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Cerium(III) Chloride-Mediated Reactions of Sulfonamide Dianions

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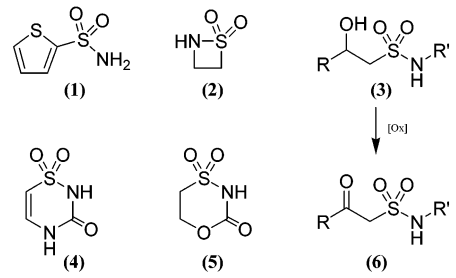
Received January 1, 2003

Presented here is the first report on the ability of cerium(III) chloride to mediate high-yielding and, oftentimes, highly diastereoselective additions of *N*-benzyl-α, *N*-dilithio methanesulfonamide to aldehydes and ketones of biological importance. Smooth addition was effected to base-sensitive substrates such as Fmoc-protected alaninal, citral, 5-cholesten-3-one, uridine 5′-aldehyde, 3′-ketouridine, and 3′-ketothymidine. The reaction was chemoselective for aldehydes in the presence of nitriles. Acetoxy groups are labile and thus not suitable protecting groups for alcohols under these conditions. *N*-Benzyl-α, *N*-dilithio methanesulfonamide was found to be of sufficient basicity to cause enolate formation with sensitive substrates, such as 1-phenylacetone. However, the addition of cerium(III) chloride mediated the basicity of the dianion and suppressed enolate formation in these cases. Further, cerium(III) has general utility for the addition of various *N*-aliphatic/aromatic methanesulfonamide dianions to 3′-ketouridine.

Introduction and Background

The sulfonamide functional group has received considerable attention in the pharmaceutical arena. Sulfonamides are the bioactive moiety in compounds with antibacterial, antibiotic, and antidiabetic properties and are found in compounds used to treat glaucoma and edema. Sulfanilamide, an antibacterial sulfonamide, has played a historically fundamental role in the advancement of structure−activity relationships, the theory of antimetabolites, the understanding of prodrugs, and the use of pharmacokinetics in drug development.[1] The pharmaceutical industry continues to explore new scaffolds that incorporate the sulfonamide moiety. A few examples are shown in Chart 1 and include 5-substituted thiophene-2-sulfonamides (**1**),[2] β-sultams (**2**),[3] and *N*-alkyl-β-hydroxy-sulfonamides (**3**).[4] Interest in new sulfonamide scaffolds has also extended to such compounds as 2*H*-1, 2, 4-thiadiazin-3(4*H*)-one 1,1-dioxides (**4**) and 5,6-dihydro-1,4,3-oxathiazin-2(3 *H*)-one 4,4-dioxides (**5**).[5] Other moieties related to *N*-alkyl-β-hydroxy-sulfonamides are *N*-alkyl-2-oxoalkanesulfonamides (**6**). This group, whose properties and applications[6] are not yet fully realized, has received limited description in the literature.[7,8] Aside from these important sulfonamide functional moieties, sulfonamide derivatives such as *N*-alkyl sulfonamides are of current interest in a variety of applications.[9] The zinc-chelating properties of *N*-alkyl sulfonamides have been utilized in ligands for the enantioselective titanium tetraisopropoxide-promoted addition of dialkylzinc to aldehydes.[10−12] In addition, *N*-alkyl sulfonamides have been exploited as nuclease-resistant phosphate surrogates[13,14] and as peptide mimetics.[15−18]

CHART 1. Sampling of Sulfonamide Scaffolds



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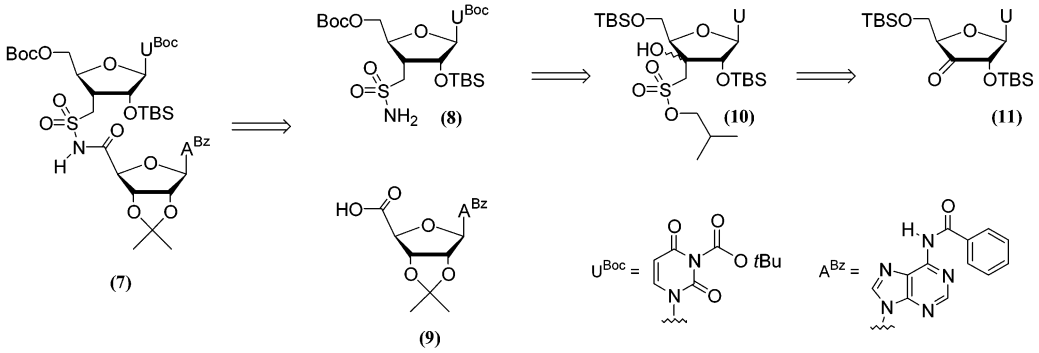
10.1021/jo034001w CCC: $25.00
Published on Web 05/31/2003

SCHEME 1. *N*-Acyl Sulfonamide-Bridged Dinucleoside



We have recently described the synthesis of *N*-acyl sulfonamide derivatives of nucleosides.[19,20] In one of these studies, we prepared the first *N*-acyl sulfonamide-bridged dinucleoside (**7**). The strategy relied upon condensation of sulfonamide **8** with adenosine carboxylic acid **9**. The synthesis of sulfonamide **8** was lengthy and necessitated a functional group interconversion from a sulfonate to a sulfonamide. Briefly, sulfonamide **8** was obtained from ketouridine **11** through the intermediacy of isobutyl sulfonate **10**[21] (Scheme 1). We desired a more facile entry into molecules resembling sulfonamide **8**. One approach would be to *C*-alkylate methanesulfonamide with ketouridine **11**, thus introducing the sulfonamide functional group in a more direct fashion. Thompson has described a direct and useful method for the *C*-alkylation of *N*-protected methanesulfonamide derivatives via the corresponding sulfonamide dianion.[22] We felt that this method could be adapted to provide a more facile entry to nucleoside sulfonamides such as **8**. However, the possible detrimental effects of a dianion on base-sensitive 3′-ketonucleosides such as **11** raised some concerns. Miyasaka and co-workers have shown that ketouridine **11** decomposes under strongly basic conditions providing uracil as one of the byproducts.[23]

Generally, ketonucleosides give moderate yields of the carbonyl addition product upon reaction with Grignard,[23,24] organolithium,[21,23] organoaluminum,[23] and magnesium aluminate[25] reagents. Particularly problematic are carbonyl addition reactions involving 2′-deoxy-3′-ketonucleosides with basic reagents, where β-elimination of the nucleobase readily occurs. A significant advancement in carbonyl addition reactions of 3′-ketonucleosides was detailed by Bender and Moffett.[26] They demonstrated that organocerium reagents facilitate carbonyl addition reactions with 2′-deoxy-3′-ketonucleosides giving yields in excess of 90%. Since Bender and Moffet's original report, several groups have used organocerium reagents derived from vinyl,[27] allyl,[28] or trimethylsilylacetylide[29−31] to effect carbonyl addition reactions with 3′-ketonucleosides. The products were often obtained in high yields and with good diastereoselectivity. Since their introduction,[32] organocerium reagents have been utilized to promote mild and selective addition reactions to aldehydes, ketones, esters, nitriles, hydrazones, and other functional groups while minimizing side reactions.[33−39] It is interesting to note that an organocerium reagent of a dianion has never been utilized for addition to a carbonyl substrate.[40,41,42]

Typically, dianions have been employed as chiral auxiliaries[43] for cerium in synthetic applications.[44−46] In nonsynthetic applications, cerium complexes with cyclooctatetraene dianion,[47−49] porphyrin dianion,[50] and

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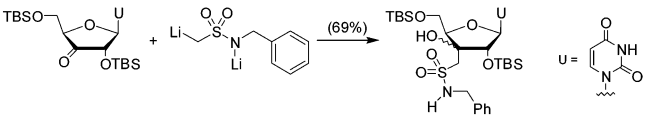
benzene dianion[51] have been investigated to illuminate bonding, structural, and atomic properties. We felt that it would be interesting to evaluate if cerium could mediate the basicity of a dianion sufficiently to promote the addition of the dianion to an easily enolizable carbonyl substrate. Heterofunctional dianions such as amides and sulfonamides have wide utility in synthesis.[52,53] Myers et al. have demonstrated the use of pseudoephedrine as a chiral auxiliary for the asymmetric alkylation of the pseudoephedrine amide enolate dianion.[54,55] The alkylation of this dianion gives facile access to enatiomerically enriched carboxylic acids, alcohols, aldehydes, and ketones.[56] Additionally, both enantiomers of α-amino acids[57] are obtainable by this methodology as are γ-lactones and γ-hydroxy ketones.[58] The methodology for alkylation of sulfonamide dianions introduced by Thompson was extended by Poss and Reid in the construction of sulfonamide-containing rennin inhibitors.[4] Campbell and Hart have utilized sulfonamide dianions in the construction of reagents for Mitsunobu reactions, subsequently used for the synthesis of manzamine alkaloids.[59] Additionally, Graham and Scholz have used sulfonamide dianions in the development of topically active carbonic anhydrase inhibitors for the treatment of glaucoma.[2] Numerous other examples, including methodology for the construction of heterocycles,[60−64] asymmetric synthesis of sulfonamides,[65] and directed *ortho* metalation of arylsulfonamides,[66] attest to the synthetic utility of sulfonamide dianions.

The utility of dianions and the applications being discovered for *N*-alkyl sulfonamides are but a few reasons to explore new methodology with *N*-alkyl sulfonamides. Further, the lack of precedent for alkylation of dianions in the presence of cerium raises a more fundamental question. Is cerium(III) chloride capable of mediating the basicity of a dianion such as *N*-benzyl-α, *N*-dilithio methanesulfonamide to promote clean, high-yielding additions with carbonyl substrates? Therefore, we sought to investigate the effect cerium(III) chloride might have upon *C*-alkylation of *N*-benzyl-α, *N*-dilithio methanesulfonamide by a variety of carbonyl compounds of biological importance such as nucleosides, α-amino aldehydes, steroids, and sugars.

Results and Discussion

Our first attempts to alkylate *N*-benzyl-α, *N*-dilithio methanesulfonamide (**12**) were with ketouridine **11**. Because ketouridine **11** contains an acidic ureido proton, the literature procedure[22] was modified to account for the additional acidic proton of **11**. Using this modified procedure, the desired *C*-alkylated sulfonamide was obtained in 69% yield (eq 1) with no recovery of ketouridine **11**. Further optimization, (careful titration[67] of BuLi/changes in BuLi stoichiometry/temperature/reaction time/cosolvents such as HMPA) led to little further improvement in yield (70−71%, OH_α:OH_β = 13:87).[68] The conditions described in the literature were clearly already optimal. We then sought to improve the yield for the addition of dianion **12** to ketouridine **11** by employing cerium(III) chloride.



(1)

Subjecting ketouridine **11** to the dianion **12**/$CeCl_3$ mixture afforded uridine-sulfonamide **13** in 28% yield as a single diastereomer[69] (3′-OH_β). Significantly, ketouridine **11** was recovered in 69% yield. Thus, the cerium-mediated addition showed potential in both its ability to provide a single diastereomer and for the recovery of unreacted starting material. Optimization of this reaction (Table 1) led to a procedure utilizing a molar ratio of 1:8:8.2 (ketone:**12**:$CeCl_3$). This ratio provided the desired uridine-sulfonamide **13** in 99% yield as a single diastereomer (3′-OH_β).

We were curious about the effect cerium(III) would have upon dianion **12** in reaction with a variety of base-sensitive compounds. Was the improved yield and diastereoselection obtained for ketouridine **11** a general trend? To examine this possibility, we subjected citral (**14**) and 1,2,5,6-di-*O*-isopropylidene-3-oxo-α-D-glucofuranose (**16**) to reaction with dianion **12**. These compounds were chosen because citral has allylic protons that could be deprotonated by strong base, and glucofuranose **16** is similar to ketouridine **11** yet lacks the acidic ureido proton and ligation sites of the nucleobase. In the absence of cerium(III), moderate yields were obtained for the

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(68) Several reports have appeared in the literature documenting problems with the generation and/or chemoselective reactivity of sulfonamide dianions (refs 3, 9, 59−61). Therefore, to ensure generation of the sulfonamide dianion was being accomplished under the reaction conditions, the dianion was generated and quenched with perdeutero acetic acid. Isolation of the products afforded *N*-benzyl methanesulfonamide with a D:H ratio of 92:8 as determined by ^{1}H NMR integration (See Supporting Information for procedure). The failure to quantitatively incorporate deuterium into the dianion is a result of a kinetic isotope effect. However, these results qualitatively established the formation of the sulfonamide dianion.
(69) Within the limits detectable by NMR analysis.

TABLE 1. Optimization of $CeCl_3$-Mediated Addition of Dianion 12 to Ketouridine 11[a]

entry	ketone **11** (M)	dianion **12** (equiv)	$CeCl_3$ (equiv)	% yield product	% yield ketone	temp (°C)	time (h)
1	0.65	2.1	2.15	28	69	−75 to −30	5
2	0.65	4.0	4.2	43	55	−75 to −30	2
3	0.65	6.4	6.6	72	25	−75 to −30	5
4	0.65	8.0	8.2	99	c	−75 to −30	5
5[b]	0.65	8.0	0	30	c	−75 to −30	5

[a] All reactions were performed with 200 mg of ketone **11**. The concentration of sulfonamide was 0.29 M for entries 1−4. [b] Control reaction: sulfonamide was diluted with the volume of THF used to suspend $CeCl_3$ in entry 4. [c] No ketone detected within the limits of NMR analysis.

SCHEME 2. Addition of Dianion 12 to Base-Sensitive Substrates Following a Literature[22] Protocol

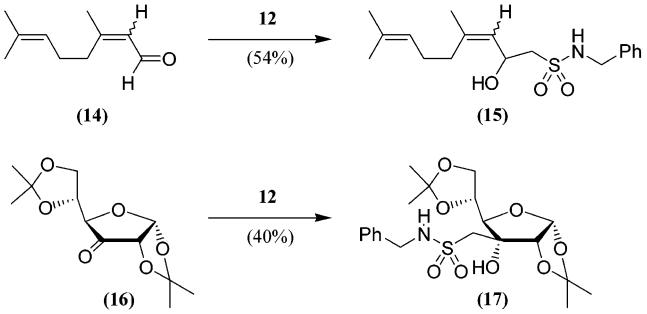

TABLE 2. Optimization of Selected Substrates with Dianion 12/$CeCl_3$ [a,b]

substrate	product	procedure/% yield this study	procedure/% yield literature[c]
14	15	82	54
16	17	84 (67)	40

[a] Reactions conducted as described in the Experimental Section with a molar ratio of 1:1.2:1.3 (substrate/**12**/$CeCl_3$). [b] Value in parentheses is the yield of reaction without $CeCl_3$ added, all other factors remaining constant. [c] Protocol for the general addition of sulfonamide dianions to carbonyl substrates.[22]

addition of dianion **12** to citral (54%) or glucofuranose **16** (40%) using the conditions described for the addition of sulfonamide dianions with carbonyl substrates in the published protocol (Scheme 2). However, in the presence of cerium(III), dianion **12** added to citral (82%) and glucofuranose **16** (84%) in considerably higher yield (Table 2). In contrast to the cerium-mediated reaction with ketouridine **11**, a more moderate molar ratio of reactants of 1:1.2:1.3 (substrate:**12**:$CeCl_3$) was found to provide good yields of the products. This stoichiometry is markedly different from that employed with ketouridine **11**.

To ensure that $CeCl_3$ was responsible for the improved yield with ketouridine **11** and glucofuranose **16**, these reactions were run in the absence of $CeCl_3$ maintaining the same concentrations and reaction conditions used for the cerium-mediated reactions. Both ketouridine **11** and glucofuranose **16** were converted to product in reduced yield in the absence of $CeCl_3$ (30 and 67% yields, respectively; Table 1, entry 5; Table 2). It should be noted that the excess of organocerium reagent required for reaction with ketonucleosides appears to be general. For example, Bender and Moffett detailed the addition of alkyl, alkenyl, and alkynyl organocerium reagents to 2′-deoxy-3′-ketonucleosides requiring in excess of 6 equiv of the alkylating species.[26] Similarly Lenz and Giese,[27] Wengel and co-workers,[28] as well as Biellmann and colleagues[29,31] employed in excess of 6 equiv of organocerium reagent with ketonucleosides.

Why such an excess of organocerium reagent is necessary in reaction with ketonucleosides is unknown. However, during optimization of the reaction, it was found that varying the stoichiometry of the cerium resulted in varying yields of the product. It is possible that the hard Lewis acidity[70,71] of cerium(III) promotes ligation to the nitrogen and oxygen functionalities of the nucleobase. Another possibility is that in this reaction the kinetic order in cerium is quite high. Our current results do not clarify which of these possibilities is operative. However, the ligation possibility is supported by the reaction of glucofuranose **16** with dianion **12**/$CeCl_3$, where a near stoichiometric ratio of substrate to organocerium reagent provides the desired product in good yield.

A series of molecules with base-sensitive functionalities were chosen to test the general ability of cerium(III) chloride to mediate the addition of dianion **12** to carbonyl substrates. For this study we selected a representative assortment of substrates that collectively possess multiple electrophilic sites and contain base-sensitive protecting groups, acidic protons (i.e., benzylic or β, γ-enones capable of isomerization), and functionality known to be reactive toward organocerium reagents (i.e., nitrile, ester, aldehyde. etc.). Table 3 summarizes the results obtained for a representative collection of biologically important molecules subjected to the optimized conditions for synthesis of uridine-sulfonamide **18** (substrate: **12**:$CeCl_3$ = 1:8:8.2). It should be mentioned that these conditions are not optimal for each substrate tested. However, applying these conditions involving an excess of the organocerium reagent toward sensitive molecules demonstrates the potential for the reagent combination of dianion **12**/$CeCl_3$ for future applications.

Dianion **12** added smoothly to carbonyl groups in the presence of $CeCl_3$ to substrates possessing base-sensitive functionality. Although we employed a protocol that had been optimized for ketouridine **11**, many other substrates were obtained in good to high yield with recovery of the unconverted starting material noted in several instances. Excellent diastereoselection was also obtained for many of the substrates. Particularly notable examples include reaction of 2′-deoxy-3′-ketothymidine **19** and ketouridine **11**. Reaction of both nucleosides with dianion **12**/$CeCl_3$

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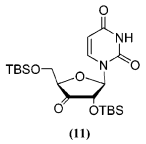
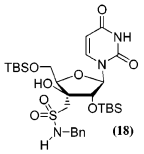
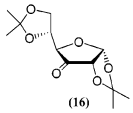
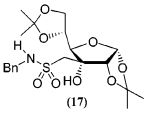
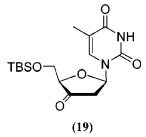
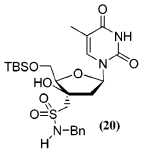
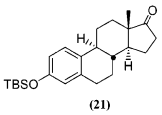
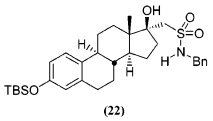
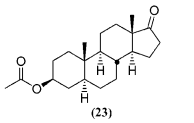
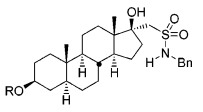
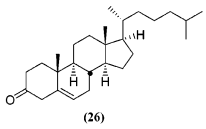
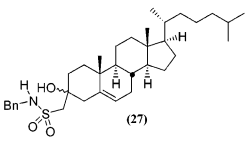
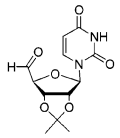
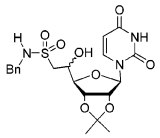
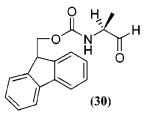
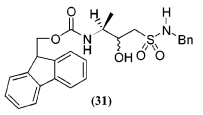
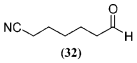
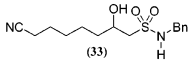
TABLE 3. $CeCl_3$-Mediated Addition of *N*-Benzyl-α, *N*-Dilithio Methanesulfonamide to Base-Sensitive Substrates[a,b]

Substrate	Product	Yield (%)	Recovered Substrate (%)
 (11)	 (18)	99 (30[c])	—
 (16)	 (17)	73	—
 (19)	 (20)	67 (25[d])	—
 (21)	 (22)	78	21
 (23)		71 (R= H) (**24**) + 6 (R= Ac) (**25**)	—
 (26)	 (27)	83 (OH_α: OH_β= 40: 60)	—
 (28)	 (29)	70 (*dr* = 76: 24)	29[e]
 (30)	 (31)	68 (*dr* = 69: 31)	—
 (32)	 (33)	92	—

[a] Reactions conducted as described in the Experimental Section using procedure A with a molar ratio of 1:8:8.2 (substrate:**12**:$CeCl_3$). [b] Values in parentheses are yields of reaction without $CeCl_3$ added, all other factors remaining constant. [c] Ratio of OH_α:OH_β = 20:80. [d] Ratio of OH_α:OH_β = 15:85. [e] Recovered as the hydrate.

were fully diastereoselective.[72] However, in the absence of $CeCl_3$, mixtures of diastereomers were obtained. In this regard, the addition of dianion **12**/$CeCl_3$ to 5-cholesten-3-one (**26**) merits comment.

Large nucleophiles such as dianion **12** approach six-membered cyclic ketones on trajectories that minimize steric strain in the transition state.[73] Presumably, minimization of steric strain is achieved by an equatorial approach of the nucleophile.[74] Therefore, addition of dianion **12**/$CeCl_3$ to 5-cholesten-3-one (**26**) is expected to yield product with the hydroxyl group α as the major product. However, the major diastereomer formed in a ratio of 3:2 is formed by axial addition of the reagent, resulting in the hydroxyl group being *β*. This suggests

(72) Within the limits detectable by NMR analysis.
(73) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546.
(74) Atkinson, R. S. In *Stereoselective Synthesis*; John Wiley & Sons: Chichester, UK, 1995; pp 273−314.

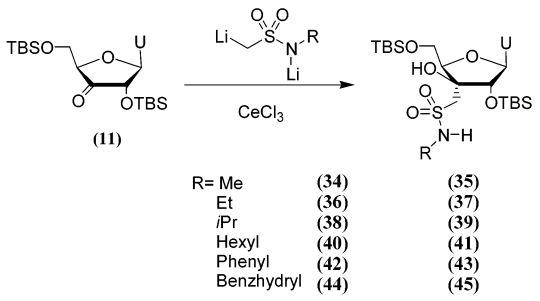
that the methyl substituent at C_{10} of 5-cholesten-3-one is not providing sufficient steric hindrance to afford a single diastereomer. However, Imamoto et al. added phenylethynyllithium/$CeCl_3$ to **26** and reported the formation of a single diastereomer.[75]

The addition of dianion **12**/$CeCl_3$ to acyclic α-amino aldehyde **30** yielded a mixture of diastereomers (dr = 69:31). Notably, the base-sensitive Fmoc protecting group is stable under these reaction conditions. The diastereoselection obtained for this reaction is comparable to vinylmagnesium bromide additions to Boc-L-phenylalaninal (dr = 70:30).[76] Moderate diastereoselection was also evident in the addition of dianion **12**/$CeCl_3$ to uridine aldehyde **28** (dr = 76:24). Unreacted starting material was recovered from this reaction as the hydrated form of aldehyde **28**. The hydrated form was not detected spectroscopically in the starting material. Since many aldehydes and some ketones readily hydrate, we tested whether dianion **12**/$CeCl_3$ would react with the hydrated form of a ketone. The hydrated form of glucofuranose **16** was subjected to reaction with dianion **12**/$CeCl_3$, and a diminished yield of the addition product was obtained that roughly corresponded to the percentage of free ketone present in the starting material. These results may suggest that the hydrated forms of ketones/aldehydes are unreactive toward the dianion **12**/$CeCl_3$ reagent combination.

The addition of dianion **12**/$CeCl_3$ to 5α-androstan-3β-ol-17-one acetate (**23**) and 7-oxo-heptanenitrile (**32**) was performed to examine the chemoselectivity of reagent **12**/$CeCl_3$. We found that acetoxy groups are labile, but the nitrile functionality is stable under these reaction conditions. It is likely that the low temperatures employed precluded attack upon the nitrile, which generally requires higher temperatures (0 °C to rt) to react with organocerium reagents.[34]

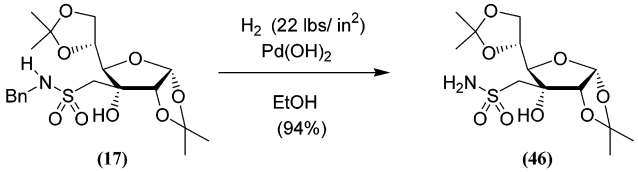
Next, we examined the generality of cerium(III) to mediate the basicity of various sulfonamide dianions in reaction with ketouridine **11**. The procedure used for addition of *N*-benzyl methanesulfonamide dianion to ketouridine **11** was unsuitable for addition of simple *N*-aliphatic or *N*-aromatic sulfonamides, as the dianions precipitated from solution. These dianions can be solubilized by the addition of 5% HMPA (v/v) to the reaction medium. However, HMPA has a detrimental effect on the yields obtained. For example, *N*-hexyl and *N*-phenyl methanesulfonamide dianions added to ketouridine **11** in 50 and 45% yields, respectively in the presence of HMPA. We subsequently found that the simple expedient of diluting the reaction mixture was sufficient to solve this problem. Under these conditions, *N*-hexyl and *N*-phenyl methanesulfonamide dianions added diastereoselectively to ketouridine **11** in 95 and 96% yields, respectively. Cerium(III) was still required to obtain high diastereoselectivity and optimal yields under these conditions. When *N*-hexyl methanesulfonamide dianion was added to ketone **11** in the absence of cerium(III), a reduced yield of the product was obtained (64%) as a mixture of diastereomers (OH_α:OH_β = 29:71). Table 4 summarizes these results. The high-yield obtained for the addition of *N*-benzhydryl dianion **44** is notable, because the benzhydryl group can be removed by hydrogenolysis with Pearlman's catalyst.[4] Similarly, high-pressure hydrogenolysis using Pearlman's catalyst was effective for the debenzylation of allofuranose **17** (eq 2). Further investigations are underway to explore the scope and limitations of the benzyl group for protection of a sulfonamide moiety.

TABLE 4. $CeCl_3$-Mediated Addition of Various Sulfonamide Dianions with Ketouridine 11[a,b]



R	yield (%)
Me	88
Et	90
*i*Pr	90
hexyl	95 (64[c])
phenyl	96
benzhydryl	96

[a] Reactions conducted as described in the Experimental Section using procedure B with a molar ratio of 1:8:8.2 (ketouridine:sulfonamide:$CeCl_3$). [b] Value in parentheses is the yield of reaction without $CeCl_3$ added, all other factors remaining constant. [c] Ratio of OH_α:OH_β = 29:71.

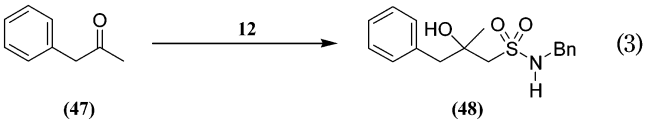


(2)

Given the successful addition of *N*-substituted aliphatic and aromatic sulfonamide dianions to many carbonyl compounds mediated by cerium(III), we wanted to examine the possibility for enolate formation promoted by dianion **12**. We chose 1-phenylacetone (**47**) as a model for ketones extremely prone to enolate formation. Subjecting dianion **12** to 1-phenylacetone under the conditions described in the literature and quenching the reaction prior to completion with perdeutero acetic acid provided β-hydroxy-sulfonamide **48** in 73% yield (eq 3). The recovered sulfonamide (24%) contained a α-CH_2D:α-CH_3 ratio of 17:83. Significant proton incorporation into the recovered *N*-benzyl methanesulfonamide was observed over that of the control (α-CH_2D:α-CH_3 = 92:8). Although no starting ketone (**47**) was recovered, a complicated mixture of byproducts was isolated by chromatography and a small amount of the aldol product of **47** was present. Under identical reaction conditions, 1-phenylacetone was subjected to cerium-mediated dianion addition (**47**:**12**:$CeCl_3$ = 1:1.2:1.3). Product **48** was obtained in 73% yield, and unreacted 1-phenylacetone was recovered in 26% yield. Further, the recovered starting material contained no deuterium incorporation

(75) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233−4236.
(76) Junusz, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164.

by mass spectroscopy or ^{1}H NMR analysis. These results demonstrate that cerium(III) is an effective additive for suppressing side reactions resulting from the basicity of dianion **12**.



(47) (48) (3)

Finally, several procedures are reported in the literature for dehydrating cerium(III) chloride heptahydrate to provide what is commonly referred to as anhydrous $CeCl_3$.[38,77−79] However, Evans and co-workers have shown by X-ray crystallography that water is still present in these preparations to give dehydrated $CeCl_3$.[78,79] Dimitrov and co-workers published an alternative dehydrating procedure and found that there was an effect on the activity and efficiency of $CeCl_3$-mediated reactions with carbonyl substrates.[41] We chose to use Dimitrov's dehydration procedure throughout this study and evaluate its efficacy for removing any adventitious moisture that might be detrimental toward dianion **12**. Transmetalation of dianion **12** with dehydrated $CeCl_3$ followed by quenching with excess CD_3CO_2D/D_2O[80] resulted in the incorporation of deuterium into *N*-benzyl methanesulfonamide with a α-CH_2D:α-CH_3 ratio of 83:17.[81] In a control experiment where $CeCl_3$ was omitted, *N*-benzyl methanesulfonamide was obtained with a α-CH_2D:α-CH_3 ratio of 85:15. From these results, the amount of detrimental water present in dehydrated $CeCl_3$ obtained by Dimitrov's method is 0.1%, corresponding to a mole fraction of 0.01.[82] Therefore, any water present in the dehydrated $CeCl_3$ obtained by Dimitrov's procedure has no effect on the overall course of the reactions investigated with sulfonamide dianions.

Conclusion

We have shown that modifying the basicity of a sulfonamide dianion with cerium(III) chloride gives high yields of addition products with carbonyl substrates, suppresses side reactions, and in many cases enhances diastereoselection. It seems likely that this methodology will be broadly applicable to other types of dianions as well. The methodology presented in this study holds potential for the construction of *N*-alkyl-β-hydroxy-sulfonamides under milder conditions than previously reported. Further, base-sensitive functionality and protecting groups are tolerated, providing good to high yields of the desired products. This methodology may find application for the construction of *N*-alkyl-2-oxo-alkanesulfonamides (**6**) by reaction of a sulfonamide dianion/$CeCl_3$ with Weinreb amides or oxidation of the *N*-alkyl-β-hydroxy-sulfonamide products of aldehydes. These reactions were not explicitly investigated but are worth mentioning for their future potential. Other potential uses for the method demonstrated include the construction of peptidomimetics by way of Fmoc-protected α-amino aldehydes. This protecting group has not been utilized with dianionic organometallic reagents, presumably due to its base lability.[83−85]

Experimental Section

General. Solvents were distilled from potassium benzophenone ketyl (THF and Et_2O) or calcium hydride (CH_3CN, DCM, HMPA, and pyridine) under an atmosphere of dry N_2. Cerium(III) chloride heptahydrate was dehydrated according to the method of Dimitrov.[41] In the procedures below, NaCl and $NaHCO_3$ refer to saturated aqueous solutions. Flash column chromatography was performed with 60 Å 230−400 mesh silica gel. Compounds **11**,[86,87] **26**,[88] and **30**[89] were prepared according to previous literature procedures. Preparation of starting materials **16**, **19**, **21**, **38**, **32**, *N*-benzyl methanesulfonamide, and *N*-benzyl deuteriomethanesulfonamide can be found in Supporting Information. Stereochemistry was determined from a combination of HMQC, two-dimensional NOE and one-dimensional NOE NMR experiments. ^{1}H and ^{13}C spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Fourier transformed infrared spectra were recorded as neat liquids or as thin films (obtained from the evaporation of chloroform). The method used to obtain high-resolution mass spectra (FAB, EI, and CI) are indicated.

Cerium(III) Chloride-Mediated Addition of Sulfonamide Dianions to Carbonyl Compounds. Procedure A: Addition of *N*-Benzyl Methanesulfonamide Dianion to Carbonyl Substrates. A 0.25 M THF solution of dehydrated $CeCl_3$ [8.2 equiv (1.025 equiv Ce/equiv sulfonamide)] was stirred overnight to homogeneity under an atmosphere of N_2. Separately, a 0.5 M THF solution of *N*-benzyl methanesulfonamide (8 equiv) was cooled to −75 °C, and titrated BuLi (16 equiv) was added dropwise under an atmosphere of N_2. The temperature of the cold bath was raised gradually to −30 °C over 15 min and the solution stirred for an additional 45 min at −30 °C. After the dianion solution was cooled to −75 °C, it was introduced via cannula into the cerium solution, also cooled to −75 °C. The temperature of the cold bath was raised gradually to −30 °C over 15 min and the solution stirred for an additional 45 min at −30 °C. The heterogeneous yellow/light orange cerium-dianion solution was recooled to −75 °C. A 0.65 M THF solution of the carbonyl compound (1 equiv), cooled to −75 °C, was then introduced via cannula. The temperature of the cold bath was raised gradually to −30 °C over 15 min. The solution was stirred at −30 °C until complete by TLC (usually 1 h). The reaction was then quenched with AcOH (16.2 equiv) and warmed to rt, at which time water was added (10 mL/mmol). THF was removed by rotary evaporator, and the resulting slurry was partitioned between ethyl acetate and water. The ethyl acetate phase was extracted with water then $NaHCO_3$. The aqueous phases, kept separate, were individually extracted with ethyl acetate; then, all organic phases were combined, dried (Na_2SO_4), and concentrated by rotary evaporation of the volatiles. Products were obtained by flash-column chromatography using the solvent systems indicated.

(77) Paquette, L. A. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; pp 1031−1034.
(78) Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 12252.
(79) Evans, W. J.; Feldman, J. D.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 4581−4584.
(80) See Supporting Information for procedure.
(81) Deuterium ratios reported are averages of both Gaussian lineshape analysis and manual integration.
(82) See Supporting Information for calculation.
(83) For addition of Grignard and Reformatsky reagents to an Fmoc-protected α-amino aldehyde derivative, see refs 86 and 87.
(84) Blaskovich, M. A.; Evindar, G.; Rose, N. G. W.; Wilkinson, S.; Luo, Y.; Lajoie, G. A. *J. Org. Chem.* **1998**, *63*, 3631−3646.
(85) Blaskovich, M. A.; Lajoie, G. A. *J. Am. Chem. Soc.* **1993**, *115*, 5021−5030.
(86) Ogilvie, K. K.; McGee, D. P. C.; Boisvert, S. M.; Hakimelahi, G. H.; Proba, Z. A. *Can. J. Chem.* **1983**, *61*, 1204−1212.
(87) Samano, V.; Robins, M. J. *J. Org. Chem.* **1990**, *55*, 5186−5188.
(88) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480−2482.
(89) Rodriguez, M.; Llinares, M.; Doulut, S.; Heitz, A.; Martinez, J. *Tetrahedron Lett.* **1991**, *32*, 923−926.

Procedure B: Used when Dianion Precipitated from Reaction Medium under the Conditions Described above. A 0.50 M THF solution of dehydrated $CeCl_3$ [8.2 equiv (1.025 equiv Ce/equiv sulfonamide)] was stirred overnight to homogeneity under an atmosphere of N_2. Separately, a 0.08 M THF solution of sulfonamide (8 equiv) was cooled to −75 °C, and titrated BuLi (16 equiv) was added dropwise under an atmosphere of N_2. The temperature of the cold bath was raised gradually to −30 °C over 15 min and the solution stirred for an additional 45 min at −30 °C. After the dianion solution was cooled to −75 °C, it was introduced via cannula into the cerium solution, also cooled to −75 °C. The temperature of the cold bath was raised gradually to −30 °C over 15 min and the solution stirred for an additional 45 min at −30 °C. The heterogeneous yellow/light orange cerium-dianion solution was recooled to −75 °C. A 0.65 M THF solution of the carbonyl compound (1 equiv), cooled to −75 °C, was then introduced via cannula. The temperature of the cold bath was raised gradually to −30 °C over 15 min. The solution was stirred at −30 °C until complete by TLC (usually 1 h). The reaction was then quenched with AcOH (16.2 equiv) and warmed to rt, at which time water was added (10 mL/mmol). THF was removed by rotary evaporator, and the resulting slurry was partitioned between ethyl acetate and water. The ethyl acetate phase was extracted with water and then $NaHCO_3$. The aqueous phases, kept separate, were individually extracted with ethyl acetate; then, all organic phases were combined, dried (Na_2SO_4), and concentrated by rotary evaporation of the volatiles. Products were obtained by flash-column chromatography using the solvent systems indicated.

***N*-Benzyl-2-hydroxy-4, 8-dimethyl-nona-3,7-diene-1-methylenesulfonamide (15).** Procedure A; eluent = 2:1 Hex/EtOAc; 1.3 equiv of $CeCl_3$, 1.2 equiv of *N*-benzyl methanesulfonamide, and 2.4 equiv of BuLi were used; **14** (225 μL, 1.314 mmol) was converted to **15** (363 mg, 1.076 mmol); yield = 82%. (The product was obtained as an inseparable mixture of diastereomers. The identity was confirmed by HRMS.) HRMS (CH_4) *m*/*z* calcd for $C_{18}H_{27}NO_3S$ (M^+) 337.17116, found 337.17111.

3-*β*-(*N*-Benzyl Methylenesulfonamide)-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (17). Procedure A; eluent = 2:1 Et_2O/Hex; **16** (242 mg, 0.9370 mmol) was converted to **17** (302 mg, 0.6809 mmol); yield = 73%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.36 (m, 5H), 5.77 (d, *J* = 3.9 Hz, 1 H), 5.15 (d, *J* = 3.9 Hz, 1 H), 5.11 (m, 1 H), 4.33 (A of ABX, J_{AB} = 13.3 Hz, J_{AX} = 8.2 Hz, 1 H), 4.24 (B of ABX, J_{BA} = 13.3 Hz, J_{BX} = 4.0 Hz, 1 H), 4.07 (dd, *J* = 8.1, 6.0 Hz, 1 H), 3.96 (m, 1 H), 3.90 (dd, *J* = 8.1, 4.5 Hz, 1 H), 3.82 (A of AB, J_{AB} = 15.0 Hz, 1 H), 3.75 (d, 8.5 Hz, 1 H), 3.31 (br s, 1 H), 3.01 (B of AB, J_{BA} = 15.0 Hz, 1 H), 1.56 (s, 3 H), 1.45 (s, 3 H), 1.35 (s, 3 H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.53, 128.86, 128.31, 128.12, 112.92, 110.04, 103.71, 82.83, 79.82, 77.97, 73.41, 67.98, 50.38, 47.91, 26.85, 26.65, 26.53, 25.31; IR (film) 3499, 3298, 3062, 3035, 2988, 2937, 2887, 2254, 1496, 1456, 1374, 1329, 1267, 1216, 1154, 1070; HRMS (CH_4) *m*/*z* calcd for $C_{19}H_{26}NO_8S$ ($M^+ - CH_3$) 428.13791, found 428.13671.

3′-α-(*N*-Benzyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-*β*-hydroxy- uridine (18). Procedure A; eluent = 10% EtOAc/DCM; **11** (200 mg, 0.4249 mmol) was converted to **28** (275 mg, 0.4192 mmol); yield = 99%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 9.90 (br s, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 7.33 (m, 5H), 5.68 (t, *J* = 6.19 Hz, 1 H), 5.64 (s, 1 H), 5.60 (dd, *J* = 8.1, 1.9, 1 H), 5.12 (s, 1 H), 4.43 (s, 1 H), 4.31 (A of ABX, J_{AB} = 14.3 Hz, J_{AX} = 7.0 Hz, 1 H), 4.25(B of ABX, J_{BA} = 14.3 Hz, J_{BX} = 4.1 Hz, 1 H), 4.19 (A of ABX, J_{AB} = 12.0 Hz, J_{AX} = 4.1 Hz, 1 H), 4.12 (B of ABX, J_{BA} = 12.0 Hz, J_{BX} = 2.4 Hz, 1 H), 4.05 (m, 1 H), 3.60 (A of AB, J_{AB} = 14.8 Hz, 1 H), 3.35 (B of AB, J_{BA} = 14.8 Hz, 1 H), 3.35 (d, *J* = 14.8 Hz, 1 H), 0.94 (s, 9 H), 0.92 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.18 (s, 3 H), 0.17 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.42, 150.27, 141.10, 136.80, 128.81, 127.96, 127.90, 100.60, 91.22, 82.77, 81.53, 79.85, 61.59, 52.40, 47.13, 26.06, 25.86, 18.19, 18.06, −4.17, −5.26, −5.48 (2); IR (film) 3276, 3113, 3064, 2954, 2930, 2885, 2858, 1704, 1699, 1695, 1683, 1652, 1471, 1412, 1391, 1331, 1269, 1118, 1066; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{49}N_3O_8SSi_2Na$ ($M + Na^+$) 678.26766, found 678.26606.

3′-α-(*N*-Benzyl Methylenesulfonamide)-5′-(*O*-*tert*-butyldimethylsilyl)- 3′-*β*-hydroxy-thymidine (20). Procedure A; eluent = 3:5 EtOAc/DCM; **19** (100 mg, 0.2821 mmol) was converted to **20** (102 mg, 0.1889 mmol); yield = 67%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 11.45 (br s, 1 H), 7.54 (d, *J* = 0.91 Hz, 1 H), 7.28 (m, 5 H), 6.11 (d, *J* = 6.2 Hz, 1 H), 5.71 (dd, *J* = 8.5, 3.4 Hz, 1 H), 5.10 (s, 1 H), 4.37 (A of ABX, J_{AB} = 13.7 Hz, J_{AX} = 4.4 Hz, 1 H), 4.24 (B of ABX, J_{BA} = 13.7 Hz, J_{BX} = 4.2 Hz, 1 H), 4.11 (A of ABX, J_{AB} = 10.3 Hz, J_{AX} = 7.0 Hz, 1 H), 3.95 (B of ABX, J_{BA} = 10.3 Hz, J_{BX} = 4.8 Hz, 1 H,) 3.84 (t, *J* = 6.0 Hz, 1 H), 3.80 (A of AB, J_{AB} = 15.0 Hz, 1 H), 3.15 (B of AB, J_{BA} = 15.0, 1H) 2.93 (A of ABX, J_{AB} = 7.6 Hz, J_{AX} = 2.9 Hz, 1 H), 2.87 (B of ABX, J_{BA} = 15.8 Hz, J_{BX} = 2.9 Hz, 1 H), 1.61 (s, 3 H), 0.97 (s, 9 H), 0.17 (s, 3 H), 0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 165.06, 151.24, 138.36, 137.11, 128.67, 127.96, 127.844, 108.16, 88.18, 86.40, 75.19, 60.40, 57.53, 47.58, 44.67, 26.08, 18.47, 12.30, −5.18; IR (film) 3408, 3290, 3070, 3039, 2954, 2929, 2884, 2857, 1699, 1683, 1472, 1432, 1331, 1275, 1154, 1098; HRMS (FAB) *m*/*z* calcd for $C_{24}H_{57}N_3O_7SSiNa$ ($M + Na^+$) 562.20195, found 562.20254.

17α-(*N*-Benzyl Methylenesulfonamide)-3-(-(*O*-*tert*-butyldimethylsilyl)-*β*-estradiol (22). Procedure A; eluent = 3:1 Hex/EtOAc; **21** (100 mg, 0.2593 mmol) was converted to **22** (116 mg, 0.2032 mmol); yield = 78%; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.38 (m, 5H), 7.10 (d, *J* = 8.6 Hz, 1 H), 6.63 (dd, *J* = 8.5, 2.4 Hz, 1 H), 6.57 (d, *J* = 2.3 Hz, 1 H), 5.28 (t, *J* = 6.2 Hz, 1 H), 4.33 (d, *J* = 6.2 Hz, 2 H), 3.40 (br s, 1 H), 3.24 (A of AB, J_{AB} = 14.1 Hz, 1 H), 3.08 (B of AB, J_{BA} = 14.1 Hz, 1 H), 2.81 (m, 2 H), 2.73 (ddd, *J* = 15.3, 9.5, 6.6 Hz, 1 H), 2.27 (m, 1 H), 2.07 (m, 1H), 1.88−1.67 (m, 3 H), 1.59−1.25 (m, 5 H), 1.11 (m, 2 H), 1.00 (s, 9 H), 0.89 (s, 3 H), 0.21 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 153.58, 137.90, 136.88, 132.71, 129.06, 128.40, 128.27, 126.18, 120.15, 117.36, 81.57, 59.73, 49.55, 48.00, 47.53, 43.80, 39.53, 34.26, 31.67, 29.69, 27.59, 26.20, 25.86, 23.81, 18.33, 13.81, −4.23; IR (film) 3515, 3297, 3065, 3031, 2961, 2931, 2858, 2249, 1607, 1571, 1496, 1472, 1456, 1418, 1288, 1258, 1148, 1062; HRMS (EI) *m*/*z* calcd for $C_{32}H_{47}NO_4SSi$ (M^+) 569.29951, found 569.30046.

5α-Androstan-17α-(*N*-benzyl Methylenesulfonamide)-3*β*-17*β*-diol (24). Procedure A; eluent = 2:1 Hex/EtOAc; **23** (215 mg, 0.6467 mmol) was converted to **25** (223 mg, 0.4307 mmol); yield = 71%; relevant data for ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34 (m, 5H), 5.32 (t, *J* = 6.2 Hz, 1 H), 4.28 (d, *J* = 6.2 Hz, 2 H), 3.57 (m, 1 H), 3.36 (br s, 1 H), 3.18 (A of AB, J_{AB} = 14.0 Hz, 1 H), 3.02 (B of AB, J_{BA} = 14.0 Hz, 1 H), 2.64 (m, 1 H), 0.82 (s, 3 H), 0.79 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 136.88, 129.02, 128.32, 128.19, 81.55, 71.32, 59.52, 54.29, 50.56, 47.76, 47.46, 45.01, 38.16, 37.17, 36.36, 35.65, 34.23, 31.87, 31.67, 31.51, 28.62, 24.09, 20.91, 13.91, 12.46; IR (film) 3505, 3296, 3066, 3027, 2927, 2856, 2251, 1720, 1605, 1496, 1454, 1384, 1320, 1299, 1272, 1142, 1085, 1042; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{41}NO_4SNa$ ($M + Na^+$) 498.26543, found 498.26597.

5α-Androstan-17α-(*N*-benzyl Methylenesulfonamide)-17*β*-ol-3*β* Acetate (25). Obtained as the minor product (19 mg, 0.0367 mmol) from above reaction; yield = 6%; relevant data for ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.33 (m, 5H), 5.34 (t, *J* = 6.2 Hz, 1 H), 4.66 (m, 1 H), 3.40 (br s, 1 H), 3.15 (A of AB, J_{AB} = 14.1 Hz, 1 H), 3.00 (B of AB, J_{BA} = 14.1 Hz, 1 H), 2.63 (ddd, *J* = 15.6, 9.4, 6.4 Hz, 1 H), 2.00 (s, 3 H), 0.81 (s, 3 H), 0.80 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 170.93, 136.89, 128.99, 128.32, 128.16, 81.47, 73.71, 59.62, 54.11, 50.43, 47.71, 47.42, 44.78, 36.89, 36.28, 35.60, 34.11, 34.01, 31.74, 31.57, 28.45, 27.50, 24.04, 21.58, 20.83, 13.86, 12.32; IR (film) 3515, 3286, 3065, 3031, 2939, 2856, 2254, 1725, 1496, 1455, 1381, 1366, 1323, 1303, 1250, 1149, 1083, 1027; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{43}NO_5SNa$ ($M + Na^+$) 540.27600, found 540.27755.

3-β-(*N*-Benzyl Methylenesulfonamide)-α-hydroxy-cholesterol (27). Procedure A used and modified as follows. A room-temperature solution of THF (1 mL) and **26** (100 mg, 0.260 mmol) was added dropwise to the $CeCl_3$-dianion suspension. Following the usual workup, trituration from EtOAc provided **27** (123 mg, 0.216 mmol) as a mixture of diastereomers; yield = 83%. An analytical sample of the minor diastereomer was obtained by silica gel chromatography (DCM): relevant data for ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5 H), 5.44 (m, 1 H), 4.95 (t, J = 6.3 Hz, 1 H), 4.30 (d, J = 6.3 Hz, 2 H), 3.14 (A of ABX, J_{AB} = 14.6 Hz, J_{AX} = 0.6 Hz, 1 H), 3.11 (B of ABX, J_{BA} = 14.6 Hz, J_{BX} = 1.1 Hz, 1 H), 2.59 (s, 1 H), 2.42 (A of ABX, J_{AB} = 14.4 Hz, J_{AX} = 2.2 Hz, 1 H), 2.26 (B of ABX, J_{BA} = 14.4 Hz, J_{BX} = 2.9 Hz, 1 H), 2.00 (m, 2 H), 1.82 (m, 2 H), 1.68 (m, 1 H), 0.97 (s, 3 H), 0.91 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 1.7 Hz, 3 H), 0.85 (d, J = 1.8 Hz, 3 H), 0.67 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.28, 136.80, 128.99, 128.33, 128.22, 125.31, 71.08, 61.92, 56.84, 56.25, 50.29, 47.74, 43.97, 42.46, 39.84, 39.68, 36.76, 36.34, 35.96, 34.47, 33.38, 32.11, 31.95, 29.89, 28.39, 28.19, 24.44, 23.99, 23.02, 22.75, 21.04, 18.89, 18.74, 12.02; IR (film) 3497, 3219, 3089, 3031, 2940, 2899, 2867, 2844, 2360, 1453, 1321, 1264, 1145, 1062; HRMS (CH_4) m/z calcd for $C_{35}H_{53}NO_2S$ ($M^+ - H_2O$) 551.37970, found 551.37842.

5′-(*N*-Benzyl Methylenesulfonamide)-2′, 3′-isopropylidene-uridine (29). Procedure A; eluent = 2:1 EtOAc/Hex; **28** (116 mg, 0.2821 mmol) was converted to **29** (135 mg, 0.2889 mmol); yield = 70%; (The product was obtained as an inseparable mixture of diastereomers: dr = 76:24. The identity was confirmed by HRMS.) HRMS (FAB) m/z calcd for $C_{20}H_{25}N_3O_8SNa$ ($M + Na^+$) 490.12604, found 490.12600.

(1*S*)-(3-Benzylsulfamoyl-2-hydroxy-1-methyl-propyl)-carbamic Acid 9*H*-fluoren-9-ylmethyl Ester (31). Procedure A; eluent = 10% EtOAc/ DCM; **30** (100 mg, 0.3398 mmol) was converted to **31** (110 mg, 0.2303 mmol); yield = 68%; (The product was obtained as an inseparable mixture of diastereomers: dr = 69:31 and 62:38 for two separate runs. The identity was confirmed by HRMS.) HRMS (FAB) m/z calcd for $C_{26}H_{28}N_2O_5SNa$ ($M + Na^+$) 503.16170, found 503.16159.

***N*-Benzyl-7-cyano-2-hydroxy-heptanesulfonamide (33).** Procedure A; eluent = Et_2O; **32** (25 mg, 0.1997 mmol) was converted to **33** (57 mg, 0.1836 mmol); yield = 92%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H), 4.90 (br s, 1 H), 4.24 (d, J = 5.4 Hz, 2 H), 4.03 (m, 1 H), 3.01 (br s, 1 H), 2.95 (A of ABX, J_{AB} = 14.4 Hz, J_{AX} = 9.8 Hz, 1 H), 2.88 (B of ABX, J_{BA} = 14.4 Hz, J_{BX} = 1.6 Hz, 1 H), 2.28 (t, J = 7.0 Hz, 2 H), 1.58 (p, J = 7.1 Hz, 2 H), 1.44−1.26 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.76, 129.09, 128.34, 128.25, 119.91, 66.74, 58.74, 47.38, 36.17, 28.41, 25.28, 24.37, 17.20; IR (film) 3424, 3148, 3027, 2944, 2922, 2895, 2852, 2362, 2241, 1455, 1420, 1294, 1130, 1088; HRMS (CH_4) m/z calcd for $C_{15}H_{22}N_2O_3SNa$ ($M + Na^+$) 333.12492, found 333.12402.

3′-α-(*N*-Methyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (35). Procedure B; eluent = 20% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **35** (108 mg, 0.1863 mmol); yield = 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (br s, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 5.65 (s, 1 H), 5.58 (dd, J = 7.94, 1.83 Hz, 1 H), 5.49 (q, J = 5.49, 1 H), 5.10 (s, 1 H), 4.42 (s, 1 H), 4.25 (A of ABX, J_{AB} = 11.6 Hz, J_{AX} = 3.8 Hz, 1 H), 4.14 (B of ABX, J_{BA} = 11.6 Hz, J_{BX} = 2.12 Hz, 1 H), 4.05 (m, 1 H), 3.54 (A of AB, J_{AB} = 14.8 Hz, 1 H), 3.36 (B of AB, J_{BA} = 14.8 Hz, 1 H), 2.77 (d, J = 14.8 Hz, 1 H), 0.93 (s, 9 H), 0.91 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.16(s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.17, 150.15, 141.04, 100.59, 91.26, 82.52, 81.52, 79.89, 61.81, 49.52, 29.48, 26.12, 25.86, 18.23, 18.15, −4.14, −5.17, −5.46, −5.55; IR (film) 3376, 3265, 3142, 2949, 2929, 2899, 2859, 1717, 1683, 1464, 1390, 1320, 1268, 1125, 1046; HRMS (EI) m/z calcd for $C23H_{46}N_3O_8SSi_2$ ($M + H^+$) 580.25442, found 580.25677.

3′-α-(*N*-Ethyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (37). Procedure B; eluent = 20% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **37** (113 mg, 0.1904 mmol); yield 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.43 (br s, 1 H), 7.80 (d, J = 8.1 Hz, 1 H), 5.65 (s, 1 H), 5.58 (d, J = 8.1 Hz, 1 H), 5.17 (t, J = 6.0 Hz, 1 H), 4.43 (s, 1 H), 4.24 (A of ABX, J_{AB} = 11.8 Hz, J_{AX} = 4.2 Hz, 1 H), 4.14(B of ABX, J_{BA} = 11.8 Hz, J_{BX} = 1.8 Hz, 1 H), 4.03 (m, 1 H), 3.56 (A of AB, J_{AB} = 14.7 Hz, 1 H), 3.35 (B of AB, J_{BA} = 14.7 Hz, 1 H), 3.13 (m, 2 H), 1.19 (t, J = 7.3 Hz, 3 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.15 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.21, 150.14, 141.08, 100.53, 91.32, 82.58, 81.52, 79.92, 61.71, 51.19, 38.12, 18.22, 18.12, 15.65, −4.16, −5.19, −5.51, −5.55; HRMS (EI) m/z calcd for $C_{24}H_{48}N_3O_8SSi_2$ ($M + H^+$) 594.27007, found 594.27131.

3′-α-(*N*-Isopropyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (39). Procedure B; eluent = 20% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **39** (116 mg, 0.1908 mmol); yield = 90%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.37 (br s, 1 H), 7.81 (d, J = 8.1 Hz, 1 H), 5.66 (s, 1 H), 5.58 (dd, J = 8.1, 1.3, 1 H), 5.06 (d, J = 6.8 Hz, 1 H), 4.94 (s, 1 H), 4.42 (s, 1 H), 4.2 (A of ABX, J_{AB} = 11.5 Hz, J_{AX} = 4.3 Hz, 1 H), 4.13(B of ABX, J_{BA} = 11.5 Hz, J_{BX} = 2.1 Hz, 1 H), 4.03 (A of AB, J_{AB} = 2.6 Hz, 1 H), 4.02 (B of AB, J_{BA} = 2.6 Hz, 1 H), 3.63 (m, J = 6.8 Hz, 1 H), 3.59 (A of AB, J_{AB} = 14.7 Hz, 1 H), 3.37 (B of AB, J_{BA} = 14.7 Hz, 1 H), 1.21 (d, J = 6.8 Hz, 6 H), 0.92 (s, 9 H), 0.91 (s, 9 H), 0.24 (s, 3 H), 0.23 (s, 3 H), 0.14 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.26, 150.11, 141.24, 100.48, 91.32, 82.72, 81.64, 79.93, 77.50, 61.55, 53.21, 46.40, 26.12, 25.92, 24.63, 23.98, 18.28, 18.12, −4.16 (2), −5.20, −5.46; IR (film) 3354, 3257, 3117, 3058, 2955, 2931, 2885, 2858, 2361, 2256, 1712, 1696, 1683, 1471, 1390, 1327, 1269, 1118, 1065; HRMS (EI) m/z calcd for $C_{25}H_{50}N_3O_8SSi_2$ ($M + H^+$) 608.28572, found 608.28603.

3′-α-(*N*-Hexyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (41). Procedure B; eluent = 10% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **41** (131 mg, 0.2015 mmol); yield = 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.60 (br s, 1 H), 7.79 (d, J = 8.1 Hz, 1 H), 5.64 (s, 1H), 5.58 (d, J = 8.1 Hz, 1 H), 5.17 (t, J = 5.6 Hz, 1 H), 5.04 (s, 1 H), 4.42 (s, 1 H), 4.23 (A of ABX, J_{AB} = 11.5 Hz, J_{AX} = 4.3 Hz, 1 H), 4.13 (B of ABX, J_{BA} = 11.5 Hz, J_{BX} = 2.1 Hz, 1 H), 4.04 (m, 1 H), 3.54 (A of AB, J_{AB} = 14.9 Hz, 1 H), 3.35 (B of AB, J_{BA} = 14.9 Hz, 1 H), 3.04 (m, 2 H), 1.52 (m, 2 H), 1.28 (m, 2 H), 0.92 (s, 9 H), 0.90 (s, 9 H), 0.86 (t, J = 6.4 Hz, 3 H), 0.23 (s, 3 H), 0.23 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.32, 150.19, 141.10, 100.53, 91.28, 82.66, 81.55, 79.89, 77.52, 61.68, 51.05, 43.53, 31.43, 30.17, 26.39, 26.12, 25.87, 22.63, 18.22, 14.12, −4.14, −5.20, −5.48, −5.54; IR (film) 3319, 3113, 3050, 2957, 2931, 2887, 2859, 2253, 1712, 1695, 1471, 1424, 1391, 1363, 1329, 1269, 1117; HRMS (EI) m/z calcd for $C_{28}H_{56}N_3O_8SSi_2$ ($M + H^+$) 650.33267, found 650.33474.

3′-α-(*N*-Phenyl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (43). Procedure B; eluent = 20% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **43** (131 mg, 0.2041 mmol); yield = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.44 (br s, 1 H), 8.08 (br s, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.29−7.08 (m, 5H), 5.62 (s, 1 H), 5.55 (d, J = 8.1 Hz, 1 H), 5.03 (s, 1 H), 4.53 (s, 1 H), 4.14 (A of ABX, J_{AB} = 11.9 Hz, J_{AX} = 4.0 Hz, 1 H), 3.95 (B of ABX, J_{BA} = 11.9 Hz, J_{BX} = 0 Hz, 1 H), 3.91 (m, 1 H), 3.54 (A of AB, J_{AB} = 15.0 Hz, 1 H), 3.35 (B of AB, J_{BA} = 15.0 Hz, 1 H), 0.86 (s, 9 H), 0.83 (s, 9 H), 0.24 (s, 3 H), 0.24 (s, 3 H), 0.02 (s, 3 H), −0.02 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.70, 149.79, 141.54, 137.37, 129.75, 125.17, 120.64, 100.03, 91.82, 82.65, 81.39, 80.34, 61.47, 49.64, 26.10, 25.92, 18.23, 18.09, −4.08, −5.28, −5.64 (2); IR (film) 3381, 3265, 3109, 3054, 2955, 2930, 2885, 2858, 2254, 1712, 1700, 1683, 1600, 1497, 1471, 1404, 1390, 1348, 1269, 1152, 1119; HRMS (EI) m/z calcd for $C_{28}H_{48}N_3O_8SSi_2$ ($M + H^+$) 642.27007, found 642.26933.

3′-α-(*N*-Benzhydryl Methylenesulfonamide)-2′,5′-bis-(*O*-*tert*-butyldimethylsilyl)-3′-β-hydroxy-uridine (45). Pro-

cedure B; eluent = 10% EtOAc/DCM; **11** (100 mg, 0.2126 mmol) was converted to **45** (150 mg, 0.2050 mmol); yield = 96%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.33 (br s, 1 H), 7.83 (d, J = 8.1 Hz, 1 H), 7.35−7.24 (m, 10H), 5.79 (s, 1 H), 5.59 (s, 1 H), 5.57 (d, J = 8.1 Hz, 1 H), 4.98 (s, 1 H), 4.26 (s, 1 H), 4.05 (A of AB, J_{AB} = 11.8 Hz, 1 H), 3.99 (B of AB, J_{BA} = 11.8 Hz, 1 H), 3.90 (br s, 1 H), 3.40 (A of AB, J_{AB} = 14.7 Hz, 1 H), 3.05 (B of AB, J_{BA} = 14.7 Hz, 1 H), 0.89 (s, 9 H), 0.84 (s, 9 H), 0.17 (s, 3 H), 0.11 (s, 3 H), 0.10 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.08, 150.32, 141.42, 141.01, 140.93, 129.07, 128.88, 128.09, 127.97, 127.69, 127.43, 100.86, 91.26, 83.01, 82.08, 80.10, 61.79, 61.32, 54.89, 26.06, 25.97, 18.32, 18.06, −4.16, −5.20, −5.30, −5.40; IR (film) 3463, 3346, 3262, 3063, 3027, 2954, 2929, 2884, 2857, 1708, 1695, 1680, 1471, 1390, 1326, 1268, 11118, 1062; HRMS (FAB) m/z calcd for $C_{35}H_{53}N_3O_8SSi_2$-Na (M + Na^+) 754.29900, found 754.29575.

3-β-Methylenesulfonamide-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (46). Allofuranose **17** (10 mg, 0.02255 mmol) was dissolved in EtOH (0.5 mL). Pearlman's catalyst [$Pd(OH)_2$, 6 mg] was added to the solution. The reaction was stirred under an atmosphere of hydrogen gas at 22 lbs/in^2 for 2 days at which time the reaction was filtrated through Celite 545. Purification by flash-column chromatography (ether) provided **46** (7.5 mg, 0.02122 mmol) as a white solid; yield = 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79 (d, J = 3.9 Hz, 1 H), 5.23 (d, J = 3.9 Hz, 1 H), 5.01 (br s, 2 H), 4.13 (A of AB, J_{AB} = 8.5 Hz, J_{AX} = 6.1 Hz, 1 H), 3.98 (m, 1 H), 3.92 (B of ABX, J_{BA} = 8.5 Hz, J_{BX} = 4.8 Hz, 1 H), 3.85 (A of AB, J_{AB} = 14.9 Hz, 1 H), 3.75 (d, 8.7 Hz, 1 H), 3.39 (s, 1 H), 3.19 (B of AB, J_{BA} = 14.9 Hz, 1 H), 1.60 (s, 3 H), 1.46 (s, 3 H), 1.39 (s, 3 H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.18, 110.47, 103.74, 83.01, 79.55, 78.10, 73.31, 68.40, 54.81, 26.93, 26.79, 26.64, 25.38; IR (film) 3382, 3299, 3264, 2989, 2934, 2883, 1375, 1344, 1272, 1217, 1160, 1071; HRMS (EI) m/z calcd for $C_{13}H_{24}NO_8S$ (M + H^+) 354.12226, found 354.12147.

2-(*N*-Benzyl Methylenesulfonamide)-2-hydroxy-1-phenylpropane (48). Procedure A; eluent = 2:1 Et_2O/Hex; 1.3 equiv of $CeCl_3$, 1.2 equiv of *N*-benzyl methanesulfonamide, and 2.4 equiv of BuLi were used; CD_3CO_2D was used in place of AcOH; **47** (54 mg, 0.4025 mmol) was converted to **48** (93 mg, 0.2912 mmol); yield = 72%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.17 (m, 10H), 5.29 (t, J = 6.1 Hz, 1 H), 4.22 (A of ABX, J_{AB} = 14.3 Hz, J_{AX} = 6.3 Hz, 1 H), 4.18 (B of ABX, J_{BA} = 14.3 Hz, J_{BX} = 6.5 Hz, 1 H), 3.19 (br s, 1 H), 3.11 (A of AB, J_{AB} = 14.3 Hz, 1 H), 3.02 (B of AB, J_{BA} = 14.3 Hz, 1 H), 2.85 (br s, 2 H), 1.35 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.73, 136.10, 130.77, 128.93, 128.42, 128.16, 128.13, 127.00, 71.45, 61.06, 48.37, 47.30, 27.13; IR (film) 3470, 3284, 3147, 3063, 3033, 2981, 2921, 1454, 1309, 1269, 1152, 1139, 1087, 1068; HRMS (CH_4) m/z calcd for $C_{10}H_{14}NO_3S$ ($M^+ - C_7H_7$) 228.06944, found 228.06982.

Supporting Information Available: Complete experimental procedures for the synthesis of **16**, **19**, **21**, **28**, **32**, **34**, **36**, **38**, **40**, **42**, **44**, *N*-benzyl methanesulfonamide, and *N*-benzyl deuteriomethanesulfonamide and appropriate spectral data, including ^{1}H and ^{13}C NMR, IR, MS, HMQC, and NOESY diagrams. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034001W