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Furan Approach to Vitamin D Analogues. Synthesis of the A-Ring of Calcitriol and 1α-Hydroxy-3-deoxyvitamin D_3

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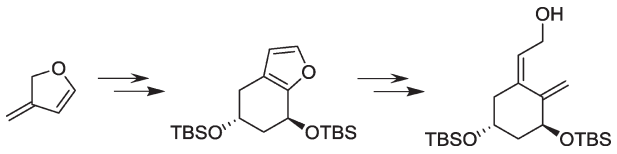

The A-rings of calcitriol (1α,25-dihydroxyvitamin D_3) and 1α-hydroxy-3-deoxyvitamin D_3 were synthesized using the furan approach. The critical steps in the synthesis of the A-ring of calcitriol involved an asymmetric carbonyl-ene reaction of 3-methylene-2,3-dihydrofuran with 3-(*tert*-butyldimethylsiloxy)-propanal, a diastereoselective Friedel−Crafts hydroxyalkylation, an oxidation of the 2,3-disubstituted furan to give a γ-hydroxybutenolide, and a Peterson olefination. The A-ring (*Z*)-dienol of calcitriol was synthesized in 12 steps from 3-(*tert*-butyldimethylsiloxy)propanal in 17% yield.

Introduction

Calcitriol (**1a**), the active metabolite of vitamin D_3 (**1b**), has a broad range of biological activity (Figure 1).[1] In addition to its well-known role in maintaining calcium and phosphorus homeostasis, **1a** has also been shown to promote cell differentiation and inhibit tumor cell proliferation. Although the clinical efficacy of **1a** has been demonstrated in the treatment of hyperproliferation diseases such as psoriasis, therapeutic levels of **1a** often lead to hypercalcemia. In order to retain the desired biological activity but attenuate the effects of hypercalcemia, thousands of analogues of **1a** have been prepared and undergone biological testing.[2] The continued interest in synthesizing new analogues has spurred the development of new methodologies for the synthesis of vitamin D_3 analogues.

One of the most popular synthetic strategies for the synthesis of vitamin D_3 analogues is based on the work of Lythgoe.[3] The general strategy involves the coupling of A-ring phosphine oxides (**2**) with C,D-ring ketones (**3**) (Scheme 1). This highly convergent synthetic strategy was used by the Hoffmann-La Roach chemists to synthesize **1a** for the first time, a benchmark in vitamin D_3 chemistry.[4a] Many different approaches to the A-ring have been developed over the years, including the synthetic manipulation of (*S*)-carvone[4] and (5*S*)-*tert*-butyldimethylsiloxy-2-cyclohexenone,[5] the Diels−Alder reaction of electron-rich pyrones with dienophiles,[6] and the intramolecular Heck reaction.[7]

We recently demonstrated that the furan approach to the synthesis of the A-ring of 1α-hydroxy-3-deoxyvitamin D_3 (**1c**) was a viable strategy.[8] Our synthesis of **4c** was a significant step in defining the conditions for the conversion of 2,3-disubstituted furans **5** into the required (*Z*)-dienols **4**, but the synthesis of (*Z*)-dienols **4a** and **4b** also required the successful introduction of the C-3 sterogenic center. This paper gives a full account of our synthesis of **4c** as well as our successful synthesis of **4a** and attempted synthesis of **4b**.

Results and Discussion

Synthesis of 3-Substituted Furans. We envisioned that the synthesis of the prerequisite 2,3-disubstituted furans **5** would

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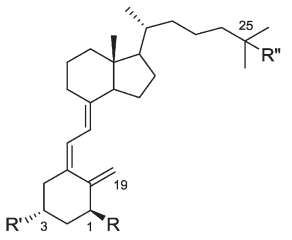
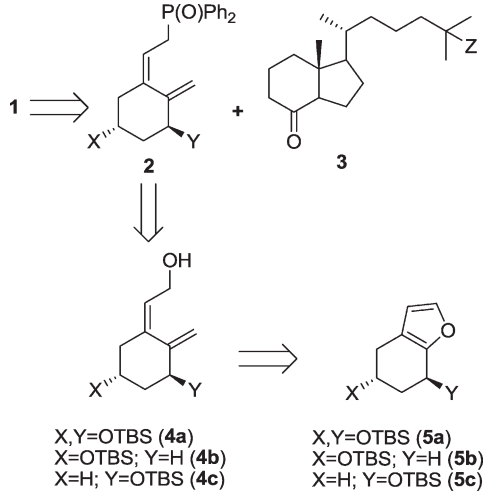


1a (Calcitriol; R,R',R"=OH)
1b (Vitamin D_3; R,R"=H; R'=OH)
1c (3-deoxy-1-hydroxyvitamin D_3; R=OH; R', R"=H)

FIGURE 1. Structure of calcitriol, vitamin D_3, and 3-deoxy-1-hydroxyvitamin D_3.

SCHEME 1. Retrosynthetic Analysis

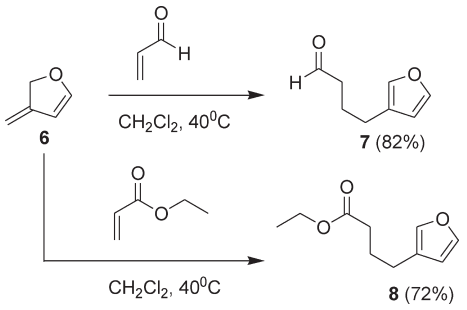


X,Y=OTBS (**4a**)
X=OTBS; Y=H (**4b**)
X=H; Y=OTBS (**4c**)

X,Y=OTBS (**5a**)
X=OTBS; Y=H (**5b**)
X=H; Y=OTBS (**5c**)

be available by the cyclization of suitably substituted 3-substituted furans. The readily available starting materials for the synthesis of 3-substituted furans include 3-furoic acid, 3-furaldehyde, 3-furylmethanol, 3-furylmethylbromide, and 3-methylene-2,3-dihydrofuran (**6**). Our numerous investigations of 3-methylene-2,3-dihydrofuran (**6**), the abnormal reduction product of 3-furaldehyde, have demonstrated that it is a convenient starting material for a variety of 3-substituted furans.[9] The thermal ene reaction of **6** with simple monosubstituted alkenes proceeds at a nearly unprecedented rate (refluxing CH_2Cl_2 for 1 day), presumably reflecting the aromatic nature of the transition state in a concerted reaction.[9a] For comparison, the ene reaction of β-pinene, a reactive ene, with maleic anhydride, an excellent enophile, required heating for 8 h at 140 °C.[10] The synthesis of aldehyde **7** (82% yield), previously prepared in five steps from 3-furanmethanol,[11] and ester **8** (72% yield), which was previously prepared in three steps from 3-furoic acid,[12] is

SCHEME 2. Thermal Ene Reactions of 6



illustrative of the utility of alicyclic isomer **6** in the synthesis of 3-substututed furans (Scheme 2).

In addition to the thermal ene reaction of **6** with alkenes and electron-poor carbonyl compounds, such as butyl glyoxylate, **6** undergoes Lewis acid-catalyzed carbonyl-ene reactions with simple aldehydes.[9b,c] The Lewis acids required for catalysis of the carbonyl-ene reaction of **6** with aliphatic and aromatic aldehydes are relatively weak: $Yb(fod)_3$, $Eu(fod)_3$, $Al(CH_3)_3$ and $Ti(O\text{-}i\text{-}Pr)_4$ are all effective.[9b] The most serious limitation we have encountered is the low reactivity of α-substituted aldehydes, which invariably leads to the isomerization/decomposition of **6** and low yields of alcohol product. We also have demonstrated that the asymmetric carbonyl-ene reaction of **6** with benzaldehyde using $Ti(O\text{-}i\text{-}Pr)_4$/(*S*)-BINOL gives nonracemic 2-(3-furyl)-1-phenyl-1-ethanol (90% yield and 95% ee),[9c] a reaction modeled after Mikami's asymmetric carbonyl-ene reaction of electron-poor glyoxylates with alkenes[13a] and Keck's asymmetric allylation of aldehydes.[13b] We envisioned the asymmetric carbonyl-ene reaction of **6** with a suitably substituted aliphatic aldehyde as the key reaction in establishing the C-3 stereogenic center (vitamin D_3 numbering).

We choose 3-(*tert*-butyldimethylsiloxy)propanal (**9**) as the aldehyde partner in the asymmetric carbonyl-ene reaction with **6**. The $Ti(O\text{-}i\text{-}Pr)_4$/(*R*)-BINOL-catalyzed reaction of **6** with **9** (prepared by the TEMPO oxidation of 3-(*tert*-butyldimethylsiloxy)propan-1-ol) gave alcohol **10** in 78% yield and >95% ee (Scheme 3). As we found with the carbonyl-ene reaction of **6** with benzaldehyde,[9c] the level of hydration of the molecular sieves (achieved by storing the molecular sieves at 110 °C) was critical for good enantioselectivity.[14] Protection of alcohol **10** as a TBS ether to give **11** was accomplished by the use of TBSOTf with 2,6-lutidene as the base (96% yield). The selective deprotection of the primary silyl ether of **11** to give alcohol **12** required a careful balance of conversion and yield, since the further cleavage of the secondary silyl ether of **12** to give the corresponding diol was a serious side reaction. The deprotection of **11** with a mixture of $THF/H_2O/AcOH$ (50:15:35) gave recovered **11** (19% yield) and **12** (65% yield; 81% yield based on recovered **11**). We also

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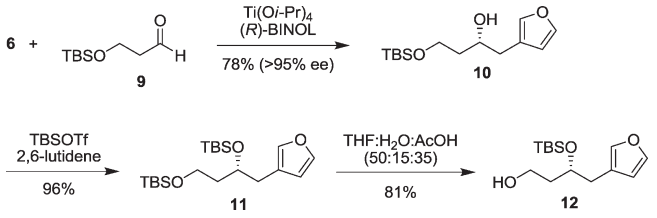
SCHEME 3. Synthesis of Furanyl Alcohol 12

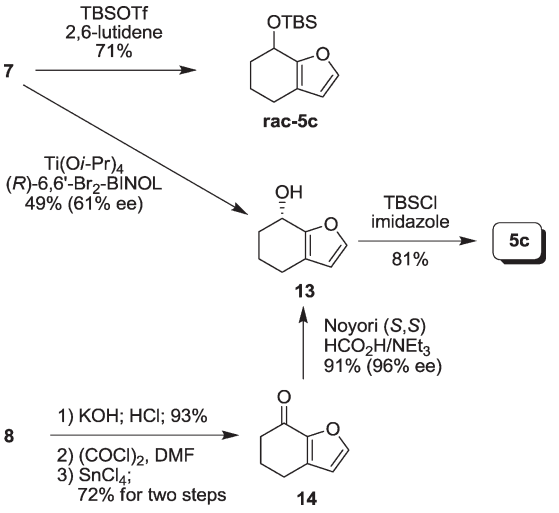


investigated several other protecting groups (Ac, TES, and Bn instead of TBS) for the primary alcohol center in the three-step synthetic sequence of **12**, but one or more steps were problematic. The Ti(O-*i*-Pr)$_4$/(*R*)-BINOL-catalyzed reaction of **6** with 3-(triethylsiloxy)propanal and 3-benzyloxypropanal gave good yields and enantioselectivity of the corresponding alcohol, but 3-acetoxypropanal gave only moderate yields. Protection of the secondary alcohol of (2*R*)-4-(triethylsilyoxy)-1-(3-furyl)butan-2-ol as a TBS ether was complicated by the migration of the TES group from the primary position to the secondary position. The major problem with using a benzyl protecting group occurred in the last step of the three-step sequence; the reduction of the furan ring competed with the reductive deprotection of the primary benzyl ether corresponding to **11**.

Synthesis of 2,3-Disubstituted Furans 5. The cyclization of 3-substituted furans is an excellent method for the synthesis of 2,3-disubstituted furans,[15] although there are serious limitations as to what kind of reaction conditions can be employed due to the sensitivity of the furan moiety to acidic conditions. Further, the Friedel−Crafts cyclization reactions of aromatic aldehydes to α-hydroxy or α-alkoxy aromatic compounds are often complicated by the further Friedel−Crafts reactions of the initial product due to the facile formation of a carbocation.[16] The reactivity of α-hydroxy aromatic compounds under Friedel−Crafts conditions can be turned into an advantage; the condensation of electron-rich aromatic compounds with aldehydes and ketones provides ready access to diaryl- and triarylmethanes, important classes of organic compounds.[16c−e]

Although **5c**, the furan necessary for the synthesis of (*Z*)-dienol **4c**, has been previously prepared in racemic form,[17] an enantioselective synthesis was not known until our initial communication appeared.[8] We explored several methods for the synthesis of **5c** and *rac*-**5c** in hopes of defining suitable conditions for the cyclization reaction. We first developed an alternative synthesis of *rac*-**5c** based on the Friedel−Crafts silyloxyalkylation of aldehyde **7**, a reaction that has very little precedent (Scheme 4).[18] The addition of TBSOTf to aldehyde **7** and 2,6-lutidine gave *rac*-**5c** in 71% yield. This racemic material was critical for the initial exploration of the

SCHEME 4. Synthesis of Furan 5c



oxidation of furans, but nonracemic **5c** was necessary for testing the durability of the C-1 (vitamin D_3 numbering system) stereogenic center in the subsequent synthetic steps.

One approach we explored for the synthesis of **5c** was the enantioselective intramolecular Friedel−Crafts hydroxyalkylation of aldehyde **7** (Scheme 4). Although there are many reports of diastereoselective intermolecular and intramolecular Friedel−Crafts hydroxyalkylations[19] and, more recently, enantioselective intermolecular Friedel−Crafts hydroxyalkylations,[20] we are unaware of any enantioselective intramolecular Friedel−Crafts hydroxyalkylation reactions. We obtained nonracemic alcohol **13** in moderate yield and enantioselectivity using Ti(O-*i*-Pr)$_4$/(*R*-BINOL) (entries 1−3; Table 1). There was an incremental increase in enantioselectivity in using the Ti(O-*i*-Pr)$_4$/(*R*)-6,6′-Br$_2$−BINOL catalyst system (entries 4−7), with a 10 mol % loading of Ti(O-*i*-Pr)$_4$ in a 1:2 ratio of Ti(O-*i*-Pr)$_4$/ligand in ether (entry 7) giving **13** in 49% yield and 61% ee. Alcohol **13** was obtained in good yields using (*R*)-BINAP with either AgOTf (entry 8) or Cu(OTf)$_2$ (entry 9) as the catalyst, but the product was racemic. We also tried several metal/BOX (BOX = bisoxazoline) catalyst systems (entry 10−12); as expected, the product was racemic, since these catalyst systems appear to require a bidentate electrophile.[20a−c]

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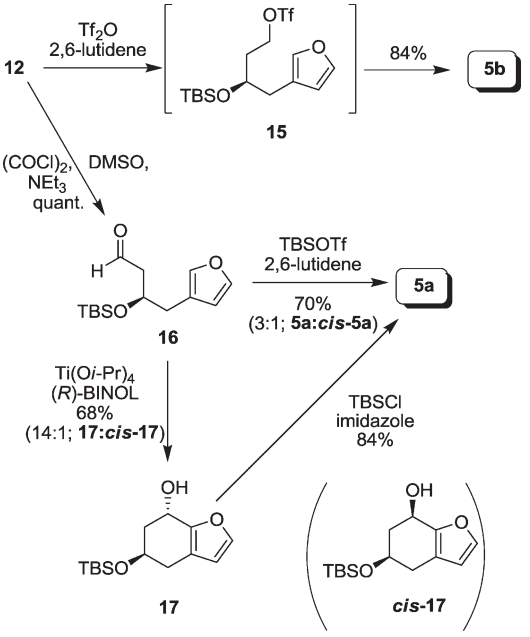
TABLE 1. Intramolecular Friedel−Crafts Hydroxyalkylation of 17

entry	catalyst	M/ligand; mol % M	solvent	T (°C)	time (h)	% yield; % ee
1	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 5	Et_2O	0 → 22	1	50; 40
2	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 10	Et_2O	0 → 22	20	69; 53
3	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 20	CH_2Cl_2	0	0.5	87; 40
4	Ti(O-*i*-Pr)$_4$/(*R*)-6,6′-Br_2−BINOL	1:2; 5	CH_2Cl_2	0 → 22	1	60; 39
5	Ti(O-*i*-Pr)$_4$/(*S*)-6,6′-Br_2−BINOL	1:2; 10	toluene	0 → 22	1	53; 48
6	Ti(O-*i*-Pr)$_4$/(*R*)-6,6′-Br_2−BINOL	1:2; 5	Et_2O	22	22	55; 48
7	Ti(O-*i*-Pr)$_4$/(*R*)-6,6′-Br_2−BINOL	1:2; 10	Et_2O	0 → 22	1	49; 61
8	AgOTf/(*R*)-BINAP	1:1; 10	THF	22	1	85; 0
9	Cu(OTf)$_2$/(*R*)-BINAP	1:1; 10	THF	22	0.75	56; 0
10	Cu(OTf)$_2$/*t*-BuBOX	1:1; 3	Et_2O	22	1	85; 0
11	Sc(OTf)$_3$/pyBOX	1:1; 10	CH_2Cl_2	22	1	0; 0
12	Cu(OTf)$_2$/pyBOX	1:1; 2	CH_2Cl_2	22	1	26; 0

Since we obtained alcohol **13** in only moderate enantioselectivity with the preceding asymmetric hydroxyalkylation reaction, we used an alternative method for the preparation of nonracemic **13**. One of the most attractive methods for the synthesis of nonracemic benzylic alcohols is by the asymmetric reduction of aromatic ketones.[21] Of all the methods currently available, Noyori's ruthenium(II) asymmetric transfer hydrogenation[21a] was the most appealing because of its simplicity and remarkably high enantioselectivity. The requisite ketone **14** has been previously prepared in one step by the condensation of 1,2-cyclohexadione and chloroacetaldehyde,[17] but in our hands the reaction proceeded in relatively low yields to give ketone **14** of questionable purity (Scheme 4). High-purity **14** was obtained in three steps from ester **8** with some minor modifications of Walsh's synthesis[12] of **14** and remained the preferred method for the preparation despite the greater number of steps. Subjecting **14** to the standard Noyori reduction conditions gave alcohol **13** in 91% yield and 96% ee. The assignment of the stereochemistry of the stereogenic center as *S* was accomplished by the synthesis of the methoxytrifluoromethylphenyl (MPTA) ester of **13** and analysis by ^{1}H NMR.[22] The enantiofacial selectivity found in the reduction of ketone **13** is consistent with previous studies employing this catalyst system.[21a] Alcohol **13** was converted into the corresponding TBS ether **5c** in 81% yield using standard conditions (the conversion of *rac*-**13** into *rac*-**14** was reported to proceed in 96% yield[17]).

We envisioned the synthesis of furans **5a** and **5b** from a common intermediate, alcohol **12**. For the synthesis of furan **5b**, the cyclization of the primary alcohol posed serious problems under standard conditions due to the sensitivity of the furan to standard cyclization conditions and the potential for carbocation rearrangements. A report by Trost and Toste[23] suggested a solution to this problem, in which they found that the conversion of a very electron-rich aromatic alcohol into the corresponding triflate rapidly gave cyclized product under slightly basic conditions. We used conditions similar to those reported and initially obtained triflate **15**, which cyclized at room temperature to furan **5b** in 84% yield (Scheme 5). This cyclization reaction may be limited to very electron-rich aromatic compounds with a favorable conformational bias, since the cyclization of the triflate of 4-(3-furyl)butan-1-ol did not give cyclized product under these reaction conditions.[24]

SCHEME 5. Synthesis of Furans 5a and 5b



In order to incorporate the desired C-1 (vitamin D_3 numbering system) oxygenated stereogenic center in furan **5a**, we envisioned two possible solutions: selective reduction of the appropriate ketone (available from the Friedel−Crafts acylation reaction) or selective cyclization of aldehyde **16**, relying on the possible directing effects of the existing C-3 stereogenic center and/or relying on asymmetric catalysis. The Swern oxidation of **12** gave unstable aldehyde **16** in nearly quantitative yield (Scheme 5). Since the silyloxyalkylation reaction of **16** to give **5a** offered the most direct solution to the problem, we investigated many different conditions for this reaction. Although we obtained acceptable yields (65−70%) of **5a** under the conditions we developed for the cyclization of **7** to *rac*-**5c**, the diastereoselective ratio was only 3:1 (**5a**:*cis*-**5a**). As an alternative route to **5a**, we investigated the hydroxyalkylation of **16** under a variety of

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(24) The Au(III)-catalyzed Friedel−Crafts reactions of triflates or mesylates with electron-rich aromatic compounds may offer a more general solution to Friedel−Crafts cyclization reactions. See: Shi, Z; He, C. *J. Am. Chem. Soc.* **2004**, *126*, 13596–13597. In our hands, however, the cyclization of the triflate or mesylate of 4-(3-furyl)butan-1-ol under these conditions did not give the desired bicyclic furan.

TABLE 2. Intramolecular Friedel−Crafts Hydroxyalkylation of 16[a]

entry	catalyst	Ti(O-*i*-Pr)$_4$/BINOL; mol % Ti(O-*i*-Pr)$_4$	solvent	*T* (°C)	time (h)	% yield (ratio of **17**/*cis*-**17**)
1	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 10	CH_2Cl_2	22	3	77 (16:1)
2[b]	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 10	CH_2Cl_2	22	3	52 (26:1)
3	Ti(O-*i*-Pr)$_4$/(*S*)-BINOL	1:2; 10	CH_2Cl_2	22	0.75	73 (8:1)
4	Ti(O-*i*-Pr)$_4$/*rac*-BINOL	1:2; 10	CH_2Cl_2	22	1	67 (14:1)
5	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 10	Et_2O	22	1	62 (5:1)
6	Ti(O-*i*-Pr)$_4$/(*S*)-BINOL	1:2; 10	Et_2O	22	20	61 (5:1)
7	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 10	$CH_3C_6H_5$	22	4	41 (6:1)
8	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:1; 10	CH_2Cl_2	22	22	73 (28:1)
9	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 20	CH_2Cl_2	0→22	1.3	66 (38:1)
10	Ti(O-*i*-Pr)$_4$/(*R*)-BINOL	1:2; 20	Et_2O	0→22	3.5	67 (4.5:1)

[a]Molecular sieves were dried at 160−180 °C under vacuum (0.05 mm) except for entry 2. [b]Molecular sieves were dried in an oven at 110 °C at atmospheric pressure.

conditions (Table 2). Many catalysts we investigated (e.g., $ZnCl_2$, $SnCl_4$, $Cu(OTf)_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, AgOTf/(*R*)-BINAP, Ti(O-*i*-Pr)$_4$/(*R*)-6,6′-Br_2−BINOL; not included in Table 2) gave poor yields of **5a**, but we were successful in using the Ti(O-*i*-Pr)$_4$/BINOL catalyst system. One important variable that distinguished this reaction from our previous work with this catalyst system in the asymmetric carbonyl-ene reaction was the need to scrupulously dry the molecular sieves for maximum chemical yields. The ideal level of hydration for the molecular sieves for the asymmetric hydroxyalkylation reaction of **16** was achieved by heating them to 160−180 °C under vacuum (0.05 mm) for 16 h (entries 1 and 2), in contrast to the asymmetric carbonyl-ene reaction of **6** with aldehydes, in which the optimal level of hydration for the molecular sieves was achieved by storing the molecular sieves in an oven at 110 °C. The preferred solvent was CH_2Cl_2 (entries 1−4, 8, and 9), with Et_2O giving good yields but lower diastereoselectivity (entries 5, 6, and 10) and toluene (entry 7) giving poor yields and moderate selectivity. Surprisingly, the diastereoselectivity was only weakly dependent on the chirality of the BINOL ligand, since we observed only incremental diminishment of diastereoselectivity using either (*S*)-BINOL (entry 3) or *rac*-BINOL (entry 4). The ratio of Ti(O-*i*-Pr)$_4$/(*R*)-BINOL does not appear to be a major factor in the diastereoselectivity, although the reaction proceeds much faster with a 1:2 ratio of Ti(O-*i*-Pr)$_4$/(*R*)-BINOL (entries 1 and 8). On a preparative scale, alcohol **17** (isolated as a 14:1 mixture of **17**:*cis*-**17**) was synthesized in 68% yield. There was some epimerization and/or decomposition of alcohol **17** during the workup procedure, especially on the preparative scale, as evidenced by the higher diastereoselectivity observed in the rapid workup of small aliquots of larger scale reactions. Alcohol **17** was then converted into **5a** in 84% yield under standard reaction conditions, with the unwanted *cis*-**5a** cleanly separated from **5a** by flash chromatography.

Our working model for the observed diastereoselectivity in the intramolecular cyclization of **16** is given in Figure 2. We assume the OTBS group occupies a pseudoequatorial position in a chairlike transition state. The orientation of the aldehyde must then be such that the hydrogen is pseudoequatorial and the aldehyde is stacking with the furan ring. The diminished diastereoselectivity observed in some cases (e.g., **16** → **5a**) may be due to competing steric factors that disfavor the transition state given in Figure 2. There are very few examples of intramolecular Friedel−Crafts hydroxyalkylation reactions in the literature with this level of stereochemical control.[19e] The definitive assignment of the stereochemistry

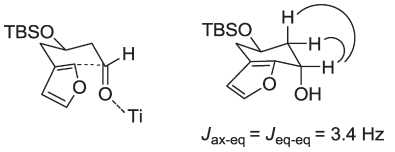

FIGURE 2. Transition state for Friedel−Crafts cyclization of **16** and conformation of alcohol **17**.

for the two possible alcohol products **17** and *cis*-**17** was based on the coupling constants of the benzylic protons (Figure 2). The preferred conformation for **17** appears to be one in which the C-7 alcohol occupies a pseudoaxial position, while the C-5 OTBS group is pseudoequatorial.[25]

Synthesis of *Z*-Dienol 4c. The usefulness of furans in the synthesis of oxygenated natural products has been extensively demonstrated in many elegant applications.[26] The literature suggested that the oxidation of a bicyclic 2,3-disubstituted furan with peracids would give unsaturated 1,4-dicarbonyl compounds.[27] For example, the perbenzoic acid oxidation of 4,5,6,7-tetrahydrobenzo[2,1-*b*]furan gave the unsaturated ketoaldehyde.[27] Our initial studies were consistent with the literature; when we oxidized furan **5c** with MCPBA, we obtained **18** (approximately 50% yield) along with several other products. In an attempt to improve the yield, the reaction mixture was buffered with NaOAc or $NaHCO_3$ (Scheme 6). There was a dramatic change in the product profile, in which one of the minor products (**19c**) became the sole product. A 2 equiv amount of *m*-CPBA were necessary for complete conversion of furan **5c**; if only one equiv of buffered *m*-CPBA was used, we observed 50% conversion of **5c** to **19c** and no evidence for any other product. The oxidation of furans to γ-hydroxybutenolides is usually achieved by singlet oxygen addition to silylfurans, although there is some precedent for peracid oxidation of 3-substituted[28a,b] and 2,3-disubstituted furans[28c,d] to γ-hydroxybutenolides. Since the separation of **19c** from 3-chlorobenzoic acid was problematic,

(25) Although the intramolecular Friedel−Crafts reaction of **16** is mechanistically distinct from the intramolecular carbonyl-ene reaction of substrates used in the synthesis of the A-ring of calcitriol, there are some interesting similarities in the transition state. See: Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701–7704. Mikami, K.; Osawa, A.; Isaka, A.; Sawa, E.; Shimizu, M.; Terada, M.; Kubodera, N.; Nakagawa, K.; Tsugawa, N.; Okano, T. *Tetrahedron Lett.* **1998**, *39*, 3359–3362.

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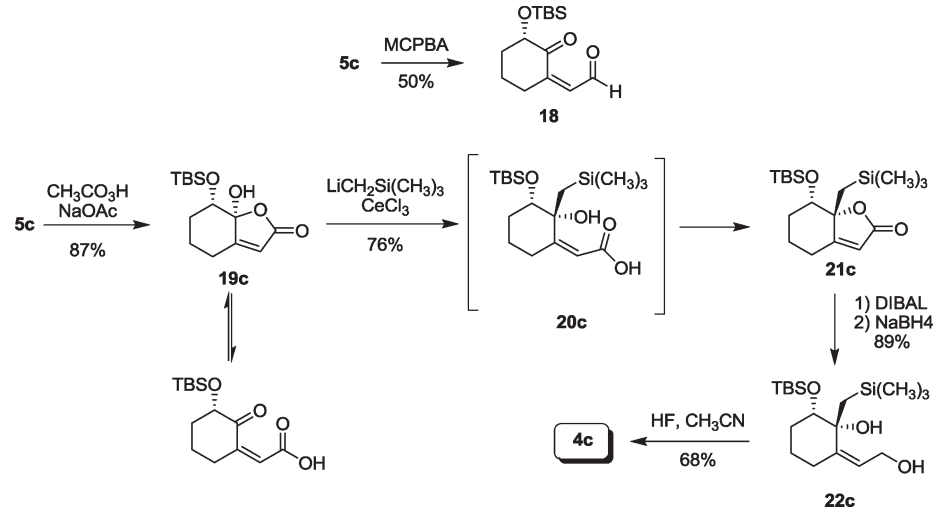
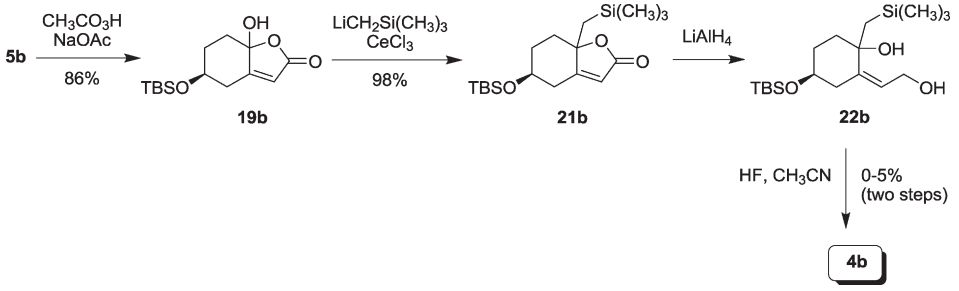
(27) Manfredi, K. P.; Jennings, P. W. *J. Org. Chem.* **1989**, *54*, 5186–5188.

SCHEME 6. Synthesis of 4c



SCHEME 7. Synthesis of 4b



the optimal procedure employed peracetic acid with NaOAc acting as a buffer (87% yield). We observed one major diastereomer for **19c**, in which we have assigned the stereochemistry based on the equatorial disposition of the OTBS group at C-1 (deduced from the coupling constants) and the geometric constraints of the bicyclic γ-hydroxybutenolide, in which the OH group occupies a pseudoaxial position.

With γ-hydroxybutenolide **19c** in hand, a method was needed to convert the ketone (of the open-chain form) into a terminal alkene. Many of the standard synthetic methods, such as the Wittig reaction or Tebbe procedure, failed to give synthetically useful yields of methylenation product. Converting γ-hydroxybutenolide **19c** into the corresponding ethyl ester and subjecting it to methylenation conditions (Wittig or Tebbe) also failed. We then turned to the Peterson olefination reaction,[29] employing the modifications developed by Johnson.[30] The reaction of excess $LiCH_2Si(CH_3)_3/CeCl_3$ (at least 2 equiv is necessary since 1 equiv is consumed in an acid−base reaction with **19c**) with **19c** gave **20c** after hydrolysis, which lactonized upon acidic workup to give lactone **21c** in 76% yield (Scheme 6). The reaction was very diastereoselective, with only one diastereomer observed in the crude product. The assignment of the stereochemistry of **21c** was based on NOESY experiments and the coupling constants. Although excess DIBAL readily reduces lactones to diols in many cases, we were unable to obtain synthetically useful yields of **22c** by the reaction of excess DIBAL with **21c**. The reduction of **21c** with $LiAlH_4$ gave significant cleavage of the TBS ether, a side reaction noted in the literature for α-silyloxycarbonyl compounds.[31] The reduction of lactone **21c** to diol **22c** was optimized in a two-step procedure: DIBAL reduced lactone **21c** to the lactol, which then was reduced to diol **22c** with $NaBH_4$ (89% yield). The elimination of trimethylsilanol from **22c** to give the desired (*Z*)-dienol **4c**[32] (68% yield) was best done with aqueous HF in CH_3CN.

Attempted Synthesis of *Z*-Dienol 4b. The conversion of furan **5b** into (*Z*)-dienol **4b** proceeded in a fashion similar to the aforementioned synthesis of **5c**. The peracetic acid oxidation of **5b** gave γ-hydroxybutenolide **19b** as a 2:1 mixture of diastereomers in 86% yield (Scheme 7). The reaction of excess $LiCH_2Si(CH_3)_3/CeCl_3$ and **19b** gave **21b** in 98% yield, again as a 2:1 mixture of diastereomers. The lack of diastereoselectivity is not surprising given the 1,4-relationship of the chiral center to the reacting ketone. Unlike the reduction of

(28) (a) Ferland, J. M.; Lefebvre, Y.; Deghenghi, R. *Tetrahedron Lett.* **1966**, 3617–3620. (b) Wiesner, K.; Tsai, T. Y. R.; Jin, H. *Helv. Chim. Acta* **1985**, *68*, 300–314. (c) González, A. G.; Darias, J.; Martín *Tetrahedron Lett.* **1973**, 3625–3626. (d) Takikawa, H.; Ueda, K.; Sasaki, M. *Tetrahedron Lett.* **2004**, *45*, 5569–5571.

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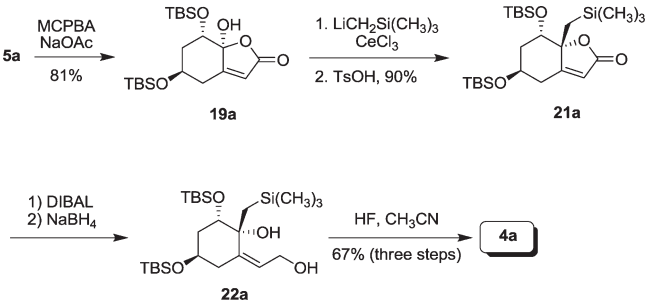
(32) For previous syntheses of **4c** and *rac*-**4c**, see: Uskokovic, M. R.; Baggiolini, E.; Shiuey, S.; Iacobelli, J.; Hennessy, B. In *Vitamin D: Gene Regulation, Structure Function Analysis and Clinical Application*; Norman, A. W., Bouillon, R., Thomasset, M., Eds.; Walter de Gruyter and Co.: Berlin, 1991; p 139. Mascareñas, J. L.; García, A. M.; Castedo, L.; Mouriño, A. *Tetrahedron Lett.* **1992**, *33*, 4365–4368.

SCHEME 8. Synthesis of 4a



21c and the subsequent elimination to give **4c**, the reduction of **21b** was complicated by the instability of the resulting diol **22b** under the many different reaction conditions. Since there was no neighboring TBS ether group, the reduction of **21b** could be carried out with $LiAlH_4$, but diol product (**22b**) could not be purified without significant loss of material. Since purification of the reduction product was not possible, crude **22b** was used directly in subsequent elimination reaction (aqueous HF in CH_3CN), but subjecting **22b** to the conditions we used for **22c** led to a significant amount of cleavage of the TBS ether, as evidenced by the lack of a TBS group in the crude product. By reducing the quantity of HF, running under more dilute conditions, and carefully monitoring the reaction by TLC, we were able to keep the cleavage of the TBS ether to a minimum, although there were other undefined side reactions leading to diminished yield. Our optimal conditions gave (*Z*)-dienol **4b**[33] from **21b** in two steps in 5% yield. Even this unacceptable procedure was capricious, as we were unable to replicate the yields in later studies. Since we were unable to isolate pure side compounds and identify them, we do not have an explanation for the difference between **22b** and **22c** but note that in the preparation of 2-hydroxysilanes side reactions can lead to complex mixtures under certain conditions.[30] As in the case of γ-hydroxybutenolide **19c**, we found alternative olefination procedures (Tebbe reagent, Lombardo's reagent, etc.) with either **19b** or its corresponding methyl ester gave complex mixtures and very low yields of the desired product.

Synthesis of *Z*-Dienol 4a. In contrast to the difficulties we encountered in the synthesis of **4b**, the synthesis of **4a** proceeded in a manner similar to our approach for the synthesis of **4c**. The peracetic acid oxidation of furan **5a**, however, was significantly slower than the peracetic acid oxidation of either **5b** or **5c**. Fortunately, the *m*-CPBA oxidation was fast, and γ-hydroxybutenolide **19a** (81% yield) was easily separated from 3-chlorobenzoic acid, the side product of the oxidation reaction (Scheme 8). γ-Hydroxybutenolide **19a** has been previously prepared by an alternate route using (*S*)-5-(*tert*-butyldimethylsiloxy)-2-cyclohexenone as the starting material.[5b] In this paper, **19a** was converted into (*Z*)-dienol **4a** in three steps, with the critical methylenation reaction achieved by the use of the Tebbe reagent with the corresponding ethyl ester of **19a**, but the reported yield (48%) was modest. Since we had not been successful in using the Tebbe reagent, which is expensive and difficult to handle, with **19b**, **19c** or their corresponding esters, we felt that the Peterson protocol was worth pursuing in the context of synthesizing (*Z*)-dienol **4a**. The reaction of $LiCH_2Si(CH_3)_3/CeCl_3$ and γ-hydroxybutenolide **19a** gave lactone **21a** (90% yield) as a single diastereomer. Lactonization of the intermediate carboxylic acid/alcohol was slower than the lactonization of **21c** and incomplete with the standard workup procedure, so a catalytic amount of TsOH was added, which gently lactonized the intermediate, before doing the column. The stereochemistry shown for **21a** was consistent with the coupling constants and NOE measurements, which established the *cis* relationship between the (trimethylsilyl)methyl group and the C-7 hydrogen on the ring. The reduction of lactone **21a** to **22a** (90% crude yield) was accomplished in a manner similar to the two-step procedure for the reduction of **21c**, although the reduction of the intermediate lactol was slower and required a greater amount of $NaBH_4$. As in the case of diol **22b**, crude diol **22a** was used without purification and subjected to conditions that minimized the cleavage of the TBS ether. The conversion of **21a** to (*Z*)-dienol **4a** was accomplished in 67% overall yield in three steps.

Conclusion

We have demonstrated the viability of the furan approach to the (*Z*)-dienol moiety of the A-ring of vitamin D_3 analogues. The A-ring (*Z*)-dienol of calcitriol (**4a**), an important intermediate in the synthesis of calcitriol and numerous analogues, was synthesized in 12 steps from 3-(*tert*-butyldimethylsiloxy)propanal in 17% overall yield. The key step in the conversion of **5a** into **4a**, the methylenation of the prerequisite γ-hydroxybutenolide by the Peterson olefination, will not always be the answer (cf. **5b** to **4b**), although in our hands, the Peterson olefination is an excellent alternative to the reaction of the ester of the γ-hydroxybutenolide with the Tebbe reagent.[5b] We are continuing to explore different methylenation methodologies in the hopes of developing a more general protocol for the methylenation of γ-hydroxybutenolides and new alkenylation methodologies for the synthesis of C-19 analogues of vitamin D_3.[34] Further, the synthesis of 2,3-annulated furans with different substitution patterns may allow for the synthesis of A-ring derivatives, which continue to be of interest in the vitamin D field.[35] The reactions of γ-hydroxybutenolides are a rich but underdeveloped field; the diastereoselective addition of the $LiCH_2Si(CH_3)_3/CeCl_3$ to **5a** and **5c** is a glimpse into possible stereoselective synthetic approaches to lactones.[36]

The genesis of this project was our interest in using the highly reactive alicyclic isomer **6** as an ene partner in the ene reaction. Although alicyclic isomer **6** is representative of only a small class of compounds, the potential of alicyclic isomers of aromatic compounds for synthesis has been realized in several studies.[9a−c,37] The asymmetric carbonyl-ene reaction

(33) Blakemore, P. R.; Kocienski, P. J.; Marzcak, S.; Wicha, J. *Synthesis* **1999**, 1209–1215.

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of **6** with electron-rich aldehydes nicely compliments the extensive literature for the asymmetric carbonyl-ene reaction of electron-rich enes with electron-poor enophiles, such as ethyl glyoxylate.[13a] In addition, the intramolecular Friedel–Crafts alkylation (**12** → **5b**), silyloxyalkylation (**7** → *rac*-**5c** and **16** → **5a**), and hydroxyalkylation (**16** → **17**) of 3-substituted furans offers new approaches to 2,3-disubstitued furans. The ability to efficiently and stereoselectively synthesize 2,3-disubstituted furans will not only provide new intermediates for the synthesis of analogues of vitamin D_3 but also potential starting materials for the synthesis of diverse natural products.

Experimental Section

(2*R*)-4-(*tert*-Butyldimethylsiloxy)-1-(3-furyl)butan-2-ol (10). (*R*)-1,1′-Bi-2-naphthol (4.56 g, 15.9 mmol) and $Ti(OCH(CH_3)_2)_4$ (2.35 mL, 2.26 g, 7.96 mmol) were added to 4 Å molecular sieves (5.0 g) in dry ether (100 mL). The reaction mixture was heated to reflux for 1 h, the heating mantel was replaced with a cold (20 °C) water bath, and 3-(*tert*-butyldimethylsiloxy)-propanal (**9**) (16.6 g, 88.1 mmol) was added. 3-Methylene-2,3-dihydrofuran (**6**)[9c] (14.4 g of a 3.5:1 mixture of **6**:3-methylfuran, approximately 136 mmol) then was added immediately over 8 min, with a mild exothermic reaction evident. After the mixture was stirred for an additional 15 min, saturated $NaHCO_3$ (12 mL) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was filtered through a Celite bed, washed with 10% NaOH/brine (150 mL), and filtered through silica gel, washing with additional ether. The volatiles were removed on a rotary evaporator, and the crude product was purified by vacuum distillation (0.5 mm, 110−122 °C) to give **10** (18.68 g, 78% yield, >95% ee) as an oil: $[\alpha]^{22}_D$ +12.3 (*c* 2.0, CH_2Cl_2); IR (neat) 3446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (br s, 1H), 7.28 (br s, 1H), 6.31 (br s, 1H), 3.98 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 3.37 (d, J = 2.2 Hz, 1H), 2.62 (dd, J = 6.8, 14.5 Hz, 1H), 2.55 (dd, J = 5.9, 14.3 Hz, 1H), 1.66 (m, 2H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.0, 140.1, 121.5, 111.6, 72.0, 62.7, 37.8, 31.1, 26.0, 18.3, −5.40, −5.43. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.40; H, 9.96. The enantiomeric excess was determined by the use of the chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene)-(+)-camphorate]. The C-2 furanyl proton resonates at δ 8.34 for (*S*)-**10** and δ 8.25 for **10** as a broad singlet (0.1 M of **10** with 30 mol % $Eu(hfc)_3$ in $CDCl_3$).

(3*R*)-Bis-1,3-(*tert*-butyldimethylsiloxy)-4-(3-furyl)butane (11). To a solution of alcohol **10** (18.33 g, 67.8 mmol) and 2,6-lutidine (12.0 mL, 11.0 g, 103 mmol) in methylene chloride (350 mL) was added TBSOTf (18.0 mL, 20.7 g, 78.4 mmol) over 8 min at 0 °C. After the reaction mixture was stirred for 25 min at 0 °C, methanol (1.0 mL) was added to quench the reaction. After being stirred for an additional 5 min, the reaction mixture was transferred to a separatory funnel with CH_2Cl_2 (200 mL). The organic phase was washed with 0.25 M HCl (200 mL) and brine (200 mL) and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was dissolved in 10% EtOAc in hexanes (300 mL) and filtered through a plug of silica gel. After removal of the volatiles on the rotary evaporator, the crude product was distilled under vacuum (0.3 mm, 125−135 °C) to give **11** (25.09 g, 96% yield) as an oil: $[\alpha]^{22}_D$ −15.9 (*c* 2.0, CH_2Cl_2); IR (neat) 1502 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (t, J = 1.6 Hz, 1H), 7.22 (br s, 1H), 6.28 (br s, 1H), 3.97 (app pentet, J = 5.8 Hz, 1H), 3.65 (m, 2H), 2.59 (dd, J = 6.2, 14.3 Hz, 1H), 2.54 (dd, J = 5.5, 14.3 Hz, 1H), 1.62 (m, 2H), 0.87 (s, 18H), 0.03 (s, 3H), 0.02 (s, 3H), 0.01 (s, 3H), −0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 140.2, 121.4, 112.1, 69.4, 59.9, 39.7, 33.1, 26.05, 26.01, 18.4, 18.2, −4.5, −4.7, −5.3 (2C). Anal. Calcd for $C_{20}H_{40}O_3Si_2$: C, 62.44; H, 10.48. Found: C, 62.39; H, 10.54.

(3*R*)-3-(*tert*-Butyldimethylsiloxy)-4-(3-furyl)butan-1-ol (12). Furan **11** (17.99 g, 46.8 mmol) was added to $THF/H_2O/AcOH$ (300 mL, 50:15:35) and stirred for 16 h at ambient temperature. Na_2CO_3 (120 g) in water (400 mL) was added carefully to quench the reaction. The reaction mixture was transferred to a separatory funnel with EtOAc (250 mL), and the organic phase was separated. The aqueous phase was extracted with EtOAc (2 × 250 mL), the combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (150 g of silica gel; hexanes →15% ethyl acetate in hexanes) to give starting material **11** (3.48 g, 19% yield) and **12** (8.27 g, 65% yield; 81% yield based on recovered starting material) as a clear oil: $[\alpha]^{22}_D$ −19.5 (*c* 0.9, CH_2Cl_2); IR (neat) 3366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (br s, 1H), 7.23 (br s, 1H), 6.26 (br s, 1H), 4.06 (ddd, J = 4.1, 6.5, 12.7 Hz, 1H), 3.81 (m, 1H), 3.70 (app pentet, J = 5.4 Hz, 1H), 2.63 (m, 1H), 2.32 (br s, 1H), 1.78 (m, 1H), 1.62 (m, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.8, 140.2, 121.0, 111.7, 71.8, 60.2, 37.7, 32.7, 26.0, 25.8, 18.1, −4.5, −4.8. Anal. Calcd for $C_{14}H_{26}O_3Si$: C, 62.18; H, 9.69. Found: C, 62.10; H, 9.83.

(5*S*)-5-(*tert*-Butyldimethylsiloxy)-4,5,6,7-tetrahydrobenzo-[2,1-*b*]furan (5b). To a solution of alcohol **12** (5.11 g, 18.9 mmol) and 2,6-lutidine (5.50 mL, 5.06 g, 47.2 mmol) in CH_2Cl_2 (300 mL) was added triflic anhydride (3.40 mL, 5.70 g, 20.2 mmol) dropwise while the reaction mixture was cooled in a cold water bath. The reaction mixture was stirred for 20 h at 22 °C. The reaction mixture was transferred to a separatory funnel, washed with 0.25 M HCl (100 mL), water (100 mL), 5% Na_2CO_3 (100 mL), and brine (100 mL), and dried over Na_2SO_4. After removal of the volatiles on the rotary evaporator, the crude product was purified by flash chromatography (100 g of silica gel; hexanes) to give **5b** (4.36 g) as a yellow oil. Further purification by bulb-to-bulb distillation (125−135 °C, 0.5 mm) gave **5b** (4.00 g, 84% yield) as a colorless oil: $[\alpha]^{22}_D$ −34.6 (*c* 1.0, CH_2Cl_2); IR (neat) 1504 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (br s, 1H), 6.15 (d, J = 1.8 Hz, 1H), 4.05 (m, 1H), 2.56−2.76 (m, 3H), 2.41 (m, 1H), 1.81−1.99 (m 2H), 0.89 (s, 9H), 0.082 (s, 3H), 0.076 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 141.0, 114.9, 110.7, 68.6, 32.1, 32.0, 26.0, 25.8, 21.3, 18.3, −4.5, −4.6. Anal. Calcd for $C_{14}H_{24}O_2Si$: C, 66.61; H, 9.58. Found: C, 66.42; H, 9.61.

(3*R*)-3-(*tert*-Butyldimethylsiloxy)-4-(3-furyl)butanal (16). DMSO (6.8 mL, 7.5 g, 96 mmol) in CH_2Cl_2 (12 mL) was added to oxalyl chloride (4.2 mL, 6.1 g, 48 mmol) in CH_2Cl_2 (100 mL) over 5 min at −65 °C. After the mixture was stirred at −65 °C for 8 min, alcohol **12** (8.240 g, 30.5 mmol) in CH_2Cl_2 (20 mL) was added to the reaction mixture over 10 min. After the mixture was stirred for an additional 10 min, NEt_3 (16.5 mL, 12.0 g, 120 mmol) was added over 1 min. After the reaction mixture was allowed to warm to ambient temperature, it was transferred to a separatory funnel with water (200 mL) and additional CH_2Cl_2 (100 mL). The organic phase was separated and the aqueous phase extracted with CH_2Cl_2 (100 mL). The combined organic phases were washed with brine (100 mL) and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was redissolved in petroleum ether (250 mL), washed with water, and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator to give the crude **16** (8.122 g, 99% yield) as an oil that was used without further purification: IR (CH_2Cl_2) 2726, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, J = 2.2 Hz, 1H), 7.35 (t, J = 1.6 Hz, 1H), 7.24

(37) For recent examples, see: Camp, J. E.; Craig, D. *Tetrahedron Lett.* **2009**, *50*, 3503–3508. Miles, W. H.; Dethoff, E. A.; Tuson, H. H.; Ulas, G. *J. Org. Chem.* **2005**, *70*, 2862–2865. Tidwell, J. H.; Senn, D. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 4685–4686.

(br s, 1H), 6.28 (br s, 1H), 4.34 (app pentet, J = 5.9 Hz, 1H), 2.65 (m, 2H), 2.51 (m, 2H), 0.87 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.9, 143.0, 140.5, 120.4, 111.8, 68.3, 50.3, 33.3, 25.9, 18.1, −4.5, −4.8. Aldehyde **16** is thermally unstable and unstable on silica gel; we used it immediately or stored it in the freezer.

(5*R*,7*S*)-5-(*tert*-Butyldimethylsiloxy)-4,5,6,7-tetrahydro-1-benzofuran-7-ol (17). Small-Scale Procedure (Entry 1, Table 2). Molecular sieves (3 Å, 0.25 g) were dried under vacuum (0.05 mm) at 180 °C for 16 h. After they were cooled to room temperature, CH_2Cl_2 (3 mL), (*R*)-BINOL (0.098 g, 0.34 mmol), and Ti(O-*i*-Pr)$_4$ (0.050 mL, 0.048 g, 0.169 mmol) were added, and the mixture was refluxed for 1 h. Aldehyde **16** (0.45 g, 1.68 mmol) was added in one portion at 22 °C, and the reaction mixture was stirred for 1 h. Saturated Na_2CO_3 (1 mL) was added, and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was filtered, transferred to a separatory funnel with CH_2Cl_2 (100 mL), washed with 0.25 M NaOH (2 × 30 mL) and brine (200 mL), and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (30 g of silica gel; 5→10% ethyl acetate in hexanes) to give **17** (0.348 g, 77% yield; **17**:*cis*-**17**, 16:1) as a clear oil.

(5*R*,7*S*)-5-(*tert*-Butyldimethylsiloxy)-4,5,6,7-tetrahydro-1-benzofuran-7-ol (17). Preparative Procedure. Molecular sieves (3 Å, 2.5 g) were dried under vacuum (0.05 mm) at 170 °C for 16 h. After they were cooled to room temperature, CH_2Cl_2 (50 mL), Ti(O(CH(CH$_3$)$_2$)$_4$ (1.00 mL, 0.963 g, 3.39 mmol), and (*R*)-BINOL (2.00 g, 6.98 mmol) were added, and the mixture was refluxed for 1 h. Aldehyde **16** (7.90 g, 29.4 mmol) was added in one portion, and the reaction mixture was stirred at 0 °C for 0.5 h and then for 4 h at 22 °C. Saturated Na_2CO_3 (20 mL) was added, and the reaction mixture was stirred for 1 h at ambient temperature. The reaction mixture was transferred to a separatory funnel with water (200 mL) and CH_2Cl_2 (300 mL) and separated, and the aqueous phase was extracted with additional CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with 0.25 M NaOH (100 mL) and brine (200 mL) and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was dissolved in EtOAc (100 mL) and filtered through a plug of silica gel, washing with additional EtOAc. After removal of the solvent on the rotary evaporator, the crude product was purified by flash chromatography (100 g of silica gel; 10% ethyl acetate in hexanes) to give **17** (5.40 g, 68% yield; **17**:*cis*-**17**, 14:1) as a clear oil: $[\alpha]^{22}_D$ −41.5 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 3352 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 1.8 Hz, 1H), 6.18 (d, J = 1.8 Hz, 1H), 4.88 (br t, J = 3.5 Hz, 1H), 4.30 (m, 1H), 2.75 (dd, J = 4.9, 15.6 Hz, 1H), 2.37 (dd, J = 8.6, 15.6 Hz, 1H), 1.9−2.1 (m, 3H), 0.90 (s, 9H), 0.102 (s, 3H), 0.097 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 143.1, 118.5, 110.5, 65.6, 62.4, 41.8, 32.3, 26.0, 18.3, −4.5, −4.6. Anal. Calcd for $C_{14}H_{24}O_3Si$: C, 62.64; H, 9.01. Found: C, 62.88; H, 9.02. Partial ^{1}H NMR (400 MHz, $CDCl_3$) of *cis*-**17**: δ 7.35 (d, J = 1.5 Hz), 6.21 (d, J = 1.5 Hz), 4.69 (m), 4.43 (m), 0.86 (s).

(5*R*,7*S*)-5,7-Bis(*tert*-butyldimethylsiloxy)-4,5,6,7-tetrahydro-1-benzofuran (5a). To a solution of alcohol **17** (5.22 g, 19.4 mmol; **17**:*cis*-**17**, 14:1) in DMF (20 mL) were added imidazole (2.00 g, 29.4 mmol) and *tert*-butyldimethylsilyl chloride (3.92 g, 26.0 mmol). After being stirred for 1.5 h at 22 °C, the reaction mixture was poured into water (150 mL) and extracted with ether (3 × 150 mL). The combined organic extracts were washed with 0.1 M HCl (100 mL) and brine (200 mL) and dried over Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product (composed of **5a** and *cis*-**5a**) was purified by flash chromatography (100 g of silica gel; hexanes → 2% ethyl acetate in hexanes) to give **5a** (6.24 g, 84% yield) as a colorless oil: $[\alpha]^{22}_D$ −40.9 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (br s, 1H), 6.15 (br s, 1H), 4.81 (m, 1H), 4.34 (m, 1H), 2.73 (dd, J = 5.1, 15.4 Hz, 1H), 2.33 (dd, J = 9.2, 15.4 Hz, 1H), 2.10 (m, 1H), 1.92 (m, 1H), 0.91 (s, 9H), 0.90 (s, 9H), 0.14 (s, 3H), 0.09 (br s, 6H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.7, 142.5, 117.9, 110.4, 65.8, 62.8, 43.0, 32.4, 26.1, 26.0, 18.42, 18.39, −4.58, −4.60, −4.65, −4.8. Anal. Calcd for $C_{20}H_{38}O_3Si_2$: C, 62.77; H, 10.01. Found: C, 62.82; H, 10.15.

(5*R*,7*S*)-5,7-Bis(*tert*-butyldimethylsiloxy)-4,5,6,7-tetrahydro-1-benzofuran (5a) from 16. Aldehyde **16** (0.220 g, 0.820 mmol) was dissolved in methylene chloride (3 mL), the solution was cooled to 0 °C, and 2,6-lutidine (0.25 mL, 0.32 g. 2.1 mmol) was added. TBSOTf (0.25 mL, 0.29 g, 1.1 mmol) was added dropwise. After being stirred for 5 min at 0 °C, the reaction was allowed to warm to room temperature and quenched with water (2 mL). The reaction mixture was transferred to a separatory funnel with water (30 mL) and methylene chloride (30 mL). The organic phase was separated, washed with 0.5 M HCl (50 mL) and brine (50 mL), and dried over $MgSO_4$, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (20 g of silica gel; hexanes) to give a 3:1 mixture of **5a** and *cis*-**5a** (0.22 g, 70% yield) as an oil.

(5*R*,7*S*)-Bis(*tert*-butyldimethylsiloxy)-7a-hydroxy-5,6,7,7a-tetrahydro-1-benzofuran-2(4*H*)-one (19a)[5b]. Sodium acetate (1.89 g, 23.0 mmol) and *m*-CPBA (4.32 g, 77%; 19.3 mmol) were added to furan **5a** (3.041 g, 7.95 mmol) in CH_2Cl_2 (100 mL) at 22 °C. After the initial exothermic reaction, the reaction mixture was stirred for an additional 1.25 h at ambient temperature. The reaction mixture was washed with water (100 mL), the aqueous phase was extracted with additional CH_2Cl_2 (100 mL), and the combined milky organic phases were filtered through a plug of silica gel, washing the silica gel with CH_2Cl_2 (50 mL). After the volatiles were removed on the rotary evaporator, the crude product was redissolved in hexanes and ether (100 mL; 3:1), washed with 10% $NaHCO_3$ (2 × 20 mL), water (50 mL), 1 M HCl (25 mL), and brine (2 × 50 mL), and dried over Na_2SO_4, and the solvent was removed on the rotary evaporator. The crude product was purified by flash chromatography (100 g of silica gel; hexanes → 15% ethyl acetate in hexanes) to give **19a** (2.646 g, 81% yield) as a white solid: mp 99−105 °C; $[\alpha]^{22}_D$ −73.6 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 3498, 1763, 1665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, J = 2.2 Hz, 1H), 4.49 (s, 1H), 4.26 (m, 1H), 4.07 (dd, J = 5.1, 11.0 Hz, 1H), 2.66 (dt, J = 2.6, 13.6 Hz, 1H), 2.53 (dt, J = 2.6, 13.6 Hz, 1H), 1.89 (m, 1H), 1.69 (ddd, J = 2.3, 11.1, 13.5 Hz, 1H), 0.91 (s, 9H), 0.82 (s, 9H), 0.16 (s, 3H), 0.11 (s, 3H), 0.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 163.7, 119.3, 104.0, 72.5, 66.5, 39.3, 34.4, 25.6, 25.5, 18.2, 18.0, −4.6, −4.8, −4.93, −4.95.

(5*R*,7*S*,7a*R*)-5,7-Bis(*tert*-butyldimethylsiloxy)-7a-[(trimethylsilyl)methyl]-5,6,7,7a-tetrahydro-1-benzofuran-2(4*H*)-one (21a). $CeCl_3 \cdot 7H_2O$ (1.98 g, 5.31 mmol) was dried under vacuum (0.1 mm) at 140 °C for 2 h. THF (15 mL) was added, and the slurry was stirred for 1 h at room temperature. After the mixture was cooled to −78 °C, $LiCH_2Si(CH_3)_3$ (5.3 mL, 4.5 mmol, 0.85 M in pentane) was added dropwise over 5 min, and the reaction mixture was stirred at −78 °C for 0.5 h. γ-Hydroxybutenolide **19a** (0.518 g, 1.25 mmol) was added in one portion, and the reaction mixture was stirred at −78 °C for 0.5 h and then at −42 °C for 3 h. TMEDA (0.57 mL, 3.8 mmol) was added, and the reaction mixture was stirred for 0.25 h. The reaction mixture was poured into saturated ammonium chloride (20 mL) and 2.5 M HCl (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine (100 mL), dried over sodium sulfate, and decanted into a clean Erlenmeyer flask. The solution of the crude product (^{1}H NMR indicated variable ratios of the lactone **21a**, and the corresponding open-chain carboxylic acid/alcohol) was treated with TsOH (0.060 g) in CH_2Cl_2 (20 mL) for 30 min. The mixture was transferred to a separatory funnel, washed with 5% Na_2CO_3 (100 mL) and brine (100 mL), and dried over sodium sulfate, and

the solvent was removed on the rotary evaporator. The crude product was purified by flash chromatography (50 g of silica gel; 5% ethyl acetate in hexanes) to give the lactone **21a** (0.549 g, 90% yield) as a solid: mp 126.0−128.0 °C; $[\alpha]^{22}_{D}$ +52.2 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 1750, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.73 (d, J = 1.8 Hz, 1H), 4.00−4.10 (m, 2H), 2.90 (ddd, J = 2.0, 5.3, 12.8 Hz, 1H), 2.33 (ddd, J = 2.0, 10.4, 12.6 Hz, 1H), 1.93 (m, 1H), 1.82 (ddd, J = 1.9, 10.7, 14.0 Hz, 1H), 1.22 (d, J = 15.0 Hz, 1H), 1.16 (d, J = 15.0 Hz, 1H), 0.88 (s, 9H), 0.81 (s, 9H), 0.06 (s, 3H), 0.05 (br s, 6H), 0.04 (br s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 169.9, 115.7, 89.2, 73.5, 68.3, 39.5, 36.8, 25.9, 25.8, 23.7, 18.2, 18.0, −0.0, −4.7 (2C), −5.0, −5.2. Anal. Calcd for $C_{24}H_{48}O_4Si_3$: C, 59.45; H, 9.98. Found: C, 59.29; H, 10.31.

(2*Z*)-2-[(3*S*,5*R*)-3,5-Bis(*tert*-butyldimethylsiloxy)-2-methylenecyclohexylidene]ethanol (4a). Lactone **21a** (0.575 g, 1.19 mmol) was dissolved in toluene (10 mL) and cooled to −78 °C, and DIBAL (2.9 mL, 1.2 M in toluene, 3.5 mmol) was added dropwise. The reaction mixture was stirred for 1 h at −78 °C and then allowed to slowly warm to −30 °C. Methanol (0.25 mL) and then 30% sodium potassium tartrate (20 mL) were added to quench the reaction mixture. The reaction mixture was transferred to an Erlenmeyer flask and stirred vigorously with ether (40 mL) for 1 h. The organic phase was separated, and the aqueous phase was extracted with ether (2 × 40 mL). The combined extracts were washed with brine (100 mL), dried over sodium sulfate, and concentrated on the rotary evaporator. The crude lactol was dissolved in ethanol (5 mL), and $NaBH_4$ (0.40 g, 10 mmol) was added. After the reaction mixture was stirred at 22 °C for 18 h, water (15 mL) and ether (15 mL) were added, and the reaction mixture was stirred for 30 min. The reaction mixture was transferred to a separatory funnel, the phases were separated, and the aqueous phase was extracted with ether (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, and concentrated on the rotary evaporator to give crude diol **22a** (0.574 g), which was used in the next reaction without further purification due to loss of yield on silica gel. Diol **22a** was an oil that slowly solidified: mp 58−60 °C; $[\alpha]^{22}_{D}$ +9.1 (*c* 1.1, CH_2Cl_2); IR (CH_2Cl_2) 3443, 1646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.51 (t, J = 6.2 Hz, 1H), 4.21−4.35 (m, 2H), 3.92 (m, 1 H), 3.67 (br t, J = 3.0 Hz, 1H), 3.32 (br s, 1H), 2.58 (dd, J = 3.7, 8.1 Hz, 1H), 2.20−2.25 (m, 2H), 1.91 (m, 1H), 1.81 (ddd, J = 2.2, 11.0, 13.9 Hz, 1H), 1.23 (d, J = 15.0 Hz, 1H), 1.17 (d, J = 15.4 Hz, 1H), 0.90 (s, 9H), 0.88 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H), 0.07 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.7, 126.5, 78.8, 78.1, 67.8, 59.3, 45.8, 39.7, 26.9, 26.0, 25.9, 18.3, 18.1, 0.5, −4.1, −4.5, −4.6, −4.9.

Crude diol **22a** was dissolved in CH_3CN (15 mL), and HF in CH_3CN (0.35 M; 1.0 mL, 0.35 mmol; stock solution prepared by the addition 48% HF to CH_3CN) was added in one portion. Additional HF in CH_3CN (0.35 M; 2 × 0.5 mL, 0.35 mmol) was added after 10 and 20 min. After the mixture was stirred at room temperature (while carefully monitoring the reaction mixture by TLC) for a total of 30 min, hexane (50 mL) was added followed by water (6 mL). After being stirred for 1 min, the hexane layer was decanted, and the aqueous CH_3CN phase was extracted with further hexane (2 × 50 mL). The combined hexane extracts were dried with Na_2SO_4, and the volatiles were removed on the rotary evaporator. The crude product was purified by flash chromatography (50 g of silica gel; 5% ethyl acetate in hexanes) to give **4a** (0.301 g, 67% yield from **21a**) as a white solid: mp 68−70 °C (lit.[4a] mp 69−71 °C). $[\alpha]^{25}_{D}$ +7.8 (*c* 0.40, EtOH) [lit.[4a] $[\alpha]^{25}_{D}$ +7.9 (*c* 0.4, EtOH)]; IR (CH_2Cl_2) 3609, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (t, J = 7.0 Hz, 1H), 5.15 (m, 1H), 4.76 (m, 1H), 4.39 (m, 1H), 4.15−4.21 (m, 3H), 2.40 (br dd, J = 3.7, 13.2 Hz, 1H), 2.18 (dd, J = 6.8, 13.0 Hz, 1H),1.78−1.85 (m, 2H), 1.30 (br s, 1H), 0.87 (s, 9H), 0.86 (s, 9H), 0.06 (s, 3H), 0.052 (s, 3H), 0.050 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 139.6, 126.8, 110.8, 71.5, 67.5, 59.8, 45.4, 44.7, 25.93, 25.91, 18.3, 18.2, −4.6, −4.72, −4.74, −4.9.

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Supporting Information Available: Experimental details and characterization data for **4b**,**c**, **5b**,**c**, *rac*-**5c**, **7**−**14**, **16**, **17**, **19b**,**c**, **21b**,**c**, and **22c**; copies of ^1H and ^{13}C NMR spectra for **4**, **5**, **7**−**14**, **16**, **17**, **19**, **21**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.