.

Introduction

During the course of another investigation, a need arose in this laboratory to convert an ester group into a benzene ring that incorporated the ester carbonyl carbon, as summarized in eq 1. This problem arose because an intramolecular conjugate displacement,[1] which worked well with an acrylate subunit (eq 2, R = CO_2Me),[1] was unsuccessful with the corresponding styrene subunit (eq 2, R = Ph). As an aromatic ring was required in the final product, the possibility of modifying an ester group along the lines of eq 1 was considered, and we report here a straightforward method of effecting this type of process.



(1)

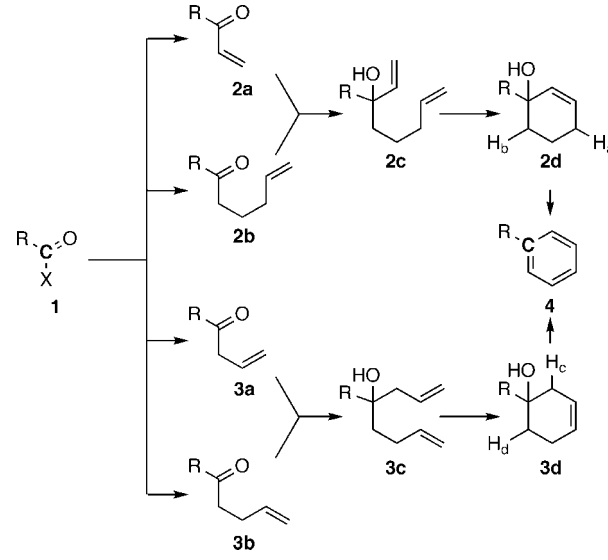


(2)

Results and Discussion

The plan was to modify the ester (or its parent acid) in such a way that two consecutive reactions with different Grignard reagents would lead to a tertiary alcohol (**2c** or **3c**) that was correctly constituted to undergo ring-closing metathesis (**2c** → **2d** and **3c** → **3d**), so as to form a six-membered ring; dehydration and dehydrogenation would then generate the required aromatic compound **4** (Scheme 1). The Weinreb amide

SCHEME 1. Synthetic Plan



[**1**, X = N(Me)OMe][2] was obviously an appropriate derivative of the starting ester, but the proper selection of organometallic reagents required a choice among several possibilities.

Sequential use of vinyl and 4-pentenyl Grignard reagents would lead to a tertiary alcohol of type **2c**, via **2a** or **2b**, the path depending on which reagent was used first. After ring-

(1) Clive, D. L. J.; Li, Z.; Yu, M. *J. Org. Chem.* **2007**, *72*, 5608–5617.

(2) (a) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815–3818. For leading references to the preparation of Weinreb amides, see: (b) Deagostino, A.; Larini, P.; Occhiato, E. G.; Pizzuto, L.; Prandi, C.; Venturello, P. *J. Org. Chem.* **2008**, *73*, 1941–1945.

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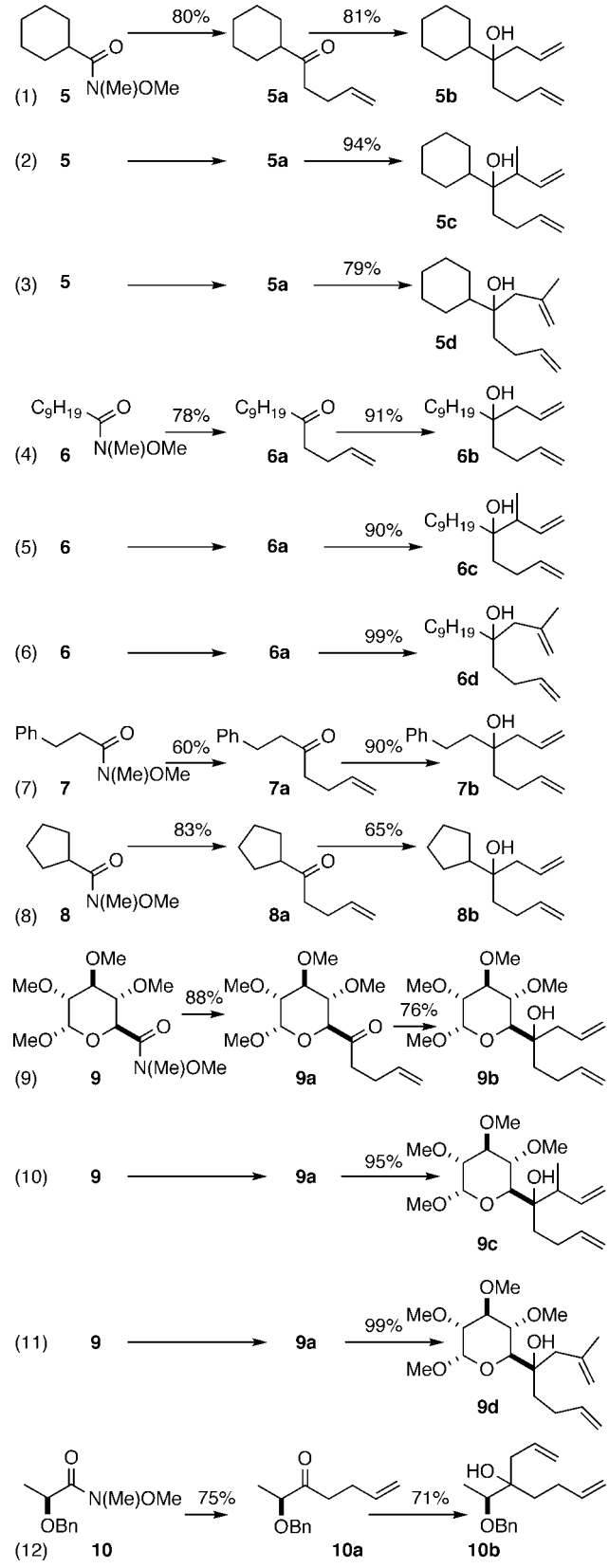
closing metathesis, the possible dehydration steps would involve loss of an allylic hydrogen (H_a) distal to the OH group or of a nonallylic hydrogen (H_b) from **2d**. On the other hand, sequential use of an allylmagnesium halide and a 3-butenyl Grignard reagent would give a tertiary alcohol of type **3c**, via **3a** or **3b**, again depending on the sequence of operations. In this case, endocyclic dehydration of the ring-closing metathesis product **3d** could involve loss of a proximal allylic hydrogen (H_c) or a nonallylic hydrogen (H_d). Intermediates of type **3a** might be susceptible to isomerization to the corresponding conjugated ketone. Of these pathways, we decided to examine the route **1** [X = N(Me)OMe] → **3b** → **3c** → **3d** and found that it represents a practical method for the transformation summarized in eq 1. Most of the examples we have studied are listed in Tables 1 and 2, which show, respectively, the formation of the substrates for ring-closing metathesis and the generation of the final aromatic systems.

The starting Weinreb amides **5**−**10** were usually made from the corresponding acid chloride by known procedures; some of these amides had already been reported, but some were new. Sequential treatment with butenyl-, allyl-, 2-methyl-2-propen-1-yl-, and 1-methyl-2-propen-2-yl Grignard reagents led to the expected tertiary alcohols (Table 1), and ring-closing metathesis worked well with the Grubbs I[3] or Grubbs II[4] catalysts, which were generally used at a 5 mol % level in dichloromethane (Table 2). Most of these reactions were done at the reflux temperature for 2−12 h. In the examples where we used the Grubbs II catalyst (Table 2, entries 3, 6, and 11), we were guided by literature precedent,[5] which indicated that for the olefin substitution patterns involved, the Grubbs II catalyst is superior; we did not try the Grubbs I catalyst with these substrates.

In principle, both of the Grignard reagents can carry appropriately placed substituents, and this fact allows the construction of benzene rings having various substitution patterns; entries 2, 3, 5, 6, 10, and 11 of Tables 1 and 2 illustrate the formation of *ortho*- and *meta*-disubstituted benzenes.

For the dehydration, we examined the use of acid ($TsOH \cdot H_2O$) and of $SOCl_2$ in pyridine. In the former case, both the acid (1 equiv) and DDQ (1 equiv) were added at the start of the reaction,[6] which was conducted in refluxing PhH, so that both dehydration and dehydrogenation were effected without isolation of the intermediate diene. With $SOCl_2$, the dehydration and dehydrogenation (DDQ) were performed separately and no acid was used with the DDQ. Both procedures gave the aromatized products in satisfactory yields (ca. 66−90%, Table 2). The advantage of using the classical $SOCl_2$/pyridine procedure is that potentially acid-sensitive groups are unaffected. Only in the case of the dihydrocinnamic acid derivative (Table 2, entry 7) did the dehydration−dehydrogenation prove to be problematic, as a significant byproduct in our early experiments, using $TsOH \cdot H_2O$ and DDQ, was *trans*-stilbene. However, when we used $SOCl_2$/pyridine for the dehydration and were careful to stop the subsequent dehydrogenation as soon as it was complete (about 30 min), formation of the stilbene was insignificant (^1H NMR) and a satisfactory yield (84%) of **7d** was obtained.

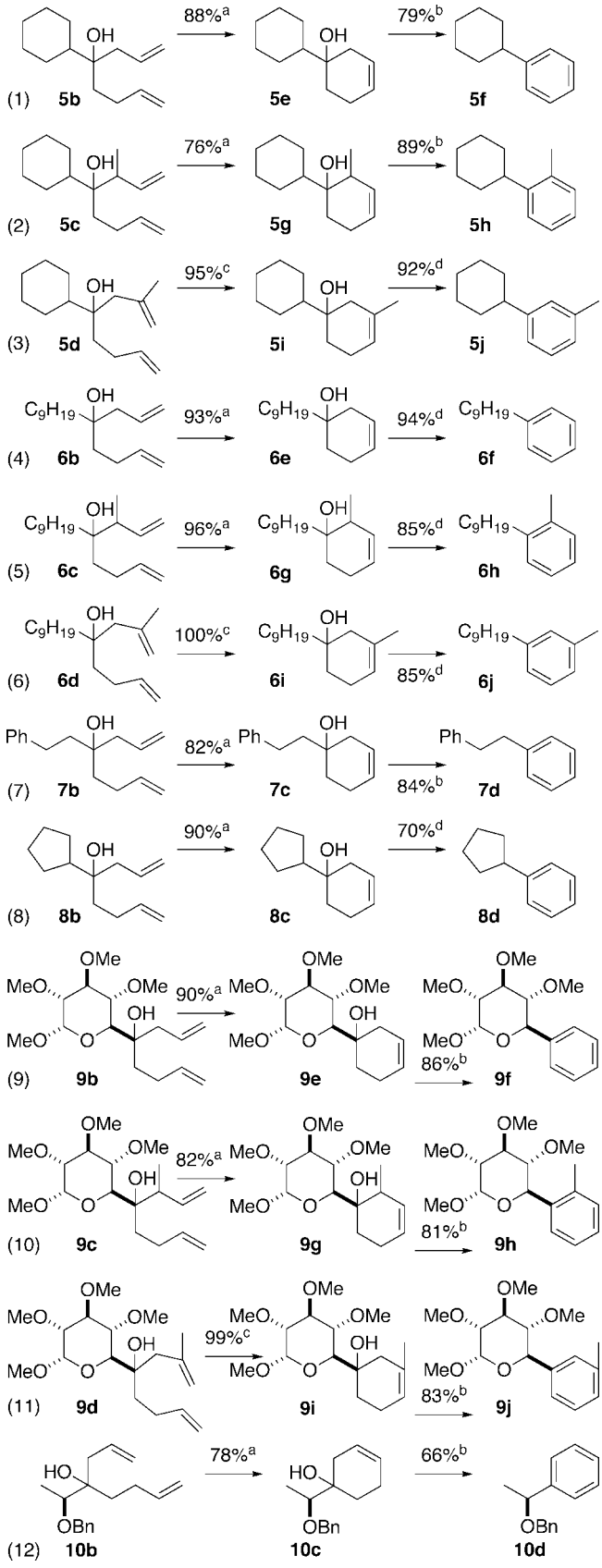
TABLE 1. Preparation of Ring-Closing Metathesis Precursors



The examples of entries 9−11 of Tables 1 and 2 show that in the carbohydrate sequence the overall transformation can be effected with preservation of the original stereochemistry. Carbohydrates bearing an aromatic ring directly linked to C-5

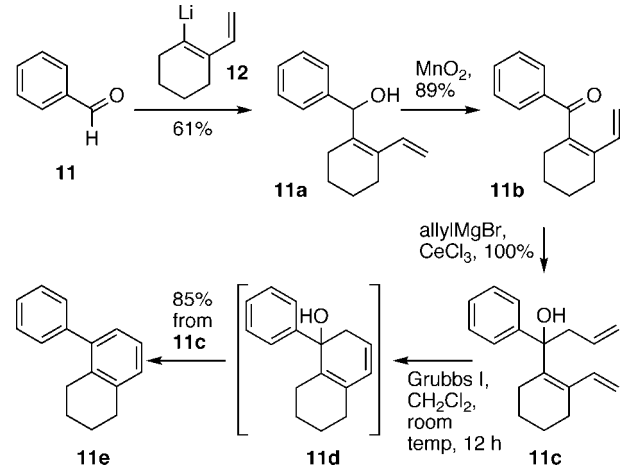
(3) Dichloro(phenylmethylene)bis(tricyclohexylphosphine)ruthenium.
(4) [1,3-Bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium.
(5) See: Fürstner, A. *Angew. Chem., Int. Ed* **2000**, *39*, 3012–3043, and references therein. .
(6) Compare: Brown, W.; Turner, A. B. *J. Chem. Soc. C* **1971**, 2566–2572.

TABLE 2. Generation of Aromatic Rings by Ring-Closing Metathesis, Dehydration, and Dehydrogenation



[a] Grubbs I catalyst. [b] $SOCl_2$, pyridine, then DDQ. [c] Grubbs II catalyst. [d] $TsOH \cdot H_2O$ and DDQ.

SCHEME 2. Use of an Aldehyde



have previously been made by de novo assembly of the pyranose ring,[7] often by Diels−Alder reaction with a Danishefsky diene,[7a−c] or by addition of a carbanion to a dialdehydofuranose, followed by ring expansion to the pyranose system.[8,9] Some carbohydrate derivatives with C-5 aryl groups are reported[8a,b] to inhibit sodium glucose co-transporter type 2 and might provide a mechanism to lower the elevated blood glucose levels of patients with diabetes.[10]

The series based on (*S*)-methyl lactate[11] (entry 12 of Tables 1 and 2) gave material (**10d**) that we judge to have an ee of >98%,[12] indicating that in this stereochemically unbiased system (in contrast to our carbohydrate examples) the enantiomeric purity of the starting ester is largely conserved. When making the Weinreb amide **10**[13] from (*S*)-methyl lactate, we found it essential to carry out the O-benzylation using BnBr and Ag_2O[11] in order to avoid racemization; use of NaH/BnBr or benzyl 2,2,2-trichloroacetimidate-CF_3CO_2H[13] gave an inferior result.

As expected, our approach can be easily modified to accommodate other carbonyl compounds (including their corresponding precursor alcohols) besides acids and esters as the starting material. For example, Scheme 2 shows a sequence where we have used an aldehyde. In this case, the product (**11a**) of the

(7) For construction of 5-C-aryl carbohydrates by de novo synthesis of the carbohydrate segment, see, for example: (a) Bednarski, M.; Danishefsky, S. *J. Am. Chem. Soc.* **1986**, *108*, 7060–7067. (b) Berkowitz, D. B.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1992**, *114*, 4518–4529. (c) Helliwell, M.; Phillips, I. M.; Pritchard, R. G.; Stoodley, R. J. *Tetrahedron Lett.* **1999**, *40*, 8651–8655, and references therein. (d) Hauser, F. M.; Ganguly, D. *J. Org. Chem.* **2000**, *65*, 1842–1849. (e) Cheng, G.; Fan, R.; Hernández-Torres, J. M.; Boulineau, F. P.; Wei, A. *Org. Lett.* **2007**, *9*, 4849–4852.

(8) (a) Harrison, B. A.; Kimball, S. D.; Mabon, R.; Rawlins, D. B. WO 2008/042688A2, 2008. (b) Goodwin, N.; Harrison, B. A.; Kimball, S. D.; Mabon, R.; Rawlins, D. B. WO 2008/109591A1, 2008. (c) Compare: Mincher, D. J.; Shaw, G. *J. Chem. Soc., Perkin Trans. 1* **1984**, *1279*, 1279–1282. (d) Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. C* **1968**, *1683*, 1692. (e) Bruns, R.; Wernicke, A.; Köll, P. *Tetrahedron* **1999**, *55*, 9793–9800. (f) Popsavin, V.; Benedekovic, G.; Sreco, B.; Popsavin, M.; Francuz, J.; Kojic, V.; Bogdanovic, G. *Org. Lett.* **2007**, *9*, 4235–4238. (g) Prakash, K. R. C.; Rao, S. P. *Synlett* **1993**, *123*, 124. For a route via a dialdehydofuranose and a derived epoxide, see: (h) Kilaas, L.; Anthonsen, T. *Acta Chem. Scand.* **1992**, *46*, 994–999.

(9) For a route via sugar-derived acetylenes, see: Kaliappan, K. P.; Subrahmanyam, A. V. *Org. Lett.* **2007**, *9*, 1121–1124.

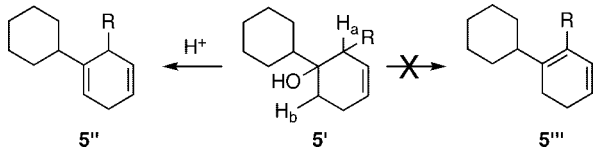
(10) Jabbour, S. A.; Goldstein, B. J. *Int. J. Clin. Pract.* **2008**, *62*, 1279–1284.

(11) Aubele, D. L.; Lee, C. A.; Floreancig, P. E. *Org. Lett.* **2003**, *5*, 4521–4523.

(12) We used chiral GC (see Experimental Section). As we did not achieve clear baseline separation, we examined a mixture of 2 wt % racemic **10d** and optically active **10d** and found that the presence of the *R*-isomer was easily detectable.

(13) Shang, S.; Iwadare, H.; Macks, D. E.; Ambrosini, L. M.; Tan, D. S. *Org. Lett.* **2007**, *9*, 1895–1898.

SCHEME 3. Dehydration Pathway



original organolithium addition must be oxidized to the ketone level, but this does not incur any danger of double bond isomerization (cf earlier comments about **3a**) because the double bond closest to the newly generated carbonyl is already in the α,β-position; such would not be the case if an allylic Grignard reagent were used first, instead of the vinylic reagent **12**. When the tertiary alcohol **11c** was treated with Grubbs I catalyst at room temperature, not only did ring-closing metathesis occur, but the intermediate product (**11d**) suffered spontaneous dehydration to afford **11e** directly in good overall yield (85%).

In the two cases we examined (Table 2, entries 1 and 2) the major dehydration products (using $SOCl_2$, pyridine) were the nonconjugated cyclohexa-1,4-dienes **5″** (R = H, Me) rather than the isomers **5‴**, as judged by the ^{1}H NMR spectra of the crude material (Scheme 3). What little experimental evidence is available[14] indicates that there is no overwhelming preference in favor of loss of a proximal allylic hydrogen (Scheme 3, H_a) over a nonallylic hydrogen (H_b), at least in simple compounds structurally related to **5e**; usually, the formation of mixtures is reported,[14] and in few cases have the proportions of conjugated and nonconjugated isomers been specified.

Conclusion

Many procedures are, of course, available for the construction of aromatic rings,[15] and some, like the present approach, involve ring-closing metathesis.[16,17] The examples summarized in Tables 1 and 2 show that the approach we describe is a general one for incorporating the carbonyl carbon of an ester (or synthetically equivalent species) into a benzene ring. Application of this method to carbohydrates appears to be especially convenient and might prove useful in the preparation of potentially important C-5 aryl pyranosides.

Experimental Section

Methyl *N*-Methoxy-*N*-methyl-2,3,4-tri-*O*-methyl-α-D-glucopyranosiduronamide (9). $(COCl)_2$ (0.53 mL, 6.1 mmol) was added slowly to a stirred solution of methyl 2,3,4-tri-*O*-methyl-α-D-glucopyranosiduronic acid[18] (0.76 g, 3.0 mmol) in CH_2Cl_2 (6 mL), and stirring was continued for 2 h. The solvent and excess of $(COCl)_2$ were evaporated with protection from moisture, and the residue was dissolved in THF (3 mL) and cooled to −78 °C.

In a separate flask, THF (3 mL) was added to *N*,*O*-dimethylhydroxylamine hydrochloride (0.44 g, 4.5 mmol), and the mixture was stirred at room temperature for 30 min. Water (0.1 mL) was added, and the solution was stirred for an additional 20 min. The solution was cooled to 0 °C, K_2CO_3 (0.94 g) was added, and stirring was continued for 30 min. The mixture was filtered and added to the above cooled (−78 °C) and stirred solution of acid chloride. Stirring at −78 °C was continued for 3 h. The cold bath was removed, saturated aqueous $NaHCO_3$ (10 mL) was added, and the mixture was extracted with Et_2O. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, water, and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 30 cm), using 70% Et_2O−petroleum ether (bp 35−60 °C), gave **9** (0.89 g, 100%) as an oil: $[\alpha]^{20}_D$ 160.20 (*c* 0.96, CH_2Cl_2); FTIR (CH_2Cl_2 cast microscope) 841, 964, 989, 1041, 1069, 1096, 1160, 1445, 1672, 2837, 2939, 3578 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.25−3.29 (m, 4 H), 3.47 (s, 3 H), 3.50 (s, 3 H), 3.52 (s, 3 H), 3.55 (dd, *J* = 2.3, 6.8 Hz, 2 H), 3.62 (s, 3 H), 3.75 (s, 3 H), 4.52 (apparent d, *J* = 6.6 Hz, 1 H), 4.84 (dd, *J* = 0.6, 3.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 32.3 (q), 55.6 (q), 59.2 (q), 60.6 (q), 60.9 (q), 61.8 (q), 65.6 (d), 80.6 (d), 81.4 (d), 83.3 (d), 98.5 (d), 169.3 (s); exact mass *m*/*z* calcd for $C_{12}H_{23}NO_7$ 293.1475, found 293.1474.

Methyl 9,10-Dideoxy-2,3,4-tri-*O*-methyl-α-D-gluco-dec-9-enopyranosid-6-ulose (9a). 3-Butenylmagnesium bromide (0.5 M in THF, 0.68 mL, 0.34 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **9** (0.1 g, 0.34 mmol) in THF (1.5 mL). Stirring at 0 °C was continued for 2 h. The mixture was diluted with CH_2Cl_2 and quenched with saturated aqueous NH_4Cl. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 30 cm), using 50% EtOAc−hexanes, gave **9a** (0.086 g, 88%) as an oil: $[\alpha]^{20}_D$ 114.57 (*c* 0.84, CH_2Cl_2); FTIR (CH_2Cl_2 cast film microscope) 1099, 1730, 2836, 2934 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.34−2.40 (m, 2 H), 2.63−2.79 (m, 2 H), 3.21 (dd, *J* = 3.6, 9.6 Hz, 1 H), 3.28 (dd, *J* = 8.8, 9.9 Hz, 1 H), 3.45 (s, 3 H), 3.49 (s, 3 H), 3.53 (s, 3 H), 3.55 (d, *J* = 9.2 Hz, 1 H), 3.63 (s, 3 H), 4.02 (d, *J* = 10.0 Hz, 1 H), 4.85 (d, *J* = 3.6 Hz, 1 H), 5.00 (apparent dq, *J* = 1.3, 10.3 Hz, 1 H), 5.06 (apparent dq, *J* = 1.6, 17.0 Hz, 1 H), 5.83 (dddd, *J* = 6.6, 6.6, 10.3, 16.9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.1 (t), 40.2 (t), 55.6 (q), 59.2 (q), 60.5 (q), 61.0 (q), 73.4 (d), 80.6 (d), 81.3 (d), 83.4 (d), 98.0 (d), 115.4 (t), 136.9 (d), 205.8 (s); exact mass (electrospray) *m*/*z* calcd for $C_{14}H_{24}NaO_6$ 311.1465 found 311.1468.

4-[[2*S*-(2α,3β,4α,5β,6β)]-3,4,5,6-Tetramethoxytetrahydro-2*H*-pyran-2-yl]octa-1,7-dien-4-ol (9b). Allylmagnesium bromide (1 M in Et_2O, 0.22 mL, 0.22 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **9a** (0.050 g, 0.17 mmol) in THF (2 mL). The cold bath was left in place but not recharged, and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (1 × 30 cm), using 50% EtOAc−hexanes, gave **9b** (0.043 g, 76%) as an oil:

(14) For examples of dehydration leading to conjugated and non-conjugated cyclohexadienes, see: (a) Brady, W. T.; Norton, S. J.; Ko, J. *Synthesis* **1985**, 704–705. (b) Andrade, R. M.; Muñoz, A. H.; Tamariz, J. *Synth. Commun.* **1992**, *22*, 1603–1609. (c) Weyerstahl, P.; Marschall-Weyerstahl, H.; Scholz, S. *Liebigs Ann. Chem.* **1986**, 1021–1029. (d) Bestmann, H. J.; Kobold, U.; Vostrowsky, O. *Liebigs Ann. Chem.* **1986**, 234–241. (e) Ohloff, G.; Giersch, W.; Näf, R.; Delay, F. *Helv. Chim. Acta* **1986**, *69*, 698–703. (f) Thomas, A. F.; Bucher, W. *Helv. Chim. Acta* **1970**, *53*, 770–775. (g) Kametani, T.; Suzuki, K.; Kurobe, H.; Nemoto, H. *Chem. Pharm. Bull.* **1981**, *29*, 105–109.

(15) For recent methods for the preparation of aromatic rings, see: (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033–4036. (b) Park, D. Y.; Kim, S. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6315–6319. (c) Grisé, C. M.; Barriault, L. *Org. Lett.* **2006**, *8*, 5905–5908. (d) Park, D. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2006**, *47*, 6641–6645. (e) Dai, M.; Sarlah, D.; Yu, M.; Danishefsky, S. J.; Jones, G. O.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 645–657. (f) Mamat, C.; Büttner, S.; Trabhardt, T.; Fischer, C.; Langer, P. *J. Org. Chem.* **2007**, *72*, 6273–6275. (g) Sher, M.; Ali, A.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 5400–5402. (h) Reim, S.; Adeel, M.; Hussain, I.; Yawer, M. A.; Ahmed, Z.; Villiger, A.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 4901–4904. (i) Reim, S.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 2329–2332. (j) Austin, W. F.; Zhang, Y.; Danheiser, R. L. *Tetrahedron* **2008**, *64*, 915–925.

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(17) (a) Kotha, S.; Mandal, K. *Tetrahedron Lett.* **2004**, *45*, 2585–2588. (b) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470–10471. (c) Yoshida, K.; Kawagoe, F.; Iwadate, N.; Takahashi, H.; Imamoto, T. *Chem. Asian J.* **2006**, *1*, 611–613. (d) Yoshida, K.; Toyoshima, T.; Imamoto, T. *Chem. Commun.* **2007**, 3774–3776. (e) Yoshida, K.; Horiuchi, S.; Iwadate, N.; Kawagoe, F.; Imamoto, T. *Synlett* **2007**, 1561–1564. (f) Yoshida, K.; Shishikura, Y.; Takahashi, H.; Imamoto, T. *Org. Lett.* **2008**, *10*, 2777–2780. (g) Yoshida, K.; Takahashi, H.; Imamoto, T. *Chem. Eur. J.* **2008**, *14*, 8246–8261.

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FTIR (CH_2Cl_2 cast film microscope) 1055, 1098, 1161, 1446, 1641, 2834, 2931, 3474 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.59−1.69 (m, 2 H), 2.10−2.25 (m, 2 H), 2.30−2.45 (m, 2 H), 3.14 (dd, J = 3.7, 9.6 Hz, 1 H), 3.31−3.64 (overlapping singlets and multiplets, 16 H), 4.77 (dd, J = 2.2, 3.7 Hz, 1 H), 4.90−4.96 (m, 1 H), 5.02 (apparent ddq, J = 1.7, 7.0, 17.1 Hz, 1 H), 5.06−5.14 (m, 2 H), 5.83 (dddd, J = 6.3, 6.3, 10.3, 16.9 Hz, 1 H), 5.89−6.02 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.2 (t), 27.7 (t), 35.5 (t), 35.8 (t), 40.7 (t), 41.5 (t), 56.0 (q), 56.1 (q), 58.9 (q), 59.9 (q), 60.0 (q), 60.69 (q), 60.71 (q), 71.4 (d), 72.0 (d), 74.6 (s), 74.7 (s), 80.6 (d), 80.7 (d), 82.0 (d), 84.3 (d), 84.4 (d), 97.4 (d), 97.5 (d), 114.0 (t), 114.1 (t), 117.4 (t), 117.5 (t), 134.1 (d), 134.3 (d), 139.1 (d), 139.2 (d); exact mass (electrospray) m/z calcd for $C_{17}H_{30}NaO_6$ 353.1935, found 353.1934.

1-[[2*S*-(2α,3*β*,4α,5*β*,6*β*)]-3,4,5,6-Tetramethoxytetrahydro-2*H*-pyran-2-yl]cyclohex-3-enol (9e). A solution of **9b** (0.030 g, 0.091 mmol) in CH_2Cl_2 (2 mL) was degassed for 30 min with a stream of Ar. Grubbs I catalyst (0.0037 g, 0.0045 mmol) was added, and the Ar stream was continued for 15 min. The mixture was then refluxed overnight under a static pressure of Ar, cooled, and filtered through flash chromatography silica gel (1 × 5 cm), using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 20 cm), using Et_2O−hexanes, gave **9e** (0.0136 g, 90%) as an oil: FTIR (CH_2Cl_2 cast film) 1058, 1100, 1159, 2835, 2912, 3484 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.58−1.68 (m, 1 H), 1.78−1.88 (m, 1 H), 1.92−2.14 (m, 2 H), 2.26−2.54 (m, 2 H), 3.03 (d, J = 1.0 Hz, 0.5 H), 3.17 (apparent dtd, J = 0.5, 4.2, 9.6 Hz, 1 H), 3.31−3.43 (s overlapping with m, 4 H), 3.47 (dd, J = 2.4, 9.8 Hz, 1 H), 3.52 (two overlapping s, 3 H), 3.55−3.65 (overlapping singlets and m, 7 H), 3.72 (d, J = 1.4 Hz, 0.5 H), 4.77 (d, J = 3.8 Hz, 0.5 H), 4.79 (d, J = 3.7 Hz, 0.5 H), 5.60−5.67 (m, 1 H), 5.71−5.82 (m, 1 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.7 (t), 22.0 (t), 29.2 (t), 30.6 (t), 33.8 (t), 34.4 (t), 55.2 (q), 55.4 (q), 58.9 (q), 59.8 (q), 60.1 (q), 60.7 (q), 60.8 (q). 71.4 (s), 71.6 (s), 72.8 (d), 72.9 (d), 80.1 (d), 80.6 (d), 82.0 (d), 82.1 (d), 84.4 (d), 84.5 (d), 97.2 (d), 97.3 (d), 123.6 (d), 124.0 (d), 126.1 (d), 127.1 (d); exact mass (electrospray) m/z calcd for $C_{15}H_{26}NaO_6$ 325.1622, found 325.1624.

Methyl (5*R*)-2,3,4-Tri-*O*-methyl-5-*C*-phenyl-α-D-xylopyranoside (9f). $SOCl_2$ (0.015 mL, 0.20 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **9e** (0.015 g, 0.050 mmol) in pyridine (0.11 mL, 1.39 mmol). Stirring at 0 °C was continued for 3 h, and the mixture was poured onto crushed ice and extracted with Et_2O. The combined organic extracts were washed with water, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), and evaporated to give the crude intermediate diene as an oil. DDQ (0.011 g, 0.05 mmol) was added to a stirred solution of this diene in PhH (1 mL), and the mixture was then stirred and refluxed for 1 h, cooled to room temperature, and filtered through flash chromatography silica gel (0.5 × 30 cm), using 50% EtOAc−hexanes. Evaporation of the solvent gave **9f** (0.012 g, 86%) as an oil: $[\alpha]^{20}_D$ 88.32 (*c* 0.82, MeOH); FTIR (CH_2Cl_2 cast film microscope) 1097, 1455, 2833, 2909, 2934 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.04 (d, J = 0.5 Hz, 3 H), 3.10 (dd, J = 9.3, 9.3 Hz, 1 H), 3.35 (ddd, J = 0.5, 3.7, 9.6 Hz, 1 H), 3.44 (d, J = 0.6 Hz, 3 H), 3.58 (d, J = 0.6 Hz, 3 H), 3.62 (dd, J = 9.2, 9.2 Hz, 1 H), 3.65 (d, J = 0.6 Hz, 3 H), 4.44 (d, J = 9.8 Hz, 1 H), 4.91 (d, J = 3.7 Hz, 1 H), 7.33−7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 55.3 (q), 59.1 (q), 60.4 (q), 61.0 (q), 72.8 (d), 81.8 (d), 83.2 (d), 85.8 (d), 97.9 (d), 127.6 (d), 128.2 (d), 128.4 (d), 138.9 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{22}NaO_5$ 305.1359, found 305.1357.

(*S*)-2-(Benzyloxy)hept-6-en-3-one (10a). 3-Butenylmagnesium bromide (0.5 M in THF, 4.1 mL, 4.1 mmol) was added dropwise to a stirred and cooled (−15 °C) solution of **10**[13] (0.37 g, 1.66 mmol) in THF (12 mL). Stirring at −15 °C was continued for 3 h, and the mixture was then diluted with Et_2O and quenched with saturated aqueous NH_4Cl. The organic phase was washed with water and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% Et_2O−petroleum ether (35−60 °C), gave **10a**[19] (0.270 g, 75%) as a liquid: $[\alpha]^{20}_D$ −43.59 (*c* 1.28, $CHCl_3$); FTIR ($CHCl_3$ cast film microscope) 914, 1113, 1719, 2934, 2980 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.37 (d, J = 6.9 Hz, 3 H), 2.31−2.39 (m, 2 H), 2.60−2.79 (m, 2 H), 3.96 (q, J = 6.9 Hz, 1 H), 4.55 (AB q, J = 11.7, $\Delta\nu_{AB}$ = 19.2 Hz, 2 H), 4.98−5.03 (m, 1 H), 5.06 (apparent dq, J = 1.6, 17.1 Hz, 1 H), 5.84 (dddd, J = 6.6, 6.6, 10.3, 16.8 Hz, 1 H), 7.30−7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 17.4 (q), 27.2 (t), 36.5 (t), 71.9 (t), 80.6 (d), 115.3 (t), 127.7 (d), 127.9 (d), 128.5 (d), 137.2 (d), 137.6 (s), 212.0 (s); exact mass (electrospray) m/z calcd for $C_{14}H_{18}NaO_2$ 241.1199, found 241.1199.

4-[(*S*)-1(Benzyloxy)ethyl]octa-1,7-dien-4-ol (10b). Allylmagnesium bromide (1 M in Et_2O, 1.0 mL, 1.0 mmol) was added dropwise to a stirred and cooled (−15 °C) solution of **10a** (0.18 g, 0.83 mmol) in THF (8 mL). The cold bath was left in place but not recharged, and stirring was continued for 2 h. The mixture was quenched with saturated aqueous NH_4Cl, and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% Et_2O−petroleum ether (35−60 °C), gave **10b** (0.15 g, 71%) as an oil: FTIR (CH_2Cl_2 cast) 912, 1095, 1454, 1641, 2871, 2941, 2977, 3471, 3561 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.19 (d, J = 6.3 Hz) and 1.21 (d, J = 6.3 Hz), (3 H in all), 1.40−1.49 (m, 0.5 H), 1.54−1.62 (m, 0.5 H), 1.65−1.73 (m, 1 H), 2.03−2.27 (m, 3 H), 2.28 (s, 0.8 H), 2.36 (d, J = 0.7 Hz, 0.2 H), 2.40−2.48 (m, 1 H), 3.49 (q, J = 6.3 Hz) and 3.51 (q, J = 6.3, Hz), (1 H in all), 4.54 (AB q, J = 11.5, $\Delta\nu_{AB}$ = 124.7 Hz) and 4.55 (AB q, J = 11.5, $\Delta\nu_{AB}$ = 123.3 Hz), (2 H in all), 4.92−5.13 (m, 4 H), 5.77−5.92 (m, 2 H), 7.27−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1 (q), 13.3 (q), 27.6 (t), 33.9 (t), 35.1 (t), 39.5 (t), 40.7 (t), 71.3 (t), 71.4 (t) 75.5 (s), 75.6 (s), 79.12 (d), 79.15 (d), 114.2 (t), 117.6 (t), 117.9 (t), 127.6 (d), 127.65 (d), 127.68 (d), 128.4 (d), 134.0 (d), 134.2 (d), 138.5 (s), 139.0 (d), 139.1 (d); exact mass (electrospray) m/z calcd for $C_{17}H_{24}NaO_2$ 283.1669, found 283.1670.

1-[(*S*)-1-(Benzyloxy)ethyl]cyclohex-3-enol (10c). A solution of **10b** (0.10 g, 0.38 mmol) in CH_2Cl_2 (9 mL) was degassed for 30 min with a stream of Ar. Grubbs I catalyst (0.019 g, 0.023 mmol) was added, and the Ar stream was continued for 15 min. The mixture was then refluxed for 3 h under a static pressure of Ar, cooled, and filtered through flash chromatography silica gel (1 × 5 cm), using CH_2Cl_2. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 × 15 cm), using 10% Et_2O−petroleum ether (35−60 °C), gave **10c** (0.069 g, 78%) as an oil: FTIR (CH_2Cl_2 cast) 1075, 1088, 2916, 2972, 3026, 3467, 3566 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, J = 6.4 Hz) and 1.25 (d, J = 6.3 Hz), (3 H in all), 1.52−1.74 (m, 1.5 H), 1.80−1.88 (m, 0.5 H), 1.98−2.36 (m, 5 H), 3.43 (q, J = 6.4 Hz) and 3.47 (q, J = 6.4 Hz), (1 H in all), 4.59 (AB q, J = 11.6, $\Delta\nu_{AB}$ = 95.0 Hz) and 4.60 (AB q, J = 11.6, $\Delta\nu_{AB}$ = 96.7 Hz), (2 H in all), 5.58−5.66 (m, 1 H), 5.71−5.79 (m, 1 H), 7.29−7.41 (m, 5 H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.0 (q), 13.2 (q), 22.18 (t), 22.20 (t), 28.7 (t), 30.0 (t), 33.1 (t), 34.8 (t), 71.4 (t), 71.5 (t), 72.2 (s), 72.3 (s), 79.6 (d), 80.2 (d), 123.8 (d), 124.3 (d), 126.6 (d), 126.8 (d), 127.62 (d), 127.64 (d), 127.7 (d), 128.36 (d), 128.38 (d), 138.6 (s); exact mass (electrospray) m/z calcd for $C_{15}H_{20}NaO_2$ 255.1356, found 255.1356.

(*S*)-1-[(1-Phenylethoxy)methyl]benzene (10d). $SOCl_2$ (0.042 mL, 0.58 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **10c** (0.03 g, 0.13 mmol) in pyridine (0.33 mL, 4.07 mmol). Stirring at 0 °C was continued for 2 h, and the mixture was poured onto crushed ice and extracted with Et_2O. The combined organic extracts were washed with hydrochloric acid (2 M), water, and brine, dried ($MgSO_4$), and evaporated to give the crude intermediate diene as a colorless liquid. DDQ (0.33 g, 1.45 mmol) was added to a stirred solution of this diene in PhH (2 mL). The

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mixture was refluxed for 30 min, then cooled to room temperature and filtered through flash chromatography silica gel (0.5 × 30 cm), using 50% Et_2O−hexanes. Evaporation of the filtrate gave **10d**[20] (0.0177 g, 66%): $[\alpha]^{20}_D$ −100.62 (*c* 0.5, $CHCl_3$); FTIR (neat film microscope) 801, 1022, 1096, 1261, 2963 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.50 (d, J = 6.5 Hz, 3 H), 4.39 (AB q, J = 11.9, $\Delta\nu_{AB}$ = 74.6 Hz, 2 H), 4.51 (q, J = 6.5 Hz, 1 H), 7.27−7.39 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 24.2 (q), 70.3 (t), 77.2 (d), 126.3 (d), 127.45 (d), 127.48 (d), 127.7 (d), 128.3 (d), 128.5 (d), 138.7 (s), 143.7 (s); exact mass (electrospray) *m*/*z* calcd for $C_{15}H_{16}NaO$ 235.1093, found 235.1093.

Analysis by Chiral GC. Astec CHIRALDEX B-PM, 30 m × 0.25 mm, 0.25 μm film thickness, 120 °C, retention time = 47.05 min; retention times for racemic **10d** = 46.21 and 47.08 min. A sample containing 2 wt % of racemic **10d** mixed with optically active **10d** gave a trace with a clearly observable minor signal; hence our optically active **10d** has an ee of at least 98%.

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Supporting Information Available: Experimental procedures and copies of NMR spectra and chiral GC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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