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Asymmetric Synthesis of the Potent HIV-Protease Inhibitor, Nelfinavir

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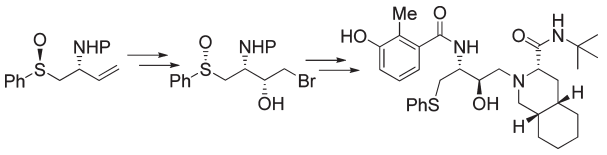

An asymmetric synthesis of nelfinavir is described starting from acrolein and (*S*)-methyl phenyl sulfoxide. The key features include (a) stereoselective preparation of a β-protected amino-γ,δ-unsaturated sulfoxide by the reaction of an α-sulfinyl carbanion with an unsaturated *t*-butyl sulfinylimine, (b) stereoselective bromohydrin formation using the pendant sulfoxide group as an intramolecular nucleophile, and (c) use of commercially or readily prepared inexpensive starting materials.

Nelfinavir **1**, a potent, orally active, effective inhibitor of an HIV-protease, is one of the most prescribed therapeutic agents to suppress the AIDS epidemic.[1] It has attracted the attention of synthetic chemists due to its huge market, unique structural features comprising five stereogenic centers and a core four carbon backbone in which each carbon is attached to a heteroatom.

Retrosynthetically, nelfinavir can be broken into three components: a benzoic acid derivative, central C4 core, and a perhydroisoquinoline derivative. The preparation of the benzoic acid[2] and perhydroisoquinoline subunit[3] has been described in the literature. However, the synthesis of an appropriate C4 unit and its coupling to the two aforementioned subunits has proved to be challenging. Earlier approaches to the C4 core have relied on (a) chiral pool starting materials including amino acid,[4] hydroxy acid,[5] and sodium erythorbate;[6] (b) desymmetrization of meso epoxide;[2a,7] and (c) Michael addition as key steps.[8] The above approaches suffer from one or more of the following drawbacks: (i) use of relatively expensive starting materials, (ii) use of expensive reagents, (iii) incomplete regio- and stereocontrol, and (iv) many steps. In continuation of our interest in the utilization of the sulfinyl moiety as an intramolecular nucleophile[9] for the regio- and stereoselective oxidative functionalization of alkenes, we describe herein a practical stereoselective synthesis of nelfinavir from β-protected amino-γ,δ-unsaturated sulfoxide **6**, Scheme 1 (retrosynthetic plan). Amino alcohol **3** was envisioned to be derived from sulfoxide **4**, which in turn can be obtained from **6**.

There are only a handful of reports on the addition of α-sulfinyl carbanions to imines.[10] To the best of our knowledge there was only a single report on the addition of α-sulfinyl carbanion to an imine derived from an unsaturated aldehyde[11] prior to our work. We have shown that the lithio anion of (*R*)-methyl *p*-tolyl sulfoxide reacted with an *N*-Ts imine derived from cinnamaldehyde,[12] with only modest stereocontrol. The first challenge toward the synthesis of nelfinavir was therefore to prepare β-protected amino-γ,δ-unsaturated sulfoxide **6**, with good diastereoselectivity. Garcia Ruano and co-workers reported[13] a diastereoselective synthesis of β-amino sulfoxides

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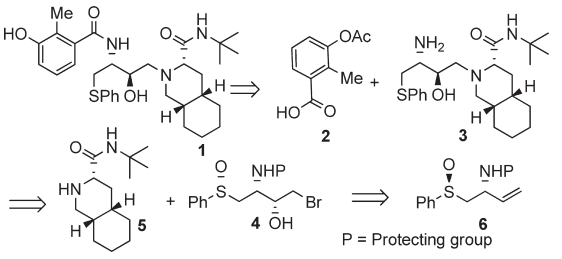
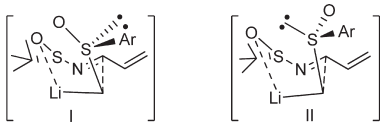
SCHEME 1. Retrosynthetic Analysis



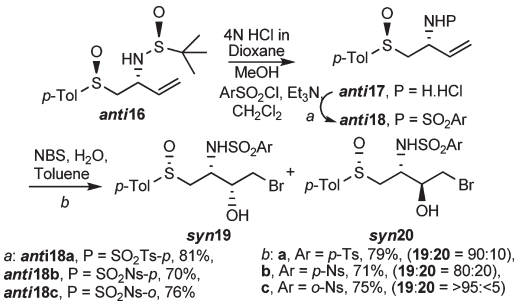
SCHEME 2. Probable Transition States



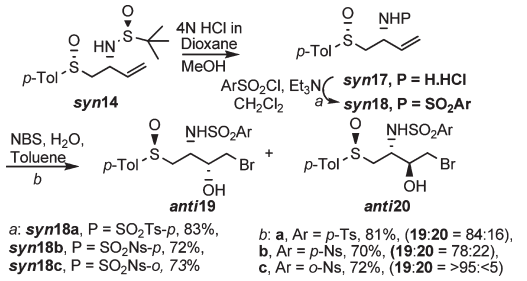
by reacting α-sulfinyl carbanions with chiral *p*-tolyl sulfinylimine derived from benzaldehyde. Inspired by this report, we began a model study[14] on the reaction of the organolithium reagent derived from methyl *p*-tolyl sulfoxide[15] **12** with sulfinylimines **10** and **11** prepared[16] from *p*-tolyl sulfinamide[17] **8** and *t*-butyl sulfinamide[18] **9**, respectively. The major diastereomers of **13**−**16** were assigned the depicted structure based on precedent.[13] The results collected in Table 1 (Supporting Information) reveal that the reaction affords products in the same ratio at different temperatures, though the yield was lower while running the reaction at higher temperatures (compare entries 1 and 2, entries 3 and 4, etc.). Also the stereoselectivity was better using sulfinylimine **11** and sulfoxide (*S*)-**12**. It is clear that the sulfinyl group on nitrogen has a large influence in determining the stereochemistry of the newly created stereogenic center. Since *t*-butyl sulfinamide is readily prepared in a large scale using asymmetric catalysis further reactions were carried out using **9**. The reaction of sulfinyl imine **11** with (*R*)- and (*S*)-sulfoxide **12** probably proceeds through transition states **I** and **II** to furnish the sulfinamides ***syn*-14** and ***anti*-16**, respectively, Scheme 2.

The sulfinamide ***anti*-16** was deprotected using HCl/dioxane,[19] and the resulting amine hydrochloride ***anti*-17** reacted with arenesulfonyl chlorides to furnish the sulfonamides ***anti*-18a**−**c** in a one-pot operation. The sulfonamides were prepared to study the influence of steric and (or) stereoelectronic effect of the aryl group on the stereoselectivity of bromohydrin formation. Thus, treatment of sulfonamide ***anti*-18a** with *N*-bromosuccinimide (NBS) in toluene in the presence of water and 2,6-lutidine afforded a mixture of bromohydrins ***syn*-19a** and ***syn*-20a** in 90:10 ratio, respectively. Similarly, sulfonamide ***anti*-18b** afforded

SCHEME 3. Stereoselectivity of Bromohydrin Formation from *anti*-18



SCHEME 4. Stereoselectivity of Bromohydrin Formation from *syn*-18



bromohydrins ***syn*-19b** and ***syn*-20b** in 80:20 ratio. The sulfonamide ***anti*-18c** reacted very stereoselectively to furnish a single product, ***syn*-19c**, Scheme 3.

To explore further, the influence of the relative configurations at carbon and sulfur on the stereoselectivity of bromohydrin formation, sulfonamides ***syn*-18a**−**c** were prepared from ***syn*-14**. Reaction of sulfonamides ***syn*-18a** and **b** with NBS furnished bromohydrins ***anti*-19a** (dr 84:16) and ***anti*-19b** (dr 78:22), while ***syn*-18c** yielded ***anti*-19c** as the sole product,[20] Scheme 4. It is apparent that the *o*-nosyl group was better than the *para*-substituted sulfonamides.

A probable reason for the high stereoselectivity observed with **18c** is the minimization of steric interactions between the π-complexed bromonium ion and the *o*-nitro substituent in the most stable conformation of **18c**, Scheme 5. It is generally agreed that the bromonium ion attacks the π-faces of the alkene reversibly and the stereochemical outcome of the neighboring group assisted reaction is dependent on the relative energies of the diastereomeric transition states. In the case of **18c**, the *o*-nitro substituent probably prevents the attack of the bromonium ion onto the *si*-face of the alkene effectively than when the substituent is in the *para*-positions as in **18a** and **b** leading to the exclusive formation of **19c**.

It is noteworthy that because the chirality of the sulfoxide has a negligible effect (if at all) in the creation of both the stereogenic centers, racemic aryl methyl sulfoxide can be

(14) Optically pure methyl *p*-tolyl sulfoxide was used in initial experiments to standardize reaction conditions because it is more readily available in excellent optical purity by a number of oxidation protocols.

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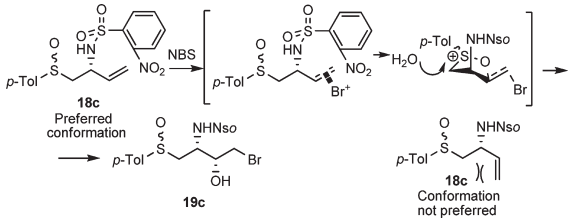
(19) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12.

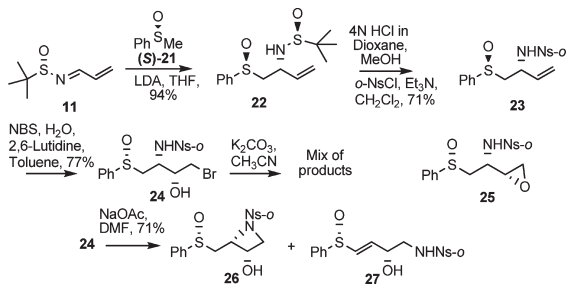
(20) The structure of ***anti*-19c** was confirmed by NOE studies on the derived *N*,*O*-acetonide by reaction with 2,2-dimethoxypropane in the presence of cat CSA. The structure assigned to ***syn*-19c** was confirmed by oxidation to a sulfone which was identical to that obtained from ***anti*-19c**.

(21) As pointed out in the text, though racemic methyl phenyl sulfoxide could be used, we chose the (*S*)-sulfoxide for the ease of interpretation of NMR spectra (single set of peaks). The sulfoxide was prepared following Jackson's protocol (ref 15) using the less expensive of the enantiomeric ligands.

SCHEME 5. Rationale for the Stereoselective Formation of 19c



SCHEME 6. Attempted Preparation of Epoxide 25



used. Having found suitable conditions for the diastereoselective preparation of bromohydrin **19c**, we began our study using (*S*)-methyl phenyl sulfoxide[21] **21**. Sulfinamide **22** (dr 98:2, HPLC) was converted to sulfonamide **23** as described before. Reaction with NBS proceeded cleanly to furnish bromohydrin **24**, the structure of which was unambiguously proven by X-ray crystallography.[22] Elaboration of **1** from **24** required inversion of the carbinol stereocenter, introduction of the perhydroisoquinoline subunit, and reduction of the sulfoxide to sulfide. This conversion was envisioned by subjecting epoxide **25** to acid-catalyzed 5-*exo* intramolecular opening by the sulfinyl group[23] and other transformations. In the event, treatment of **24** with anhydrous potassium carbonate in dry acetonitrile furnished none of the desired epoxide **25** but only a complex mixture of products.[24] In an alternative approach, we envisioned displacing the bromine in **24** by an acetate, followed by converting the secondary hydroxy group into its mesylate and forming an epoxide, thereby inverting the carbinol configuration. In the event, treatment of **24** with sodium acetate in anhydrous DMF led to the isolation of variable amounts of azetidine **26** and unsaturated sulfoxide **27**, Scheme 6.

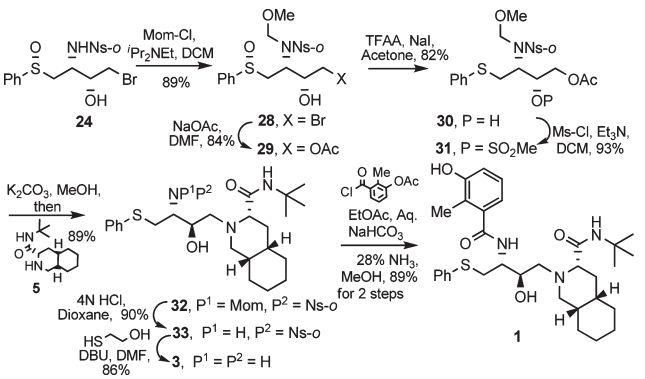
Exploring an alternate strategy, we decided to protect the hydroxy group. Thus, treatment of **24** with an equivalent of Mom-Cl in the presence of Hunig's base afforded, instead of the expected *O*-Mom ether, the *N*-Mom derivative **28**. Proceeding ahead,[25] the bromine was replaced by treatment with anhydrous sodium acetate in dry DMF to afford acetate **29**, which was reduced[26] to the sulfide **30** cleanly using TFAA in the presence of NaI. Mesylation of the hydroxy group and hydrolysis of the acetate in **31** using anhydrous potassium carbonate in dry methanol furnished an epoxide (not isolated) wherein the carbinol center was inverted. Addition

(22) See Supporting Information.

(23) Westwell, A. D.; Thornton Pett, M.; Rayner, C. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 847.

(24) The initially formed epoxide probably undergoes an aza-Payne rearrangement followed by β-elimination of the resulting aziridine. Alternately, an azetidine could be formed which then suffers β-elimination under the basic conditions.

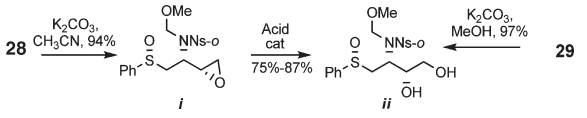
SCHEME 7. Synthesis of Nelfinavir



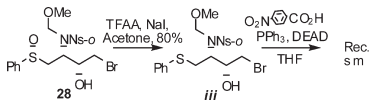
of amine **5** to the same pot furnished tertiary amine **32**. The *N*,*O*-acetal in **32** was deprotected[27] using aq 4 N HCl in dioxane to yield sulfonamide **33**. The sulfonamide was deprotected using mercapto ethanol[28] to afford amine **3**. Acylation using acid chloride derived from **2** followed by removal of the acetyl group as reported by Inaba and co-workers yielded nelfinavir **1**, Scheme 7. The physical characteristics of synthetic **1** were in good agreement with the data reported earlier.[7a]

In summary, we have designed a very highly stereoselective route to nelfinavir. The chirality of the *t*-butyl sulfinyl on the imine nitrogen group was exploited to introduce the nitrogen bearing stereocenter. By an appropriate choice of a protecting group for the nitrogen atom, the bromohydrin **24** (**19c**) was prepared stereoselectively by 1,2-asymmetric induction. Thus, in contrast to many earlier syntheses, we have introduced both the stereogenic centers without recourse to using chiral pool starting materials. We have utilized the sulfoxide as an intramolecular nucleophile. It is noteworthy that racemic methyl phenyl sulfoxide can be employed because the *N*-sulfinyl group has an overriding influence in the creation of the nitrogen bearing stereogenic center. This methodology should be useful for preparing other bioactives possessing the 1,2-amino alcohol subunit

(25) Attempted intramolecular opening of the epoxide ***i*** obtained without incident from bromohydrin **28** using $Bi(OTf)_3$, CSA and aq 3 M H_2SO_4 in dioxane furnished the diol ***ii*** as a result of nucleophilic attack at the distal carbon. The structure of the diol was assigned by comparison with the diol obtained by hydrolysis of acetate **29**. Therefore, in all the above experiments, only intermolecular attack takes place because sulfoxide configuration should be inverted if intramolecular opening were taking place.



Also attempted inversion of the carbinol center of sulfide ***iii***, obtained by reduction of **28**, using Mitsunobu protocol (*p*-nitrobenzoic acid, DEAD, PPh_3) returned only unreacted starting material.



(26) Drabowicz, J.; Oae, S. *Synthesis* **1977**, *6*, 404.

(27) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199.

(28) Miller, S. C.; Scanlan, T. S. *J. Am. Chem. Soc.* **1997**, *119*, 2301.

including HIV-protease inhibitors such as amprenavir and saquinavir.

Experimental Section

Sulfinamide 22. A round-bottom flask equipped with a magnetic stir bar and nitrogen inlet was charged with anhydrous THF (130 mL) and cooled at 0 °C. Diisopropylamine (33.6 mmol) was added followed by *n*-BuLi (2.5 M in hexane, 13.4 mL, 33.6 mmol) dropwise over 10 min. The reaction mixture was stirred at this temperature for 20 min and then cooled at −78 °C. A solution of (*S*)-methyl phenyl sulfoxide **21** (2.94 g, 21 mmol) in anhydrous THF (105 mL) was added dropwise via a syringe to the above LDA solution and the mixture stirred for 30 min at the same temperature. To a stirred solution of sulfinylimine **11** (3.34 g, 21 mmol) in anhydrous THF (150 mL) cooled at −78 °C was added the solution of the sulfinyl carbanion generated above, via a cannula, and the reaction was quenched immediately by the addition of aqueous saturated NH_4Cl solution. The two layers were separated, the aqueous layer was extracted with ethyl acetate, and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford a crude product, which was purified by column chromatography using 10% EtOAc/$CHCl_3$ (v/v) as the eluent to afford the sulfinamide **22** (5.89 g, 19.7 mmol) in 94% yield. Gummy liquid. TLC: R_f 0.2 (60% EtOAc/hexane). $[\alpha]_D^{25} = -121$ (*c* 1.2, $CHCl_3$). IR (neat): 3201, 2958, 1632, 1469, 1390, 1171, 1043, 751 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (m, 2H), 7.58−7.48 (m, 3H), 6.07−5.96 (m, 1H), 5.36 (d, J = 16.6 Hz, 1H), 5.27 (d, J = 10.5 Hz, 1H), 4.46−4.36 (m, 1H), 4.28 (d, J = 8.3 Hz, NH), 3.08−2.96 (m, 2H), 1.29 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.1, 137.1, 130.6, 128.8, 123.3, 116.8, 63.2, 56.3, 54.5, 22.3. MS (ESI): 322 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{14}H_{21}NO_2NaS_2$: 322.0911. Found: 322.0908.

Bromohydrin 24. To a stirred mixture of sulfonamide **23** (5.28 g, 13.9 mmol) and 2,6-lutidine (3.2 mL, 27.8 mmol) in toluene (70 mL) was added water (0.5 mL, 27.8 mmol) followed by freshly recrystallized *N*-bromosuccinimide (4.9 g, 27.8 mmol). The reaction mixture was stirred at room temperature until TLC examination revealed complete conversion of starting material. The reaction was quenched by adding aqueous saturated $NaHCO_3$ solution. The two layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were successively washed with water, brine, and dried over Na_2SO_4. Evaporation of the solvent afforded a crude product, which was purified by column chromatography using 10% EtOAc/$CHCl_3$ (v/v) as the eluent to furnish the bromohydrin **24** (5.1 g, 10.7 mmol) in 77% yield as a colorless solid. Mp: 169−170 °C. TLC: R_f 0.3 (20% EtOAc/$CHCl_3$). $[\alpha]_D^{25} = +49$ (*c* 0.5, $CHCl_3$). IR (neat): 3353, 3212, 2925, 1706, 1542, 1462, 1365, 1172, 1054, 1004, 752 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 8.10−8.07 (m, 1H), 7.90−7.87 (m, 1H), 7.80−7.71 (m, 2H), 7.64−7.59 (m, 2H), 7.57−7.54 (m, 3H), 6.37 (d, J = 6.8 Hz, NH), 4.92 (d, J = 3.7 Hz, OH), 4.31−4.26 (m, 1H), 4.20−4.12 (m, 1H), 3.42 (dd, J = 6.8 and 13.6 Hz, 1H), 3.31 (dd, J = 5.2 and 10.5 Hz, 1H), 3.01−2.95 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.8, 141.5, 134.0, 133.5, 132.9, 131.6, 131.0, 129.6, 125.4, 124.2, 71.8, 62.7, 52.3, 32.2. MS (ESI): 499 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{16}H_{17}N_2O_6NaS_2Br$: 498.9609. Found: 498.9607.

Compound 29. In a 50 mL round-bottom flask equipped with a magnetic stir bar were placed MOM-ether **28** (2.1 g, 4 mmol) and NaOAc (2.62 g, 32 mmol) in anhydrous DMF (20 mL). The resulting mixture was stirred at 90 °C until no remaining starting material could be detected by TLC (ca. 8 h). The reaction mixture was allowed to cool to room temperature, water (20 mL) was added, and then the mixture was extracted with EtOAc (2 × 30 mL). The combined organic extracts were successively washed with water (2 × 20 mL) and brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a crude product which was purified by column chromatography using 45% EtOAc/hexane (v/v) as the eluent to afford the acetate **29** (1.68 g, 3.36 mmol) in 84% yield as a gummy liquid. TLC: R_f 0.3 (65% EtOAc/hexane). $[\alpha]_D^{25} = +204$ (*c* 1.3, $CHCl_3$). IR (neat): 3408, 2960, 1739, 1544, 1442, 1364, 1231, 1171, 1046, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.14−8.11 (m, 1H), 7.82−7.76 (m, 2H), 7.68−7.65 (m, 1H), 7.52−7.47 (m, 3H), 7.41−7.39 (m, 2H), 5.03 (d, J = 11.8 Hz, 1H), 4.71 (d, J = 11.8 Hz, 1H), 4.34 (td, J = 3.4 and 10.1 Hz, 1H), 4.28 (dd, J = 7.6 and 11.8 Hz, 1H), 4.19−4.11 (m, 1H), 4.05 (dd, J = 4.2 and 11.8 Hz, 1H), 3.91 (d, J = 9.3 Hz, OH), 3.49 (s, 3H), 3.47 (dd, J = 10.1 and 13.5 Hz, 1H), 2.55 (dd, J = 2.5 and 13.5 Hz, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 147.7, 142.7, 134.3, 132.9, 132.2, 131.5, 131.3, 129.41 124.3, 123.6, 77.7, 69.2, 65.0, 56.6, 56.1, 54.0, 20.7. MS (ESI): 523 $[M + Na]^+$. HRMS (ESI): m/z $[M + Na]^+$ calcd for $C_{20}H_{24}N_2O_9NaS_2$: 523.0820. Found: 523.0835.

Compound 32. In a 25 mL round-bottom flask equipped with a magnetic stir bar were placed mesylate **31** (1.44 g, 2.56 mmol) and anhydrous K_2CO_3 (353 mg, 2.56 mmol) in dry MeOH (10 mL). The resulting mixture was stirred for 3 h when TLC examination revealed complete conversion of starting material. Amine **5** (691 mg, 2.9 mmol) was added in one portion and then stirred further until no remaining starting material could be detected by TLC (ca. 8 h). Ether (12 mL) was added to the reaction mixture and the precipitated solids were filtered through a pad of Celite. The filtrate was evaporated in vacuo to afford a crude product which was purified by column chromatography using 20% EtOAc/hexane (v/v) as the eluent to afford tertiary amine **32** (1.5 g, 2.28 mmol) in 89% yield as a colorless solid. Mp: 86−87 °C. TLC: R_f 0.3 (35% EtOAc/hexane). $[\alpha]_D^{25} = +6$ (*c* 1.1, $CHCl_3$). IR (neat): 3401, 2925, 2861, 1673, 1544, 1455, 1364, 1171, 1031, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.41 (t, J = 7.8 Hz, 1H), 7.16−7.13 (m, 2H), 7.09−7.06 (m, 3H), 5.94 (s, NH), 5.12 (d, J = 12.7 Hz, 1H), 4.70 (d, J = 12.7 Hz, 1H), 4.29−4.23 (m, 2H), 3.51 (s, 3H), 3.34 (dd, J = 3.9 and 13.7 Hz, 1H), 3.22 (dd, J = 2.9 and 11.7 Hz, 1H), 3.13 (dd, J = 11.7 and 13.7 Hz, 1H), 2.59 (dd, J = 8.8 and 12.7 Hz, 1H), 2.50 (dd, J = 2.9 and 11.7 Hz, 1H), 2.24 (dd, J = 5.8 and 12.7 Hz, 1H), 2.14 (dd, J = 3.9 and 11.7 Hz, 1H), 2.05−1.90 (m, 2H), 1.82−1.76 (m, 2H), 1.71−1.63 (m, 2H), 1.57−1.53 (m, 2H), 1.51−1.41 (m, 2H), 1.28 (s, 9H), 1.27−1.24 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 147.5, 135.9, 133.8, 132.6, 131.7, 131.6, 128.7, 127.6, 125.5, 124.3, 76.0, 71.9, 71.0, 58.9, 58.72, 58.7, 56.2, 50.7, 35.6, 33.3, 30.8, 30.4, 28.5, 27.3, 26.3, 25.9, 20.5. MS (ESI): 663 $[M + H]^+$. HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{32}H_{47}N_4O_7S_2$: 663.2886. Found: 663.2909.

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Supporting Information Available: Experimental procedures and physical data for compounds **10**, **11**, ***syn*-13**, ***syn*-14**, ***anti*-15**, ***anti*-16**, ***anti*-18a**, ***anti*-18b**, ***anti*-18c**, ***syn*-18a**, ***syn*-18b**, ***syn*-18c**, ***syn*-19a**, ***syn*-19b**, ***syn*-19c**, ***anti*-19a**, ***anti*-19b**, ***anti*-19c**, *N*,*O*-acetonide from ***anti*-19c**, sulfone from ***syn*-19c**, **23**, **28**, **30**, **31**, **33**, **3**, **1**, ***i***, ***ii***, ***iii***, Table 1, copies of spectra for all new compounds, cif data, and X-ray structure of **24**. This material is available free of charge via the Internet at http://pubs.acs.org.