Temporary Silicon-Tethered Ring-Closing Metathesis Approach to C_2-Symmetrical 1,4-Diols: Asymmetric Synthesis of D-Altritol

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The enantioselective construction of the C_2-symmetrical molecules, particularly 1,4-diols, continues to attract significant attention[1] owing to their importance as precursors to a variety of asymmetric catalysts,[2] as chiral auxiliaries[3] and as useful intermediates for two-directional synthesis.[4] However, a survey of the literature revealed surprisingly few methods for the preparation of this type of structural motif, despite its significance as an important asymmetric building block. The combination of temporary silicon-tethering methodology[5] with ring-closing metathesis[6,7] has been demonstrated, in an achiral system, to be a useful method for the preparation of simple 1,4-diols.[7a] Herein, we describe an adaptation of this concept, utilizing optically enriched allylic alcohols **1** to facilitate the synthesis of protected C_2-symmetrical 1,4-diols **4**, as outlined in Scheme 1.

Table 1 summarizes the results for the application of this methodology to a series of optically enriched allylic alcohols.[8] Treatment of the allylic alcohols **1a**−**e** with diphenyldichlorosilane and 2,6-lutidine furnished the bis-alkoxysilanes **2a**−**e** in excellent yield (entries 1−5). Preliminary studies established the optimum conditions for the ring-closing metathesis reaction, in terms of the catalyst loading, type of solvent, and concentration. These studies determined that an initial catalyst loading of 8 mol % followed by an additional 2.5 mol % after approximately 20 h, at a concentration of 0.05 M in refluxing dichloromethane, were required for the smooth formation of the diphenyl silaketals **4a**−**e**. Interestingly, despite the somewhat extended reaction times and elevated temperatures,[11] the process appears to be fairly general as illustrated by the alkyl and aryl examples listed in Table 1 (entries 1−5).

The diphenyl silaketals **4** represent protected C_2-symmetrical 1,4-diols that can be readily elaborated into a

Scheme 1

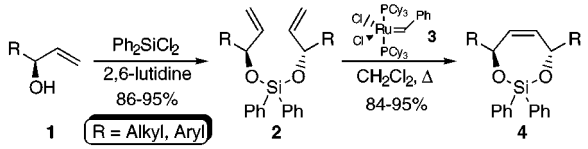
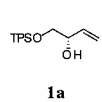
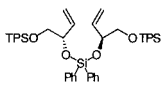
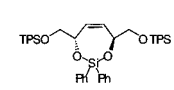
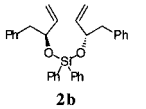
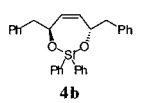
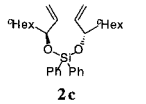
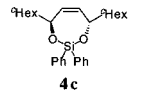
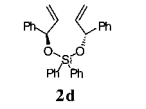
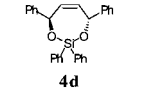
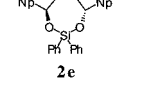
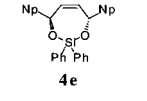


Table 1. Ring-Closing Metathesis Procedure for Coupling Optically Enriched 1,4-Allylic Alcohols

entry	allylic alcohol **1**[a]	*bis*-alkoxy silane **2**	yield (%)[b]	diphenyl silaketal **4**[c]	time (hrs)	yield (%)[b]
1	 **1a**	 **2a**	87	 **4a**	32	91
2	 **1b**	 **2b**	86	 **4b**	26	95
3	 **1c**	 **2c**	95	 **4c**	26	90
4	 **1d**	 **2d**	94	 **4d**	42	93
5	 **1e**	 **2e**	88	 **4e**	25	84

[a] All the reactions were carried out on a 1.0 mmol reaction scale.[12] [b] Isolated yields. [c] The ring-closing metathesis reactions were carried out on a 0.25 mmol reaction scale at a concentration of 0.05 M in refluxing dichloromethane.[14]

(1) For a review on C_2 symmetry in synthesis, see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. For recent synthetic approaches to C_2-symmetrical 1,4-diols, see: (a) Lieser, J. K. *Synth. Commun.* **1983**, *13*, 765. (b) Seebach, D.; Renaud, P. *Helv. Chim. Acta* **1985**, *68*, 2342. (c) Short, R. P.; Kennedy, R. M.; Masamune, S. *J. Org. Chem.* **1989**, *54*, 1755. (d) Kim, M.-J.; Lee, I. S. *Synlett* **1993**, 767. (e) Zwaagstra, M. E.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1993**, *4*, 2163. (f) Morin, C. *Tetrahedron Lett.* **1993**, *34*, 5095. (g) Vettel, S.; Knochel, P. *Tetrahedron Lett.* **1994**, *35*, 5849 and pertinent references therein.

(2) (a) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Harlow, R. L. *Tetrahedron: Asymmetry* **1991**, *2*, 569 and pertinent references therein.

(3) Chong, J. M.; Clarke, I. S.; Koch, I.; Olbach, P. C.; Taylor, N. J. *Tetrahedron: Asymmetry* **1995**, *6*, 409 and pertinent references therein.

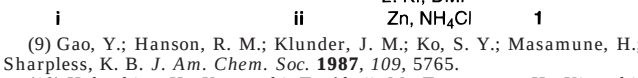
(4) For a review on two-directional synthesis, see: Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167.

(5) For recent reviews on temporary silicon-tethered strategies, see: (a) Fensterbank, L.; Malacria, M.; Sieburth, S. McN. *Synthesis* **1997**, 813. (b) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2290.

(6) For recent reviews on ring-closing metathesis, see: (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.

(7) For some recent leading references on Ru-catalyzed ring-closing metathesis, see: (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 5426. (b) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorenson, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733. (c) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Patzel, M.; Ramser, M. N.; Wagman, A. A. *Tetrahedron* **1996**, *52*, 7251. (d) Furstner, A.; Langeman, K. *J. Org. Chem.* **1996**, *61*, 8746. (e) Huwe, C. M.; Blechert, S. *Synthesis* **1997**, 61. (f) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 127. (g) Barrett, A. G. M.; Baugh, S. P. D.; Gibson, V. C.; Giles, M. R.; Marshall, E. L.; Procopiou, P. A. *J. Chem. Soc. Chem. Commun.* **1997**, 155. (h) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166. (i) Kim, S. H.; Figueroa, I.; Fuchs, P. *Tetrahedron Lett.* **1997**, *38*, 2601. (j) Harrity, J. P. A.; Visser, M. S.; Gleason, J. D.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1997**, *119*, 1488. (k) Litinas, K. E.; Salteris, B. E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2869. (l) Delgado, M.; Martin, J. D. *Tetrahedron Lett.* **1997**, *38*, 6299. (m) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919. (n) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (o) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548. (p) Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; Van der Marel, G. A.; Van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025. (q) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158. (r) Burke, S. D.; Ng, R. A.; Morrison, J. A.; Alberti, M. J. *J. Org. Chem.* **1998**, *63*, 3160 and pertinent references cited within these articles.

(8) The enantiomerically enriched allylic alcohols **1** were all prepared in the following manner. Sharpless asymmetric epoxidation[9] of the primary allylic alcohol **i** followed by the activation and rearrangement of the 2,3-epoxy alcohol **ii** furnished the allylic alcohol **1** in excellent overall yield.[10]



(1)

(9) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(10) Habashita, H.; Kawasaki, T.; Akaji, M.; Tamamura, H.; Kimachi, T.; Fujii, N.; Ibuka, T. *Tetrahedron Lett.* **1997**, *38*, 8307.

(11) The reduced rates of reaction are presumably a function of the increased steric hindrance due to allylic substituent. For related examples of this type of problem in ring-closing metathesis, see: (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757. (b) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861.

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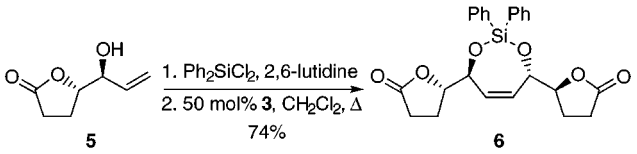
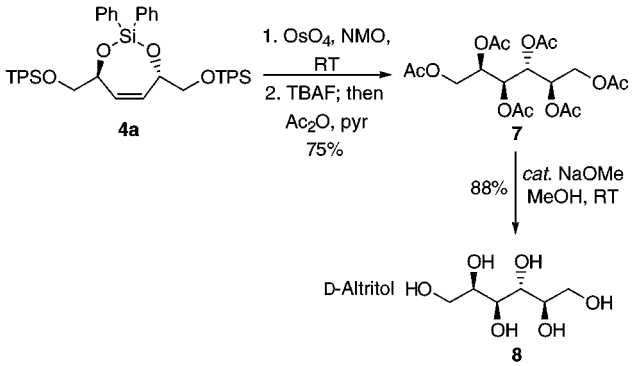
Scheme 2



variety of intermediates.[15] Scheme 2 represents an application of this type of strategy in two-directional synthesis. The allylic alcohol **5** was converted to the bis-alkoxysilane under standard conditions and then treated with 50 mol % of **3** to induce ring-closing metathesis,[16] furnishing the bis-lactone **6** in 74% overall yield. This represents a particularly useful synthetic intermediate that is currently being utilized for the total synthesis of the potent antitumor annonaceous acetogenin mucocin.[17]

Scheme 3



Scheme 3 illustrates another potentially powerful application of this methodology applicable to the preparation of the reduced carbohydrate D-altritol.[18] Dihydroxylation of the cyclic alkene **4a** (TPS = ^{t}BuPh$_2$Si) with a catalytic amount of osmium tetraoxide in the presence of *N*-methylmorpholine *N*-oxide, followed by treatment with tetra-*N*-butylammonium fluoride, furnished D-altritol **8**; this was then peracetylated to expedite isolation, affording the hexaacetate **7** in 75% overall yield.[19] Treatment of **7** with a catalytic amount of sodium methoxide in methanol furnished D-altritol **8** in 88% yield, identical in all respects to the reported data (^{1}H and ^{13}C NMR): $[\alpha]^{16}_D = 3.1$ ($c = 1.7$, H_2O) [lit.[18] $[\alpha]^{20}_D = 3.2$ ($c = 1.78$, H_2O)]. Hence, this represents a highly strereoselective and expeditious method for the construction of alditols.

In conclusion, we have developed a temporary silicon-tethered ring-closing metathesis protocol for the synthesis of protected C_2-symmetrical 1,4-diols. The advantage of this type of approach is the ability to couple a wide range of optically enriched allylic alcohols, which facilitates the preparation of useful intermediates for target directed synthesis. For example, the silaketal **4a** was converted in a highly stereoselective and expeditious manner to the reduced carbohydrate D-altritol **8**. It is anticipated that this method should also be amenable to solid-phase synthesis and thus allows for the preparation of carbohydrate libraries.

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Supporting Information Available: Full characterization and proton spectra for compounds **1/2/4b−e** and **5−9** (22 pages).

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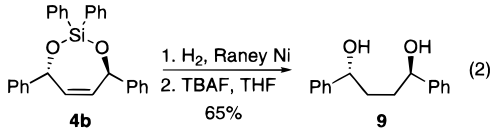
(12) **General Procedure for the Preparation of Bis-Alkoxysilanes from Allylic Alcohols.** The allylic alcohol **1a**[13] (0.718 g, 2.2 mmol) was dissolved in anhydrous dichloromethane (10 mL) and cooled with stirring to 0 °C under nitrogen atmosphere. Diphenyldichlorosilane (0.21 mL, 1.02 mmol) was then added neat via syringe followed by 2,6-lutidine (0.47 mL, 4.04 mmol). The reaction mixture was allowed to warm to room temperature and stirred for ca. 20 h. The reaction was then partitioned between dichloromethane and water. The combined organic phases were dried (Na_2SO_4), filtered, and concentrated in vacuo to afford a crude oil. Purification by flash chromatography (eluting with 5% ethyl acetate in hexanes) furnished the bis-alkoxy silane **2a** (0.74 g, 87%) as a colorless syrup: $[\alpha]^{18}_D = -16.9$ ($c = 1$, $CHCl_3$); IR ($CHCl_3$) 3072 (s), 3012 (s), 2960 (s), 2932 (s), 2850 (s) 1590 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.57 (m, 12H), 7.42−7.26 (m, 18H), 5.93 (ddd, $J = 17.1$, 10.6, 6.0 Hz, 2H), 5.20 (dt, $J = 17.1$, 1.5 Hz, 2H), 5.09 (dt, $J = 10.4$, 1.5 Hz, 2H), 4.46 (q, $J = 5.9$ Hz, 2H), 3.68 (A of ABX, $J_{AB} = 10.0$, $J_{AX} = 5.6$ Hz, 2H), 3.52 (B of ABX, $J_{AB} = 10.0$, $J_{BX} = 6.2$ Hz, 2H), 1.0 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.02 (o), 135.61 (o), 135.53 (o), 135.21 (o), 133.55 (e), 133.14 (e), 130.05 (o), 129.48 (o), 127.57 (o), 115.81 (e), 74.65 (o), 67.89 (e), 26.77 (o), 19.20 (e); HRMS (FAB) calcd for $C_{52}H_{60}NaSi_3O_4$ 855.3697, found 855.3722.

(13) Mikiko, M.; Fumiaki, O.; Mayumi, M.; Yohko, T.; Yutaka, A.; Akihiro, O. *Chem. Pharm. Bull.* **1997**, *45*, 962.

(14) **General Procedure for the Ring-Closing Metathesis of the Bis-Alkoxysilanes.** The diene **2b** (0.214 g, 0.26 mmol) was dissolved in anhydrous dichloromethane (5 mL) and the solution degassed in a sonication bath. Grubbs' catalyst **3** (0.016 g, 0.02 mmol) was added and the mixture heated at reflux for ca. 20 h. An additional amount of **3** (0.005 g, 2.5 mol %) was then added and the reaction mixture heated at reflux for a further ca. 6 h (NMR analysis). The reaction mixture was then cooled to ambient temperature and concentrated in vacuo to afford the crude product. Purification by flash chromatography (eluting with 20% benzene in hexanes) furnished the cyclic bis-alkoxysilane **4a** (0.189 g, 91%) as a white crystalline solid: mp 115−118 °C.; $[\alpha]^{18}_D = -2.4$ ($c = 1$, $CHCl_3$); IR ($CHCl_3$) 3072 (s), 2991 (s), 2960 (s), 2859 (s) 1591 (w) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.67 (m, 12H), 7.46−7.30 (m, 18H), 5.78 (s, 2H), 4.88 (t, $J = 5.2$, 2H), 3.84 (A of ABX, $J_{AB} = 10.0$, $J_{AX} = 6.4$ Hz, 2H), 3.73 (B of ABX, $J_{AB} = 10.0$, $J_{BX} = 5.6$ Hz, 2H), 1.05 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.62 (o), 134.84 (o), 133.61 (e), 133.50 (e), 131.20 (o), 130.40 (o), 129.59 (o), 127.82 (o), 127.63 (o), 71.80 (o), 67.87 (e), 26.78 (o), 19.25 (e); HRMS (FAB) calcd for $C_{50}H_{56}NaSi_3O_4$ 827.3384, found 827.3369.

(15) The diphenyl silaketal **4a** was converted to the C_2-symmetrical 1,4-diol **9**, which is a common intermediate for the preparation of the *trans*-2,5-diphenylpyrrolidine chiral auxiliary.[3] Reduction of the *cis*-alkene **4b** with Raney Ni followed by the desilylation with tetra-*N*-butylammonium fluoride furnished the C_2-symmetrical 1,4-diol **9** in 65% overall yield.



(2)

(16) This proved to be a more challenging example that required 0.5 equiv of the Grubbs' catalyst **3** for complete conversion.

(17) Shi, G.; Alfonso, D.; Fatope, M. O.; Zeng, L.; Gu, Z.-m.; Zhao, G.-x.; He, K.; MacDougal, J. M.; McLaughlin, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10409.

(18) (a) Hann, R. M.; Haskins, W. T.; Hudson, C. S. *J. Am. Chem. Soc.* **1947**, *69*, 624. (b) Angyal, S. J.; Le Fur, R. *Carbohydr. Res.* **1980**, *84*, 201. (c) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

(19) D-Altritol hexaacetate: $[\alpha]^{14}_D = 39$ ($c = 0.6$, $CHCl_3$) [lit.[18] for L-altritol hexaacetate, $[\alpha]^{20}_D = -38.7$ ($c = 0.59$, $CHCl_3$)].