Applications of Zr-Catalyzed Carbomagnesation and Mo-Catalyzed Macrocyclic Ring Closing Metathesis in Asymmetric Synthesis. Enantioselective Total Synthesis of Sch 38516 (Fluvirucin B_1)

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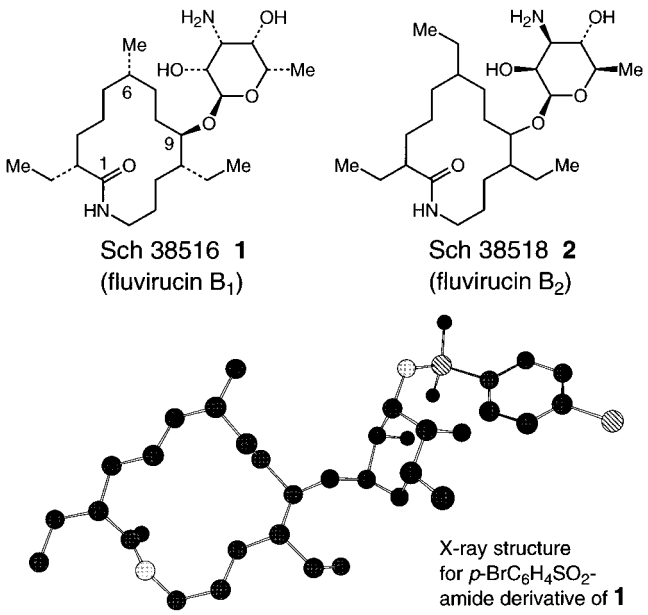
Abstract: The first enantioselective total synthesis of antifungal agent Sch 38516, also known as fluvirucin B_1, is described. The synthesis includes a convergent asymmetric preparation of amine **17** and acid **18**, which are then united to afford diene **62**. Metal-catalyzed transformations play a crucial role in the synthesis of the latter moiety. Of particular note are the diastereo- and enantioselective Zr-catalyzed alkylations, a tandem Ti- and Ni-catalyzed process that constitutes a hydrovinylation reaction, and a Ru-catalyzed alcohol oxidation to afford carboxylic acid **18**. The requisite carbohydrate **38** is synthesized in a highly diastereo- and enantioselective fashion. Optical purity of the carbohydrate moiety arises from the use of the asymmetric dihydroxylation method of Sharpless; diastereochemical control is achieved through a selective dipolar [3 + 2] cycloaddition with a readily available amine serving as the chiral auxiliary. Union of the appropriately outfitted carbohydrate **71** and diene **62** through an efficient and diastereoselective glycosylation is followed by a remarkably efficient Mo-catalyzed macrocyclization that proceeds readily at room temperature.

Background

The identification and isolation of effective antifungal agents is critical to human health care; in the past decade, the number of related infections acquired in hospitals has doubled.[1] It was therefore noteworthy when, in 1990, scientists at Schering-Plough reported a new class of antifungals. A representative member is Sch 38516 (**1**),[2] a compound active against *Candida* sp. (MIC 0.91 μg/mL) and dermatophytes (MIC >80.6 μg/mL), the detailed structure of which has been established through X-ray crystallography of the derived *p*-bromobenzenesulfonamide (Chart 1). Further interest in this natural product stems from the likelihood that Sch 38516 is identical to fluvirucin B_1,[3] an agent that is effective against influenza A virus. Other members, exemplified by Sch 38518 (**2**; fluvirucin B_2), have received less attention;[4] the relative and absolute stereochemical identity of the latter is yet to be rigorously established. We thus considered a general and modular approach to the total synthesis of this category of antifungals a worthy objective.[5]

Sch 38516 is an attractive target for enantioselective synthesis because of the paucity of stereogenic sites in the macrolactam structure, a characteristic that renders effective stereocontrol a formidable task (C2−C6 and C6−C9 relative stereocontrol). The target molecule bears a novel carbohydrate appendage that makes its debut here as part of a natural product. Furthermore, research efforts directed toward the total synthesis of Sch 38516 would allow us to challenge and establish the utility of stereoselective Zr-catalyzed ethylmagnesation, a process that has been developed in these laboratories.

Chart 1



[⊗] Abstract published in *Advance ACS Abstracts,* October 15, 1997.

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Scheme 1

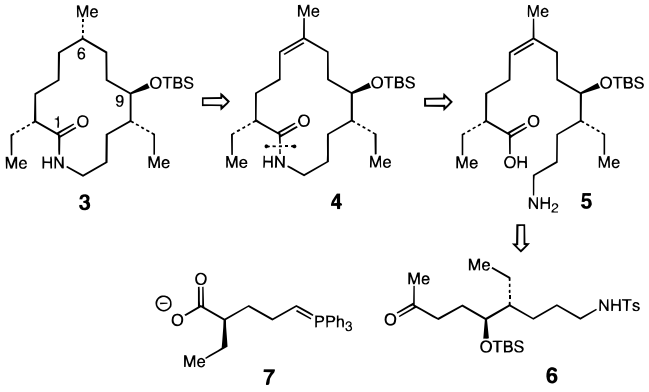
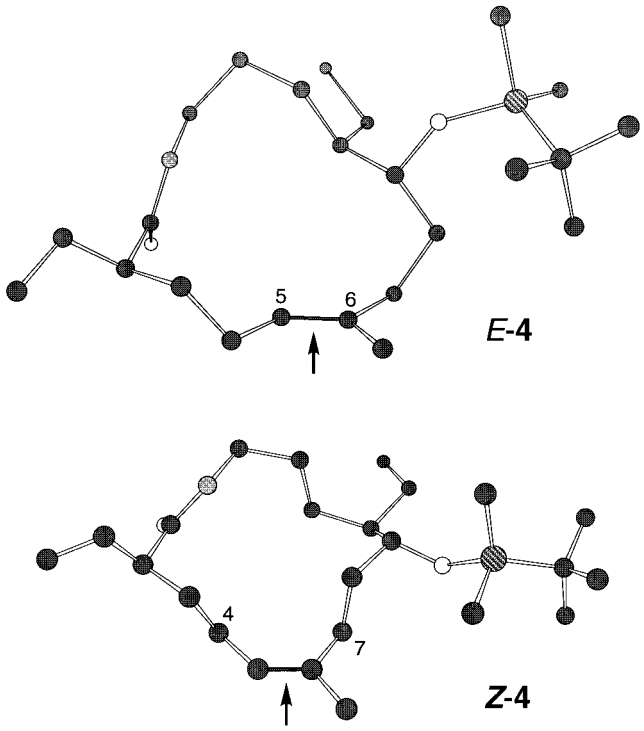
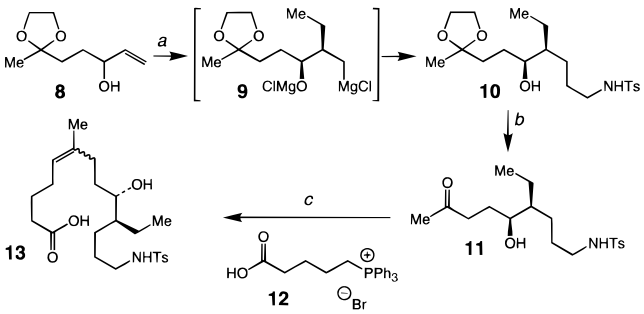


Chart 2



Scheme 2



[a] 5 equiv of EtMgCl, 10 mol % Cp_2ZrCl_2, Et_2O; $TsN(CH_2CH_2)$, 10 mol % CuI, THF (>20:1 diastereoselectivity, 52% overall yield). [b] 80% aqueous HOAc, 65 °C, 60%. [c] $Na(CH_2)SO(CH_3)$, **12**, then **11**, 20−55%.

Synthesis Plan

Many of our preliminary plans involved metal-catalyzed transformations. It was clear to us that such strategies offered exceedingly efficient routes to the requisite fragments, highlighting the effectiveness of a range of catalytic reactions, the majority of which are not feasible in the absence of a catalyst. What we did not expect was that the successful total synthesis would rely more heavily on transition metal-catalysis than originally expected.

At the outset, our overall strategy was along the established lines. We planned first to prepare the macrocyclic and carbohydrate moities; we expected that subsequent union of the two fragments would yield a protected form of the antifungal. This blueprint would eventually prove inadequate and had to be modified. Nevertheless, chemistry developed for the construction of the two segments was central to the successful implemenation of the total synthesis. Details of the enantioselective syntheses of the macrolactam and carbohydrate fragments are presented below.

Macrolactam Synthesis

With regard to the design of an efficient synthesis for the macrocyclic segment, we agreed on trisubstituted alkene **4** (Scheme 1) as a desirable intermediate. The reason for this predilection was twofold: (1) Molecular mechanics modeling (AM1 level on the TBS-protected ring structure) indicated that catalytic hydrogenation of the resident olefin would benefit from selective peripheral addition[6] to deliver the desired stereoisomer (see Chart 2, below), offering a convenient solution to the question of remote C2−C6 and C6−C9 stereocontrol. (2) A range of analogues would become readily accessible through stereoselective functionalization of the alkene.

Macrolactam Synthesis Plan A. Our initial approach to the synthesis of the macrocyclic amide **4** was influenced by the more traditional macrocyclization strategies.[7] As illustrated in Scheme 1, we planned to assemble fragments **6** and **7** through a Wittig olefination; the 14-membered ring **4** would then emerge from a macrocyclic amide bond formation (**5** → **4**). This general scheme, nevertheless, posed an important challenge in stereocontrol: Would stereoselective hydrogenation require the presence of only one of the two olefin isomers (*E*-**4** or *Z*-**4**)? If so, a difficult stereoselective synthesis of an unfunctionalized and remote trisubstituted alkene would have to be devised. Modeling studies, however, hinted that, as illustrated in Chart 2, either olefin stereoisomer would lead to the formation of the appropriate C6 stereochemistry, and that both *E* and *Z* macrocyclic alkenes are energetically within reach (AM1 level calculations indicate ∼1 kcal/mol energy difference).

To examine the viability of the olefination−macrolactamization, ketone **11** (Scheme 2) was prepared in five steps and 15% overall yield in a stereoselective manner. As shown in Scheme 2, treatment of allylic alcohol **8** with EtMgCl in the presence of 10 mol % Cp_2ZrCl_2 (Et_2O, 22 °C) resulted in diastereoselective carbomagnesation (→ **9**);[8] the derived chiral alkylmagnesium chloride was treated with 10 mol % CuI and tosyl aziridine[9] to afford ketal **10**. Subsequent removal of the

(6) (a) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.-E.; Nambia, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131−7134. (b) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996. (c) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148−1149. (d) Schreiber, S. L.; Santini, C. *J. Am. Chem. Soc.* **1984**, *106*, 4038−4039. (e) Neeland, E. G.; Ounsworth, J. P.; Sims, R. J.; Weiler, L. *J. Org. Chem.* **1994**, *58*, 7383−7394. (f) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, S. G. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467.

(7) For example, see: (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613−6615. (b) Meyers, A. I.; Reider, P. J.; Campbell, A. L. *J. Am. Chem. Soc.* **1980**, *102*, 6597−6598.

(8) (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (b) Hoveyda, A. H.; Xu, Z.; Morken, J. P.; Houri, A. F. *J. Am. Chem. Soc.* **1991**, *113*, 8950−8952. (c) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624. (d) Morken, J. P.; Hoveyda, A. H. *J. Org. Chem.* **1993**, 4237−4244.

(9) (a) Baldwin, J. E.; Adington, R. M.; Neil, I. A.; Schofield, C.; Spivey, A. C.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1989**, 1852−1854. (b) Church, N. J.; Young, D. W. *Tetrahedron Lett.* **1995**, *36*, 151−154.

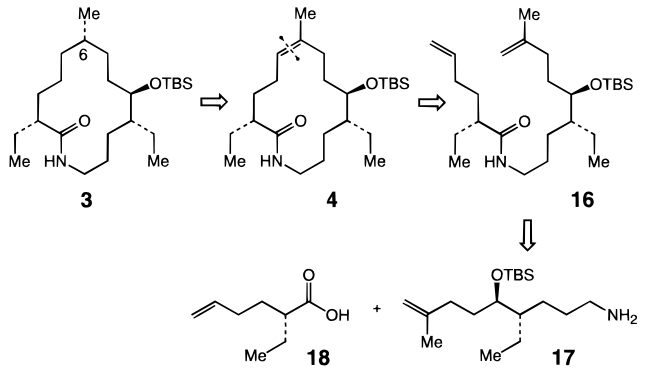
acetal unit released ketone **11** (containing the derived internal hemiketal, as judged by ^{1}H NMR analysis). To expedite our olefination studies, we selected achiral phosphonium salt **12** as the model ylide substrate. Attempts to couple **11** and **12** under various conditions based on procedures reported by Corey[10] ($Na(CH_2)SO(CH_3)$, DMSO) for similar systems afforded **13** in low yields (typically ~20−55%) and, not surprisingly, as a mixture of alkene isomers. Moreover, these reactions proved particularly irregular—we were unable to identify which factors would reliably deliver >55% yields.

We were hesitant to use elevated temperatures to facilitate olefination because of our concern that, particularly with the highly polar medium (DMSO), the integrity of the stereogenic center in the requisite phosphonium salt **7** would be compromised. Furthermore, we decided that inferior yields, at a stage where two optically pure segments are joined, would be detrimental to the efficiency of the overall plan.

Macrolactam Synthesis Plan B. In seeking an alternative and more efficient scenario to the formation of macrolactam **4**, we were intrigued by a succession of pioneering reports by Grubbs[11] and Schrock[12] on metal-catalyzed ring closing metathesis and thus considered the possibility of using this protocol. At the time (1994), synthesis of an eight- and a thirteen-membered heterocycle through the use of such catalytic procedures was reported by Martin[13] and Pandit,[14] respectively. In the former case, a disubstituted alkene was prepared with Schrock's $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))OCMe(CF_3)_2)_2$ (**14**) as the catalyst, whereas in the latter instance, Grubbs's alkylidene complex $(PCy_3)_2Cl_2RuCHCHPh_2$ (**15**) was used. In both cases, however, the diene precursor contained a rigid cyclic framework. Another disclosure by Martin[15] illustrated that efficient synthesis of 12-membered rings from conformationally mobile aliphatic starting materials could be problematic. Any doubts about the significance of the flexibility of the precursor structure on the ease of ring closing metathesis of medium and large rings was quelled by Grubbs's seminal report on the influence of structural scaffolds on the facility of eight-membered ring construction promoted by **15**.[16]

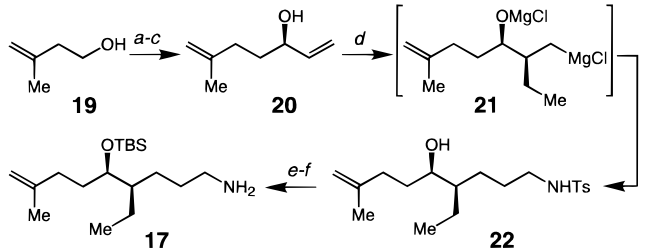
Because of the above myriad observations, the prospects for an efficient and reliable catalytic ring closure of **16** to afford **4** did not appear promising. We were aware that the presence of stereogenic centers have been reported to infer appreciable degrees of structural rigidity on a number of occasions.[17,18] However, we were also mindful of the fact that our synthesis plan required facile formation of a *tri*substituted macrocyclic alkene. We were concerned that substrate oligomerization, catalyst decomposition, and conformational freedom would not be readily overcome when the desired product is a slower-forming highly substituted alkene. To challenge the veracity of these concerns and to examine the validity of the ring formation strategy, we devised plans for an efficient and enantioselective synthesis of **16**, which would in turn demand a facile route to amine **17** and carboxylic acid **18**.

Scheme 3



Enantioselective Synthesis of Amine 17. As depicted in Scheme 4, the asymmetric synthesis of unsaturated amine **17** began with conversion of homoallylic alcohol **19** to racemic allylic alcohol **20** (51% overall yield), which was subsequently resolved according to the procedure by Sharpless (>99% ee, 66% yield, based on 50% conversion).[19] Treatment of optically pure **20** with 5 equiv of EtMgCl, 5 mol % Cp_2ZrCl_2 (THF, 22 °C),[8] and quenching of the resulting carbomagnesation product **21** with tosyl aziridine in the presence of 5 mol % CuI (or $CuBr\cdot Me_2S$) afforded **22** in 42% isolated yield, with >99% site selectivity and 97:3 diastereochemical control. The one-pot catalytic and stereoselective double-alkylation process was followed by protection of the secondary carbinol as its derived TBS ether (87% yield) and removal of the tosyl protecting group to afford **17** (90% yield). The six-step procedure was carried out with excellent diastereo- and enantioselectivity in 20−22% overall yield.

Scheme 4



[a] Ph_3P, I_2, Et_3N, CH_2Cl_2, 0 °C → 22 °C. [b] *n*-BuLi, $H_2CCHCHO$, THF, −78 °C, 51% overall. [c] $Ti(OiPr)_4$, *tert*-BuOOH, (+)-dicyclohexyl tartrate, 4 Å molecular sieves, 66%. [d] 5 equiv of EtMgCl, 5 mol % Cp_2ZrCl_2, Et_2O, 22 °C, 12 h; 6 equiv of $TsN(CH_2CH_2)$, 5 mol % CuI, THF, 42%. [e] TBSOTf, Et_3N, CH_2Cl_2, −78 °C, 87%. [f] 7 equiv of Na, NH_3, −50 °C, 95%.

Enantioselective Synthesis of Carboxylic Acid 18. To obtain the carboxylic acid piece (**18**) in the optically pure form, we first considered catalytic enantioselective ethylmagnesation of unsaturated oxocene **23** (option 1, Scheme 5). Subsequent

(10) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397−380.

(11) (a) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324−7325. (b) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 3800−3801. (c) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452 and references cited therein. (d) Schmalz, H.-G. *Angew. Chem., Int. Ed. Engl.* **1995**, *107*, 1981−1984 and references cited therein.

(12) (a) Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875−3886. (b) Bazan, G. C.; Schrock, R. R.; Cho, H.-N.; Gibson, V. C. *Macromolecules* **1991**, *24*, 4495−4502.

(13) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691−694. (c) Martin, S. F.; Liao, Y.; Chen, H.-J.; Patzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005−6008.

(14) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191−3194.

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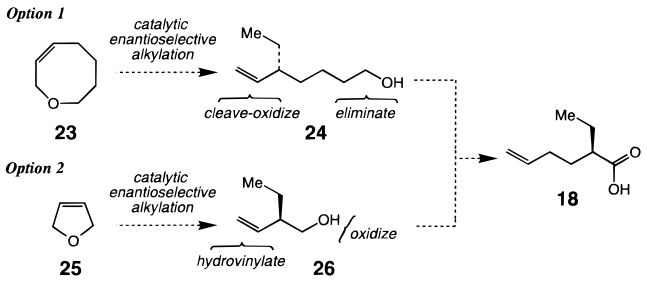
(16) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109.

(17) For a classic example, see: Woodward, R. B. et al. *J. Am. Chem. Soc.* **1981**, 3213−3215.

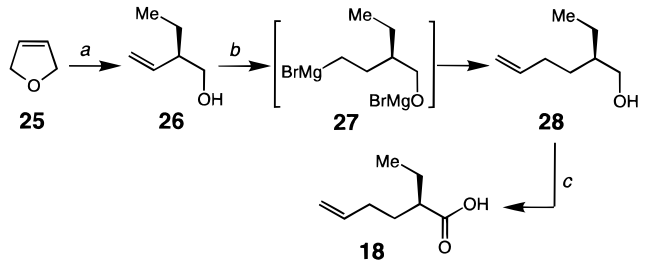
(18) Recent elegant studies by Grubbs on the effect of stereochemistry on the synthesis of macrocyclic peptides (disubstituted alkenes) by ring closing metathesis were not disclosed at the time of our planning. See: (a) Miller, S. J.; Gubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856. (b) Miller, S. J.; Blackwell, H.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614.

(19) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780. For a comprehensive review, see: (b) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: New York, 1993; pp 103−158.

Scheme 5



Scheme 6



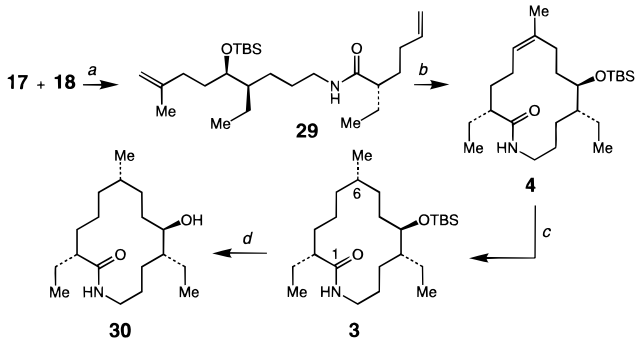
[a] 0.8 equiv of EtMgBr, 0.4 mol % (*S*)-(EBTHI)-Zr-binol, THF, 70 turnovers. [b]3 equiv of *n*-PrMgBr, 3 mol % Cp_2TiCl_2, THF; then 15 equiv of H_2CCHBr, 3 mol % $(Ph_3P)_2NiCl_2$, 72%. [c]10 mol % (n-$CH_3(CH_2)_2)_4NRuO_4$, MeCN, 2 equiv of H_2O, 3 equiv of NMO, 77%.

functionalization of the resulting alkylation product **24** would afford **18**. In practice, however, this scheme was rendered unattractive by the inefficiency of catalytic ring closing metathesis to afford **23**; significant amounts of oligomeric products were obtained instead. This outcome supported previous notions that rigidity of the structural framework is an underpinning aspect of successful ring synthesis by catalytic metathesis.[16,20]

Alternatively, we considered Zr-catalyzed enantioselective ethylmagnesation of dihydrofuran **25**,[21] a commercially available heterocycle that we had already established to be an outstanding substrate for asymmetric catalytic alkylation. If this approach were to be used successfully, an efficient hydrovinylation process would be needed (Scheme 5). A synthesis scheme was accordingly devised that made optically pure **18** available in four catalytic steps (Scheme 6).

The sequence began with asymmetric catalytic ethylmagnesation of **25** (0.4 mol % (*S*)-(EBTHI)Zr-binol, ~70 turnovers) to give **26** in >99% ee (chiral GLC analysis).[21] A one-pot catalytic hydrovinylation of the terminal alkene was effected in the following manner: Subjection of **26** to 3 equiv of *n*-PrMgBr and 3 mol % Cp_2TiCl_2 led to hydromagnesation of the olefin,[22] affording **27**. Treatment of the resulting Grignard reagent with 3 mol % $(Ph_3P)_2NiCl_2$ and 15 equiv of vinyl bromide[23] yielded the corresponding cross coupling product **28** (72% from **26**). At this juncture, a Ru-catalyzed oxidation of the primary alcohol to the derived acid was designed through a simple modification of the well-known procedure by Ley.[24]

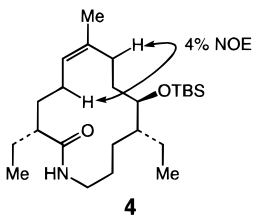
Scheme 7



[a] 1 equiv of DCC, 1.2 equiv of HOBT, 22 °C, 12 h, 85%. [b]20 mol % $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))OCMe(CF_3)_2)_2$, C_6H_6, 22 °C, 90%. [c]H_2 (1 atm), 10% Pd(C), 84%. [d]HF, MeCN, 80%.

When unsaturated alcohol **28** was treated with 10 mol % (n-$Pr)_4NRuO_4$ in the presence of 2 equiv of H_2O and 3 equiv of NMO, **18** was obtained in 77% yield (>99% ee; chiral GLC analysis). Further studies with regard to the mechanism and utility of this mild catalytic oxidation are in progress. It is plausible that the purported aldehyde intermediate undergoes hydration in the presence of H_2O; further oxidation affords the carboxylic acid product.

Macrocycle Synthesis through Catalytic Ring-Closing Metathesis. With amine **17** and carboxylic acid **18** available, these two fragments were coupled to afford diene-amide **29** in 85% yield after silica gel chromatography (Scheme 7).[25] Initially, based on previous studies on similar medium- and large-ring syntheses, we surmized that elevated temperatures would be necessary for effective macrocyclization. We therefore excluded ambient temperature conditions from our preliminary investigations. Accordingly, we established that, when **29** is treated with 20 mol % Mo catalyst **14** in benzene (0.01 M) and the mixture is heated to 50 °C (12 h), macrolactam **4** is obtained in 60−65% isolated yield as a single olefin stereo-



isomer (>98% *Z*, as judged by 500 MHz ^{1}H NMR analysis). As illustrated, the stereochemical identity of the olefin isomer was established through NOE difference experiments.

We also determined that with lower catalyst loadings (15 mol % **14**), reaction efficiency suffers significantly (<50% conversion). When Ru catalyst **15** was used (20 mol %, benzene, 80 °C), 5−10% dimer derived from reaction of the terminal olefins was formed as the only product. Further investigation of the catalytic macrocyclization indicated that, *with freshly prepared or recrystallized Mo catalyst, ring closing metathesis occurs smoothly at 22 °C to afford **4** in 90% isolated yield after only 4 h*. With 40 mol % **14**, reaction yield improved to 97%. Less than 20 mol % catalyst gave notably lower conversions and yields.

With Mo-catalyzed macrolactamization secured, we turned our attention to the critical issue of C2−C6 remote stereochemical control. Catalytic hydrogenation of unsaturated cyclic amide **4**, as predicated by initial modeling studies (Chart

(20) For an unusually facile eight-membered ring synthesis through catalytic metathesis, see: (a) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298. For a more recent related study, see: (b) Linderman, R. J.; Siedlecki, J.; O'Neill, S. A.; Sun, H. *J. Am. Chem. Soc.* **1997**, *119*, 6919−6920.

(21) (a) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (b) Reference 20. For a recent review, see: Hoveyda, A. H.; Morken, J. P. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284.

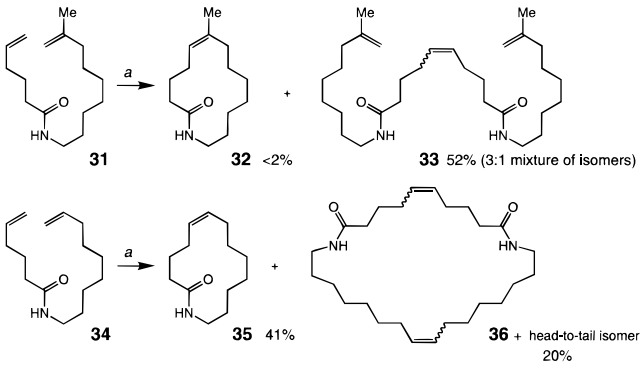
(22) (a) Eisch, J. J.; Galle, J. E. *J. Organomet. Chem.* **1978**, *160*, C8−C12. (b) Sato, F. *J. Organomet. Chem.* **1985**, *185*, 53−64.

(23) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374−4376.

(24) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639−666 and references cited therein.

(25) Li, W. R.; Ewing, W. R.; Harris, B. D.; Joullie, M. *J. Am. Chem. Soc.* **1990**, *112*, 7659−7672.

Scheme 8

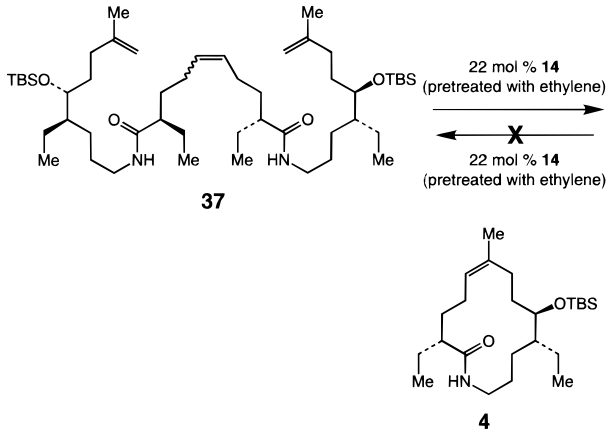


[a] Conditions: 25 mol % **14**, 0.01 M in C_6H_6, 50 °C, 18 h.

2), in the presence of 10% Pd(C) resulted in the formation of **3** in 84% yield and with >98% diastereoselectivity (400 MHz ^{1}H NMR analysis). To ascertain that our stereochemical assignment was valid, the TBS protecting group was removed and the resulting aglycon **30** acylated under standard reaction conditions (Ac_2O, Et_3N, 10 mol % DMAP). This procedure delivered material identical to that obtained from degradation of the natural product (^{1}H NMR, IR, TLC).

The Origin of the Facile Catalytic Macrocyclization. To gain insight into the remarkably efficient cyclization reaction that converts **29** to **4**, and to determine the extent to which existing stereogenic centers provide diene precursor **29** with substrate preorganization, we examined ring closing metathesis reactions of diene-amides **31** and **34**. As illustrated in Scheme 8, when **31** was subjected to 25 mol % **14** (50 °C, 18 h), <2% **32** was formed. Instead, dimer **33** was obtained in 52% yield after chromatography (3:1 mixture of olefin isomers, judged by 400 MHz ^{1}H NMR; identity of major product not determined; HRMS: Calcd, 474.4185. Found, 474.4187). When diene **34** was subjected to identical conditions, macrolactam **35** was obtained in 41% isolated yield (HRMS: Calcd, 209.1780. Found, 209.1777), along with 20% of the derived 28-membered ring cyclic dimer **36** (presumably as a mixture of head-to-head and head-to-tail isomers; HRMS: Calcd, 418.3559. Found, 418.3560); <10% of the acyclic dimer was detected. *These data clearly illustrate that with the slower forming trisubstituted olefin, the presence of stereogenic centers is required for facile ring closure* (cf. **29** → **4**, Scheme 7), whereas when reacting alkenes are terminal olefins, formation of the fourteen-membered ring is more favored (41% yield of **35**). Our results lend further credence to Grubbs's contention[16] that with conformationally mobile diene structures some form of structural restraint is needed for ring closing metathesis to occur readily.[26]

Considering the facility with which dimerization products **33** and **36** are obtained, we reasoned that, in catalytic ring closure of **29**, the derived dimer is perhaps initially formed as well. If the metathesis process is reversible,[27] such adducts may subsequently be converted to the desired macrocycle **4**. To examine the validity of this paradigm, diene **29** was dimerized (→ **37**) by treatment with Ru catalyst **15**. As eq 1 depicts, when **37** was treated with 22 mol % **14** (after pretreatment with ethylene to ensure formation of the active complex), 50−55% conversion to macrolactam **4** was detected within 7 h by 400 MHz ^{1}H NMR analysis. When **4** was subjected to the same reaction conditions, <2% of any of the acyclic products was detected. Although, we do not as yet have a positive proof that **37** is formed in cyclization of **29** (→ **4**), this observation suggests that if dimerization were to occur, the material can be readily converted to the desired macrolactam, which is kinetically immune to rupture.

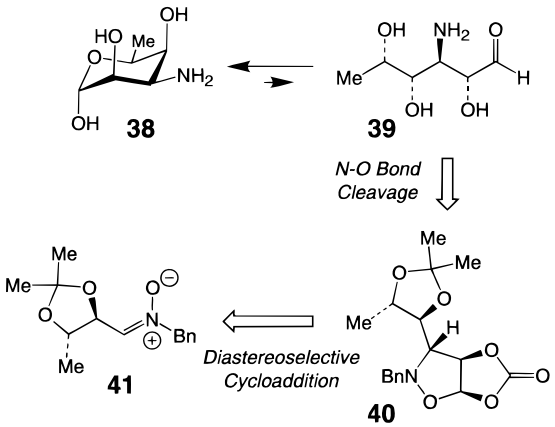


Carbohydrate Synthesis[28]

At the planning stage for the carbohydrate synthesis, we realized that this moiety of the natural product, as shown in Scheme 9, may arise from appropriate functionalization of tricycle **40**, fabricated through a [3 + 2] dipolar cycloaddition involving nitrone **41** and vinylene carbonate. In this context, we were intrigued by the possibility of using the precedence established by DeShong.[29] Below, we describe how the general synthesis plan depicted in Scheme 9 was modified to provide an efficient, diastereo- and enantioselective route to **38**.

Enantioselective Synthesis of Nitrone 41. Preparation of nitrone **41** requires aldehyde **45** (Scheme 10), which has been used in the synthesis of daunosamine, the sugar region of the notable antitumor agent daunomycin.[30] Two routes for the

Scheme 9



(26) It is likely that, as recently demonstrated by Furstner, higher yields of the disubstituted olefin **35** may be obtained under strict high dilution conditions and with longer reaction times. Our experiments clearly illustrate that the synthesis of trisubstituted macrocyclic alkenes is significantly more demanding than that of their disubstituted analogues. See: Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943.

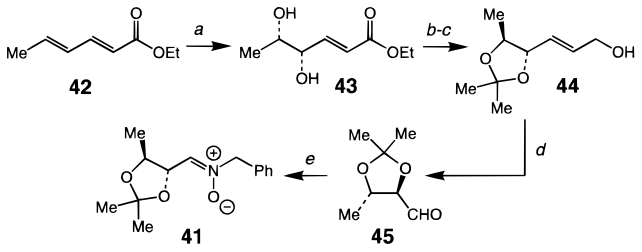
(27) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101−1103 and references cited therein.

(28) A synthesis of the carbohydrate, 3-amino-3,6-deoxy-D-talopyranose, was disclosed by Stanek and Jary in 1974. Their reported procedure affords the amino sugar only as a byproduct, formed en route to a mixture of various 3-amino-3,6-pyranoses (2.4% of total mixture). See: Capek, K; Stanek, J.; Jary, J. *Coll. Czech. Chem. Commun.* **1974**, *39*, 1462−1478.

(29) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598−5602 and references cited therein.

(30) (a) Pedersen, S. F.; Konradi, A. W. *J. Org. Chem.* **1990**, *55*, 4506−4508. (b) Hauser, F.; Ellenberger, S. R. *J. Org. Chem.* **1986**, *51*, 50−57. (c) Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Org. Chem.* **1983**, *48*, 909−910.

Scheme 10



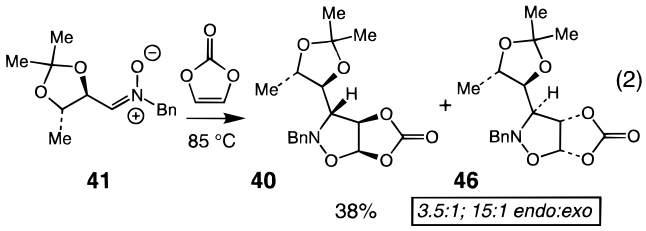
[a] AD-mix-α, 1 equiv of $MeSO_2NH_2$, *tert*-BuOH, H_2O. [b] 2,2-dimethoxypropane, 5 mol % *p*-TsOH, 52% from **42**. [c] 2.5 equiv of DIBAL-H, −78 °C, [d] O_3, 8:1 CH_2Cl_2:MeOH, −78 °C; Me_2S, 64% from **43**. [e] 1.0 equiv of *N*-hydroxybenzylamine, 20 h, 99%.

construction of **45** have been reported. One is by Mukaiyama,[31] a procedure that utilizes diethyl tartrate as starting material and is effected in 53% overall yield in seven steps. The other is that of Schmid,[32] where the target carboxaldehyde is obtained in five steps and 16% overall yield, starting with D-arabinose. We decided to outline a more concise preparation scheme, where a catalytic enantioselective process is used to introduce absolute chirality. We avoided starting with carbohydrates or other naturally available chiral sources, circumventing substrate functional group alterations and, ultimately, unnecessarily lengthy routes. A four-step protocol (Scheme 10) that delivers **45** in 33% overall yield and 80% ee is described below.

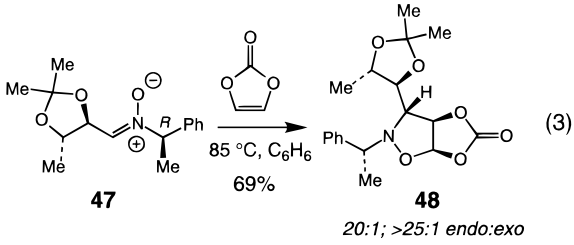
Asymmetric dihydroxylation[33] of commercially available ethyl sorbate (Scheme 10), according to the procedure by Sharpless, gave **43** in 61% yield and 80% ee (as judged by chiral GLC). Protection of the vicinal diol and subsequent reduction of the ester group led to the formation of allylic alcohol **44** in 80% yield after chromatography. Ozonolysis of **44** under standard conditions provided carboxaldehyde **45** (67%);[34] treatment of **45** with *N*-benzylhydroxylamine gave nitrone **41** in 99% yield.

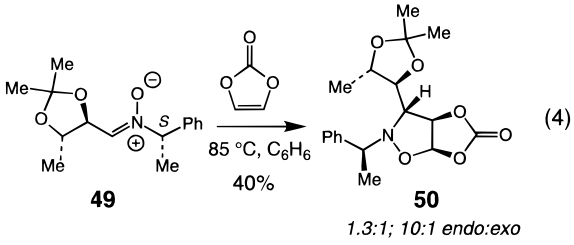
Several issues with regard to the synthesis route in Scheme 10 merit comment: (1) Enantioselective dihydroxylation of **42**, depending on which stereoisomeric chiral oxidant is used, affords different degrees of absolute facial selectivities (80% ee with AD-mix-α vs 96% ee with AD-mix-*β*). (2) The minor isomer obtained in the latter catalytic reaction can be readily separated from the desired major enantiomer at a later stage in the synthesis (see below).

The Diastereoselective [3 + 2] Cycloaddition. As illustrated in eq 2, when nitrone **41** was treated with 5 equiv of vinylene carbonate at 85 °C (22 h), cycloadducts **40** and **46** were obtained with similar selectivity as when the original DeShong protocol[35] was employed (exo products are not shown). The stereochemistry of the major diastereomer is that desired for the stereoselective synthesis of carbohydrate **38** (see below for proof of stereochemistry). However, inferior levels of diastereocontrol (38% isolated yield of **40**) made this approach less appealing, especially since chromatographic separation of isomeric cycloadducts (**40** and **46**) proved cumbersome; medium pressure liquid chromatography (MPLC) was required for this purpose. Hence, it was clear that the cycloaddition reaction would have to be rendered highly stereoselective for effective material throughput necessary in the course of the total synthesis.



To design a more selective variant of the cycloaddition process, we were encouraged by an investigation reported by Wovkulich and Uskokovic.[36] These researchers were able to enhance stereoselectivity in a similar, albeit intramolecular, [3 + 2] cycloaddition through the use of chiral amine ((*S*)-α-methylbenzylamine[37] (in place of a benzylamine). We therefore prepared nitrones **47** and **49** by treatment of aldehyde **45** with the appropriate enantiomeric antipodes of the nonracemic hydroxylamines. It was at this point that the minor isomer formed in the asymmetric dihydroxylation of **42** was separated from the desired product. As illustrated in eq 3, *(R)-N-hydroxyl-α-methylbenzylamine **47** undergoes cycloaddition with vinylene carbonate to afford **48** with >20:1 diastereoselectivity, >25:1 endo selectivity* (400 MHz ^{1}H NMR) *and in 69% yield* after silica gel chromatography.[38] In contrast, when the *S* chiral auxiliary was used, stereoselectivity reduced to 1.3:1, endo:exo ratio diminished to 10:1 (from 15:1 with benzylamine), and the combined yield of products was 40% (eq 4). It must be pointed out that thermal cycloaddition must be carried out under strictly controlled reaction conditions; temperatures above 85 °C caused significant material decomposition, whereas with temperatures below 85 °C, little or no reaction occurred.





The Origin of Stereocontrol in the [3 + 2] Cycloaddition. The following observations are critical for a better understanding of the mechanism of the cycloaddition reaction: (1) Nuclear

(31) (a) Mukaiyama, T.; Goto, Y.; Shoda, S. *Chem. Lett.* **1983**, 671−674. (b) Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *J. Org. Chem.* **1983**, *48*, 910−912.

(32) Binder, W. H.; Prenner, R. H.; Schmid, W. *Monat. Chem.* **1994**, *125*, 763−771.

(33) (a) Xu, D.; Crispino, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571. (b) Kolb, H. C.; VanNieuwehze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547.

(34) Direct ozonolytic cleavage of protected **43** affords **45** in 40% isolated yield (versus 64% for the two-step sequence shown in Scheme 10).

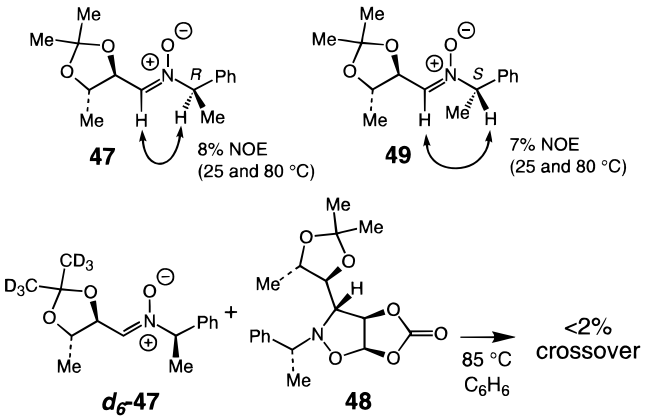
(35) Conditions originally reported by DeShong are 30 equiv of vinylene carbonate, 95 °C, 72 h (cf. ref 29).

(36) (a) Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1989**, *111*, 3956−3957 and references cited therein. For other related examples, see: (b) Belzecki, C.; Panfil, C. *J. Org. Chem.* **1979**, *44*, 1212−1216. (c) Vasella, A.; Voeffray, R. *Helv. Chim. Acta.* **1982**, *65*, 1134−1137 and references cited therein. (d) Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y. *Tetrahedron Lett.* **1987**, *28*, 1431−1434.

(37) For synthesis of the chiral hydroxylamine, see: Polonski, T.; Chimiak, A. *Tetrahedron Lett.* **1974**, 2453−2456.

(38) For the use of this chiral auxiliary in stereoselective reactions with *O*-silylketene acetals, see ref 36d.

Scheme 11



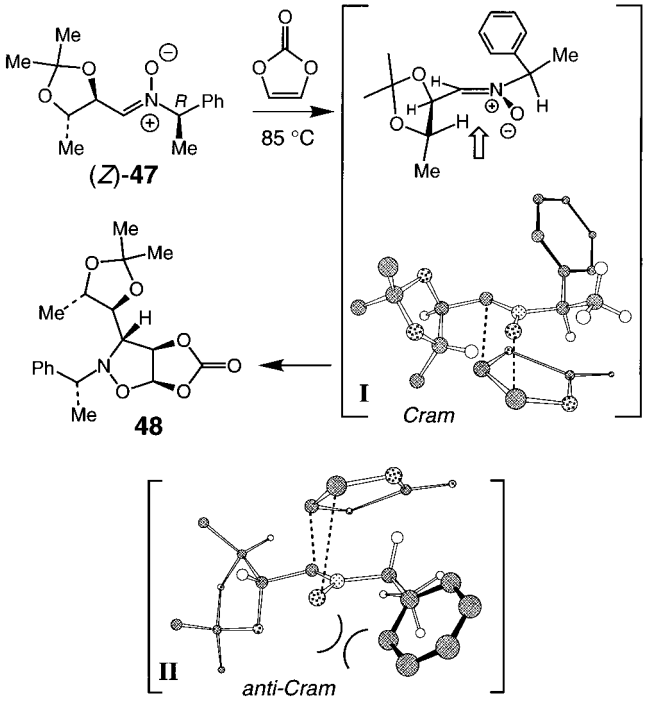
Overhauser difference spectroscopy indicated that both nitrones, as expected,[39] preferentially exist as their *Z* isomers (Scheme 11). (2) Crossover experiment shown in Scheme 11 demonstrated that cycloaddition is under kinetic control. (3) Reactions proceed in an identical fashion in the presence of 2,6-di-*tert*-butyl-4-methylphenol: radical intermediates are probably not involved.[40]

A plausible transition structure (**I**) for the cycloaddition of nitrone **47** is shown in Scheme 12. This proposal is based on the following principles: (1) Supported by previous studies, we assume that the cycloaddition is concerted but asynchronus.[41] Additionally, theoretical investigations suggest that formation of the C−C bond is more advanced than that of the C−O bond in the transition state.[42] These mechanistic considerations suggest that factors differentiating the two diastereotopic faces of the C═N unit (rather than the entire C═N−O moiety) are critical to the eventual stereoselective outcome. (2) The more reactive nitrone conformer is one where the electron-withdrawing C−O bond is antiperiplanar to the C═N π cloud; electron donation from C═N π to C−O σ^* promotes the electron deficiency and thus reactivity of the nitrone. (3) Electronic effects alone are not sufficient to give rise to significant levels of diastereodifferentiation; this is particularly likely since all reactions are carried out at elevated temperatures (both electronic and steric factors need to favor one transition structure for appreciable $\Delta\Delta G^{\ddagger}$). Electronic factors, only in conjunction with supporting steric effects, lead to high levels of stereocontrol.

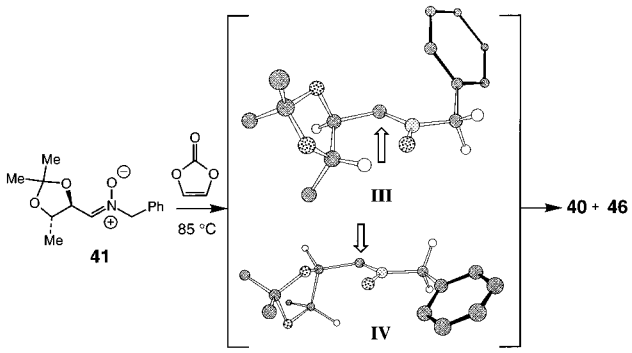
On the basis of the above principles, the favored transition structure **I** (Scheme 12) thus involves the addition of vinylene carbonate according to the Cram−Felkin−Anh model[43] (attack of dipolarophile through the Burgi−Dunitz angle). In the alternative mode of addition **II**, the incoming heterocycle adds syn to the larger alkyl substituent (anti-Cram) and the phenyl unit of the chiral auxiliary suffers from unfavorable steric interactions with the nitrone oxygen.

With benzyl nitrone **41** (without the chiral auxiliary), reaction through conformations **III** and **IV** (Cram) compete to reduce diastereoselection (Scheme 13). Modest selectivity arises from

Scheme 12



Scheme 13



electronically preferable orientation of the C−O bond with respect to the C═N unit (see above). Similarly, when (*S*)-nitrone **49** is utilized, energetically similar modes of addition **V** and **VI**, consistent with the Felkin−Anh model, lead to opposite levels of diastereoselection (Scheme 14). The present paradigm offers a mechanistically consistent picture for the observed degrees of diastereoselectivity; the dependence of endo:exo ratios on the nature of the amine group is, on the other hand, more difficult to decipher.

Reduction of the N−O Bond and Proof of Stereochemistry. Although reduction of similar cycloadducts were already reported in the literature,[29] we found that treatment of these polycyclic systems with $Pd(OH)_2$ or Pd(C) through a range of neutral and acidic conditions resulted in either recovery of the starting material or complete decomposition.[44] After extensive experimentation, the following were determined: (1) The reaction must be carried out with rigorous control of HCl stoichiometry. Control experiments indicated that too little acid (<2.5 equiv) leads to substrate recovery, and excess HCl (>2.5 equiv) promotes starting material decay. (2) Although the acidic

(39) (a) Bjorgo, J.; Boyd, D. R.; Neill, D. C. *J. Chem. Soc, Chem. Commun.* **1974**, 478−479. Energy differences between *E* and *Z* nitrones have been measured: (b) Breuer, E.; Aurich, H.; Nielsen, A. In *Nitrones, Nitronates and Nitroxides*; John Wiley & Sons: New York, 1989; p 151.

(40) Firestone, R. A. *J. Org. Chem.* **1968**, *33*, 2285−2290 and references cited therein.

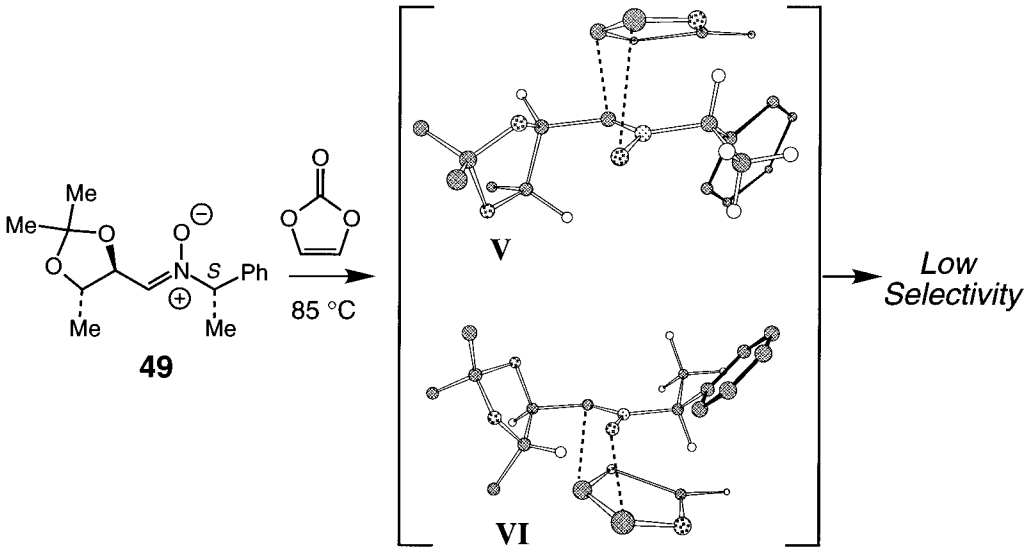
(41) (a) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 633−645. (b) Professor K. N. Houk, personal communication.

(42) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361−369.

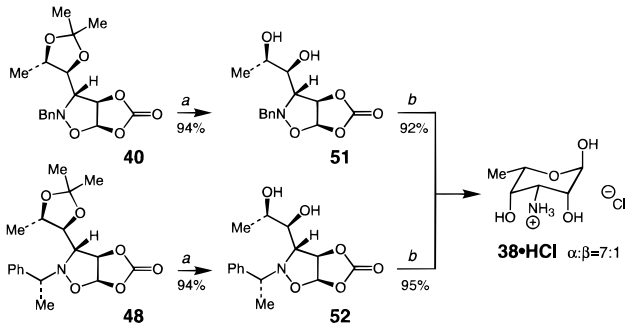
(43) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70. (b) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y.-D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108−1117 and references cited therein.

(44) Representative conditions examined (all catalysts used in 50% by weight): 50 psi H_2, $Pd(OH)_2$, 10% HCl, MeOH and 50 psi H_2, $Pd(OH)_2$, MeOH (24 h) resulted in substrate degradation; 50 psi H_2, Pd(C), MeOH and 50 psi H_2, Pd(C), HOAc (14 h) resulted in starting material recovery; 200 psi H_2, Raney Ni, MeOH (14 h) afforded a complex mixture of unidentifiable products.

Scheme 14



Scheme 15



[a] 4:1 THF:1.0 M HCl, 65 °C. [b] $Pd(OH)_2$ (50% by weight), 300 psi H_2, 2.5 equiv of MeCOCl, MeOH.

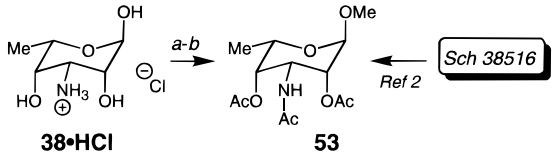
conditions required for hydrogenation are sufficient to remove an acetonide moiety, higher yields and more reliable results were obtained when excision of the protective group was carried out prior to reduction of the N−O bond. It is possible that the N−O bond rupture occurs before release of the resident diol; in such a case, the sensitive α-hydroxy, *β*-amino aldehyde may decompose before the carbinol site required for ring closure is released. (3) Pd catalysts from commercial sources were to be avoided; use of freshly prepared Pearlman's catalyst proved imperative.[45] Thus, when **51** was reduced under 300 psi H_2 with freshly prepared Pearlman's catalyst ($Pd(OH)_2$, 50% by weight) in the presence of 2.5 equiv of HCl, carbohydrate **38**·HCl was obtained in 92% yield as a 7:1 mixture of α and *β* anomers, respectively (Scheme 15). As further depicted in Scheme 15, when these conditions were applied to **52**, the desired sugar **38** was isolated in 95% yield.

To prove the stereochemical identity of **38** through comparison with the corresponding authentic sample, methoxy triacetate derivative **53** was prepared (>98% α anomer),[46] as illustrated in Scheme 16. Analysis of ^1H NMR, ^{13}C NMR, and IR spectra of **53** and comparison to the material obtained from degradation

(45) Pearlman, M. W. *Tetrahedron Lett.* **1967**, *17*, 1663−1664.

(46) Several additional issues in connection to the transformation depicted in Scheme 16 merit comment: (1) In the formation of the intermediate methoxyacetal, the initial product consists of a 3:1 mixture of α:*β* isomers (after 8 h); however, after prolonged reaction times (70 h), the α anomer becomes the sole product. (2) Whereas formation of the above mentioned α-methylacetal requires 70 h, that of daunosamine (lacking the C2 axial OH) is complete within 30 min. This rate difference may be due to destabilization of the intermediate oxonium ion by the axially disposed hydroxide.

Scheme 16



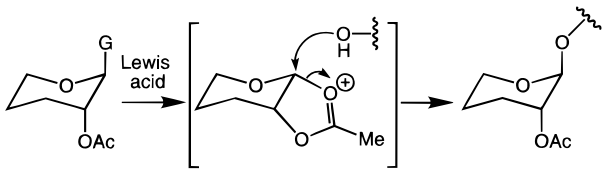
[a] 10% HCl in MeOH, 70 h, 88%. [b] 10 equiv of Ac_2O, 5 mol % 4-(dimethylamino)pyridine, pyridine, 98%.

of the natural product indicated that these compounds are identical, verifying the stereochemical assignment of the [3 + 2] cycloaddition product **48**.

Glycosylation Studies

Reactions with Acetoxy Glycosides. With a diastereo- and enantioselective carbohydrate synthesis in hand, we focused our efforts on diastereoselective glycosylation of the fourteen-membered macrolactam. First, we decided to use the stereoselective protocol put forward by Mangusson,[47] where BF_3·Et_2O is used as the Lewis acid promoter and the carbohydrate unit is introduced as an acetoxy glycoside. Control of stereochemistry would arise from participation of the neigboring axial acetoxy group, properly situated to ensure axial delivery of the macrocyclic carbinol (Scheme 17).

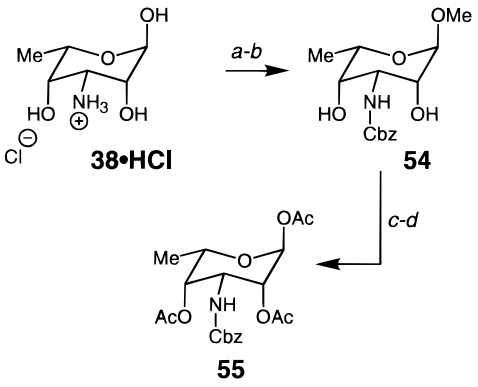
Scheme 17



To synthesize the triacetate carbohydrate derivative, we directly subjected **38** to various standard acylating conditions; this led to large amounts of decomposed materials. We argued that the protected aldehyde is unmasked under the reaction conditions and rapidly decomposes as a result of its sensitive nature (particularly if the α-OH and *β*-NH units are acylated; acylations are successful in Scheme 16, since hemiacetal OH is protected). Accordingly, we decided to protect the unstable

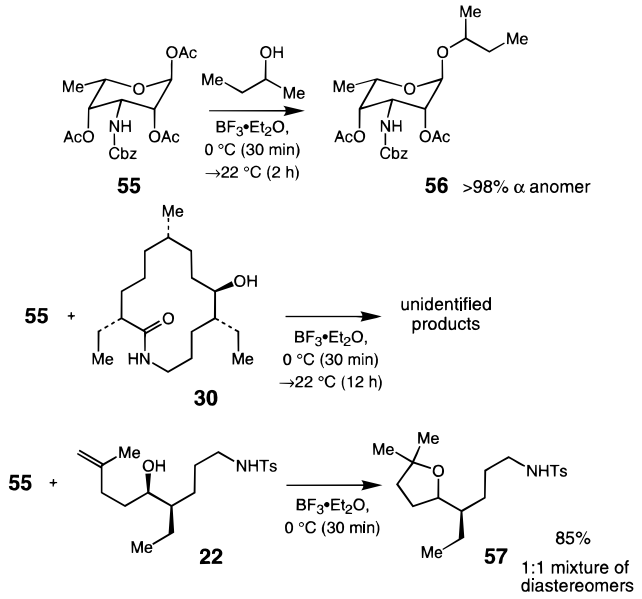
(47) (a) Dahmen, J.; Frejd, T.; Mangusson, G.; Noori, G. *Carbohydr. Res.* **1983**, *114*, 328−330. (b) Gurjar, M. K.; Viswanadham, G. *Tetrahedron Lett.* **1991**, *32*, 6191−6194.

Scheme 18



[a] 10% anhydrous HCl in MeOH, 88%. [b] 1.5 equiv of CbzCl, 1.5 equiv of $NaHCO_3$, MeOH, 78%. [c] 10 equiv of Ac_2O, 4-(dimethylamino)pyridine, pyridine, 82%. [d] 1% H_2SO_4 in Ac_2O, 0 °C, 1 h, 85%.

Scheme 19



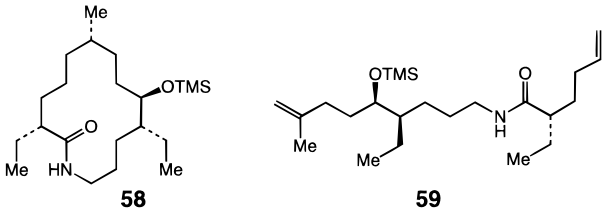
carbonyl function by first preparing the derived methyl glycoside (Scheme 18). Subsequent protection of the secondary amine (→ N-Cbz) delivered **54**. Acylation of the remaining hydroxyl groups and conversion of the methoxy acetal to its acetoxy derivative, according to the procedure documented by Pogszay,[48] afforded **55** (>98% α). The appropriately outfitted glycoside **55** was thus prepared in an overall yield of 51% (from **38**).

As depicted in Scheme 19, our initial studies with 2-butanol as substrate and BF_3•Et_2O as the Lewis acid catalyst resulted in stereoselective and efficient C−O bond formation (equal mixture of 2-butanol and **55**); **56** was formed in 90% isolated yield (>95:5, as judged by 400 MHz ^{1}H NMR analysis). When a similar glycosylation was attempted on macrolactam **30**, a large mixture of unidentifiable products was formed. The latter experiment was especially handicapped by the lack of solubility of the macrocyclic alcohol. Since stereoselective glycosylation may, in principle, be carried out prior to macrocyclization, we became interested in related acyclic alcohols as substrates. Within this context, we found that the use of the readily soluble acyclic alcohol **22**, as illustrated in Scheme 19, gave rise to the facile formation of furan **57** (85% yield) and <2% of the desired product.[49]

(48) Pozsgay, V. *J. Chem. Soc.* **1995**, *117*, 6673−6681.

(49) Although the BF_3•Et_2O used was freshly distilled, it is tenable that HF contamination gives rise to the observed intramolecular etherification.

To circumvent the aforementioned problems, we investigated reaction conditions originally put forth by Mukaiyama,[50] where the derived TMS ether and the milder Lewis acidic $SnCl_4$−$AgClO_4$ mixture are involved, and the carbinol reaction partner participates as its TMS ether derivative. A range of unsuccessful attempts rapidly followed. For example, when silyl ethers **58** and **59** were subjected to **55** in the presence of 5 mol % $SnCl_4$ and $AgClO_4$ in Et_2O at 0 °C for 10 min, desilylated substrates were obtained as the only products. Additional modification of the glycosylation protocol was no doubt needed.



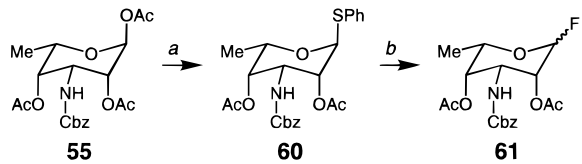
Reactions with Fluoroglycosides. The chemistry of the unusually labile TMS ethers **58** and **59** suggested to us that a glycosylation process involving the parent alcohol would be more desirable. However, attempts to couple **22** and **55** (cf. Scheme 19) in the presence of 5 mol % $SnCl_4$ and $AgClO_4$ resulted in significant carbohydrate decomposition. We therefore reasoned that the corresponding fluoroglycoside may provide an attractive option in stereoselective glycosylation, since such glycosyl derivatives are notably more stable (they survive silica gel chromatography and high temperatures) and have been successfully used by Mukaiyama[51] and Nicolaou[52] in complex molecule syntheses.

Fluoroglycoside **61** was therefore prepared, as outlined in Scheme 20. Conversion of triacetate **55** to thioglycoside **60** (82%),[52b] followed by treatment of the latter with (dimethylamido)sulfur trifluoride and *N*-bromosuccinamide delivered **61** in 85% yield after silica gel chromatography.[52a]

Our initial efforts utilizing **61** involved attempts at stereoselective glycosylation with macrolactam alcohol **30** in the presence of 5 mol % $SnCl_2$ and $AgClO_4$. Repeated initiatives along these lines resulted in complete decomposition of the fluorinated carbohydrate (it is presumably being converted to the derived oxonium ion) and low recovery of the macrocyclic substrate (<15%). The principal reason for such unsatisfactory outcomes is likely the notorious lack of solubility of **30** in Et_2O, as well as the more polar CH_2Cl_2—the fourteen-membered alcohol is sparingly soluble in methanol at ambient temperatures.

The above observations implied that a more viable strategy would be to achieve stereoselective glycosylation of the more readily soluble acyclic diene **62** (Scheme 21), which might then

Scheme 20



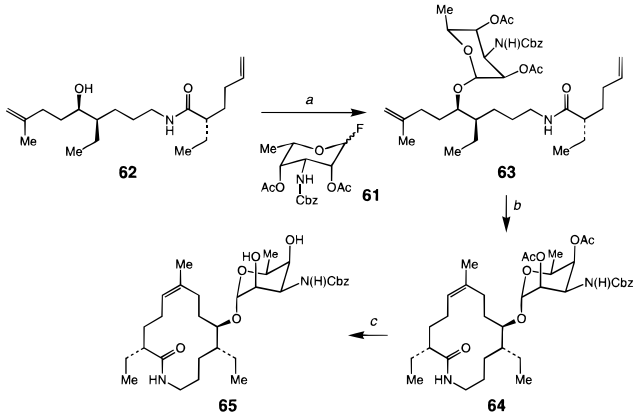
[a] 1.2 equiv of PhSH, 0.7 equiv of $SnCl_4$, 50 °C, 1 h, 82%. [b] 1.3 equiv of Et_2NSF_3, 1.5 equiv of NBS, 0 °C, 85%.

(50) Mukaiyama, T.; Katsurada, M.; Takashima, T. *Chem. Lett.* **1991**, 985−988.

(51) (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431−432. (b) Mukaiyama, T.; Hashimoto, Y.; Shoda, S. *Chem. Lett.* **1983**, 935−938.

(52) (a) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L.; *J. Am. Chem. Soc.* **1984**, *106*, 4189−4192. (b) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556−5558.

Scheme 21



[a] 2.2 equiv of $AgClO_4$, 2.2 equiv of $SnCl_2$, 4 Å molecular sieves, 1.1 equiv of **61**, −15 °C (1 h), 0 °C (1 h), 22 °C (2 h), Et_2O, 92%. [b] 20 mol % $Mo(CHCMe_2Ph)N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$, C_6H_6, 22 °C, 4 h, 92%. [c] MeOH, NH_3, 96%.

be induced to undergo catalytic ring closure. The success of the proposed route depended on whether the Lewis acidic metathesis catalyst (**14**) would remain operative in the presence of additional Lewis basic heteroatoms carried by the pendant carbohydrate moiety.

Diene alcohol **62** was prepared by desilylation of silyl ether **29** (Scheme 7; 48% HF, MeCN, 22 °C, 85% yield).[53] As illustrated in Scheme 21, after extensive experimentaion, glycosylation of **62** with **61** was effected in 92% isolated yield, in the presence of only 1.1 equiv of the fluoroglycoside, to afford carbohydrate-diene ensemble **63** as a single diastereoisomer (>98%, as judged by 400 MHz ^{1}H NMR analysis). Variations in reaction temperature are critical to the efficiency of the coupling process; when the reaction was allowed to proceed at −15 °C and then at 0 °C, notably lower conversions were achieved (<60% after 24 h). When glycosylation was not initiated at −15 °C, inferior selectivities were observed.

Catalytic Macrocyclization

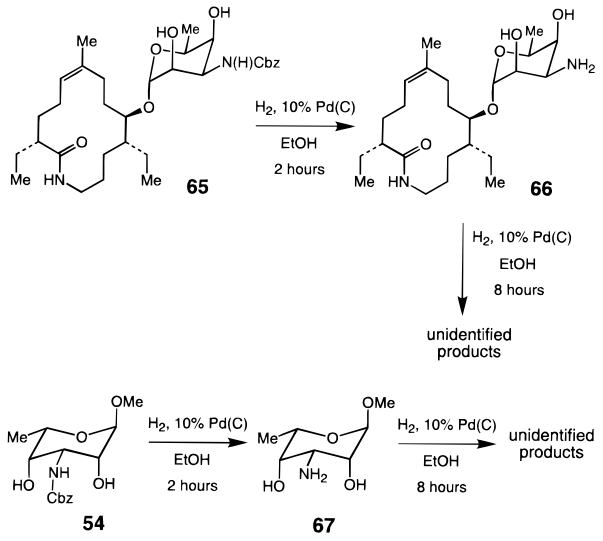
Studies with the Cbz-Protected Glycoside. We quickly established that subjection of **63** with 20 mol % of freshly prepared **14** after 4 h at 22 °C affords **64** in 92% yield after silica gel chromatography (>98% *Z*). At this juncture, what remained to be accomplished was the stereoselective hydrogenation of the trisubstituted olefin and deprotection of the pendant sugar.

Based on our preliminary studies, catalytic hydrogenation of the macrocyclic olefin promised to proceed with the desired sense and appropriate levels of stereocontrol (cf. Chart 2 and Scheme 7). In addition, the acetate and Cbz groups of the carbohydrate region were to be cleaved. We judged that removal of the Cbz unit as the first step could lead to unwanted acyl transfer to afford the derived acetamides, cleavage of which would engender the same for the macrocycle amide. Thus, as depicted in Scheme 21, the acetoxy groups were excised first to afford **65** (96%). Ammonia in MeOH was used to simplify the workup procedure; the volatile reagent and solvent were then easily evaporated *in vacuo*.

Deprotection of the Cbz group of **65** under 1 atm H_2 pressure and in the presence of Pd(C), as shown in Scheme 22, resulted

(53) Diene carbinol **62** may also be prepared by direct coupling of the amine derived from **22** (cf. Scheme 4) with carboxylic acid **18** (cf. Scheme 6). However, this procedure is significantly lower yielding than reaction with silylated derivative **17** (85% vs 55−60%). The difference in efficiency likely arises from difficulties in the purification of **22** prior to the coupling procedure.

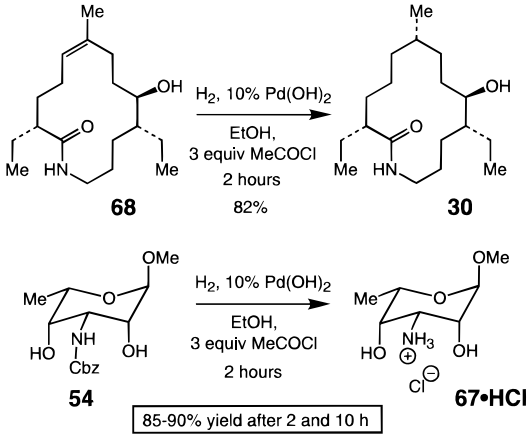
Scheme 22



in facile generation of the amine carbohydrate (2−3 h; in addition to small amounts of alkene hydrogenation products). Longer reaction times were however required for hydrogenation of the trisubstituted olefin. Toward this end, prolonged subjection of **66** to the same reaction conditions resulted in significant decomposition of the glycosidic moiety (unidentified products). When methyl glycoside **54** was treated to identical hydrogenation conditions, the deprotected sugar **67** was obtained cleanly after 2 h, but could not be recovered after 8 h of reaction time (Scheme 22).

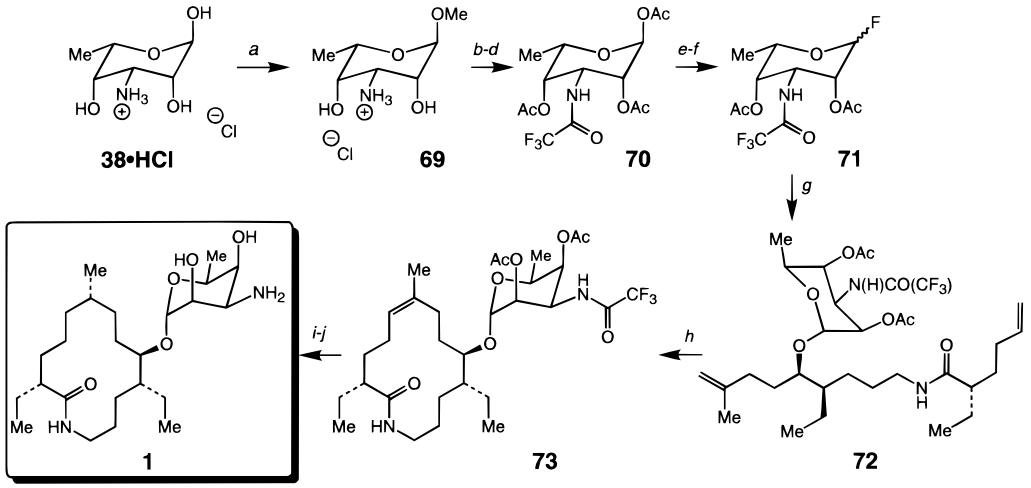
The sensitivity of the unprotected glycoside to hydrogenolysis/hydrogenation conditions was puzzling; after all, carbohydrate **38** was synthesized under 300 psi H_2 in the presence of $Pd(OH)_2$ (cf. Scheme 15). Since the latter process is effected in acidic medium (2.5 equiv of HCl), we conjectured that the ammonium salt of the carbohydrate may prove to be stable to the hydrogenation conditions. Control experiments, shown in Scheme 23, were therefore carried out, indicating that the hydrochloride salt of **54** is stable to the above conditions even after 10 h and the macrocyclic trisubstituted olefin **68** can be selectively hydrogenated in the presence of 3 equiv of HCl. In spite of these positive indications, attempts to deprotect and hydrogenate **65** under identical conditions resulted in significant substrate decomposition. Careful examination of the ^{1}H NMR indicated that alkene hydrogenation only proceeded to ∼50% conversion after 10 h, but that Cbz deprotection was complete.

Scheme 23



Studies with the Trifluoroacetate Glycoside. The above-mentioned complications suggested that deprotection of the

Scheme 24



[a] 10% anhydrous HCl in MeOH, 88%. [b] 1.5 equiv of CF_3COSEt, 1.5 equiv of Et_3N, MeOH. [c] 10 equiv of Ac_2O, pyridine, 5 mol % (dimethylamino)pyridine. [d] 1% H_2SO_4 in Ac_2O, 0 °C, 1 h, 85% from **69**. [e] 1.2 equiv of PhSH, 0.7 equiv of $SnCl_4$, 50 °C, 1 h. [f] 1.3 equiv of Et_2NSF_3, 1.5 equiv of NBS, 0 °C, 65% from **70**. [g] 2.2 equiv of $AgClO_4$, 2.2 equiv of $SnCl_2$, 4 Å molecular sieves, 1.1 equiv of **62**, −15 °C (1 h), 0 °C (1 h), 22 °C (2 h), Et_2O, 92%. [h] 20 mol % Mo(CHCMe$_2$Ph)N(2,6-(*i*-Pr)$_2$C$_6$H$_3$))(OCMe(CF$_3$)$_2$)$_2$, C_6H_6, 22 °C, 10 h, 91%. [i] H_2, 10% Pd(C), EtOH, 72%. [j] 20 equiv of N_2H_4, MeOH 24 h, 96%.

carbohydrate unit would have to be accomplished subsequent to hydrogenation of the macrolactam olefin. Such considerations, in turn, implied that a different protective group, other than a Cbz unit, would have to be employed. The most desireable amine protection would be with a group that satisfies at least two important requirements: (1) For the purpose of efficiency, it would have to be excised under the same conditions as the acetoxy groups. (2) The amine protecing group may be removable in the same vessel as the acetoxy functions; however, it would have to be more robust than the acetate groups. This would ensure that premature unmasking of the secondary amine would not lead to acyl tranfer and formation of the derived acetamide (see above). The trifluoroacetoxy moiety satisfies the required criteria.

As illustrated in Scheme 24, perfluoroglycoside **71** was prepared through similar synthesis routes as described above (1.5:1 mixture of α:*β* anomers; 58% overall yield from **38**·HCl). Diastereoselective glycosylation was carried out with **71** and diene carbinol **62** (cf. Scheme 21) to afford **72** in 92% yield (>98% α anomer, as judged by 400 MHz ^{1}H NMR analysis). Furthermore, Mo-catalyzed ring closure was effected in 91% isolated yield at ambient temperature to afford **73** (>98% *Z*). Stereocontrolled hydrogenation of the trisubstituted olefin (72%) and removal of the acetate and trifluroacetate groups, effected by subjection of the hydrogenated adduct with hydrazine in MeOH, delivered Sch 38516 (**1**) in 96% yield. The synthetic material proved identical to the natural sample based on ^{1}H NMR, ^{13}C NMR, IR, HRMS, and TLC analyses.

Conclusions

The first enantioselective total synthesis of Sch 38516 (fluvirucin B_1) has been accomplished. The key features of this study include: (i) Diastereoselective catalytic ethylmagnesation of allylic alcohol **20** and trapping of the resulting alkylmagnesium halide with tosyl aziridine (→ **22**). (ii) Zirconium-catalyzed enantioselective alkylation of unsaturated furan **25** to afford optically pure **26**. (iii) The subsequent one-pot catalytic hydrovinylation process (**26** → **28**). (iv) The Ru-catalyzed oxidation of primary alcohol to carboxylic acid (**28** → **18**). (v) Diastereoselective dipolar cycloaddition between nitrone **47** and vinylene carbonate, promoted by a readily available chiral auxiliary (α-methylphenylamine). (vi) The remarkably efficient and facile catalytic ring closing metathesis of dienes **29** (Scheme 7), **63** (Scheme 21), and **72** (Scheme 24). These examples illustrate that this process offers a mild and stereoselective route to the synthesis of highly functionalized macrocycles bearing *tri*substituted olefins. Subsequent to preliminary reports concerning this work,[5] elegant studies by Danishefsky,[54] Nicolaou,[55] Fuchs,[56] Furstner,[57] and Schinzer[58] have further demonstrated the impressive utility of this protocol in the preparation of macrocyclic disubstituted alkenes (with **15** as catalyst).[59] Finally, the macrolactam synthesis (**3**, Scheme 7) underlines the significance of inorganic chemistry and metal-catalyzed processes to organic synthesis: nine of the required thirteen steps are catalytic and every issue in stereo- and regiocontrol is resolved by the action of an organometallic complex. The reaction methods and strategies developed in this study should find applications in future endeavors in complex molecule total synthesis.

Experimental Section[60]

2-Methyl-6-(*R*)-ethyl-1-nonen-5-(*R*)-ol-9-toluenesulfonyl Amide (22). Allylic alcohol (*R*)-**20** (320 mg, 2.54 mmol) was dissolved in 6 mL of anhydrous Et_2O in a 50 mL round bottom flask. EtMgCl (6.3

(54) (a) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000−8001. (b) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733−2734.

(55) (a) Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2399−2401. (b) Yang, Z.; He, Y.; Vourloumis, D.; Vallberg, H.; Nicolaou, K. C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 166−168. (c) Nicolaou, K. C.; Sarabia, F.; Ninkovic, S.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 525−527. (d) Nicolaou, K. C.; Winssinger, N.; Pastor, J.; Ninkovic, S.; Sarabia, F.; He, Y.; Vourloumis, D.; Yang, Z.; Li, T.; Giannakakou, P.; Hamel, E. *Nature* **1997**, *387*, 268−272.

(56) Kim, S. H.; Figueroa, I.; Fuchs, P. L. *Tetrahedron Lett.* **1997**, *38*, 2601−2604.

(57) Furstner, A.; Kindler, N. *Tetrahedron Lett.* **1996**, *37*, 7005−7008.

(58) Schinzer, D.; Limberg, A.; Bauer, A.; Bohm, O. M.; Cordes, M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 523−524.

(59) More recent accounts from the laboratories of Grubbs and Sauvage indicate that the metathesis technology may be readily applied to the synthesis of marcocyclic crown ethers and [2]catenanes. See: (a) Marsella, M. J.; Maynard, H. D.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1101−1103. (b) Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1308−1310.

(60) General experimental information for select reagents and compounds not involved in the final synthesis route and copies of spectral data for all synthetic intermediates can be found in the Supporting Information section.

mL, 2.02 M, 12.70 mmol) was added to the reaction flask at 0 °C and stirred for 5 min. Zirconocene dichloride (37 mg, 0.13 mmol, 5.0 mol %) was subsequently added at 22 °C. The solution was allowed to stir for 18 h at 22 °C after which the reaction was determined to be complete by thin layer chromatography analysis (4:1 hexanes−ethyl acetate). In a separate flame-dried flask, *N*-(toluenesulfonyl)aziridine (3.0 g, 15.2 mmol, 6.0 equiv) was dissolved in 15 mL of anhydrous THF. The latter solution was quickly added to the original flask *via* cannula. The second vessel was rinsed twice with 1.0 mL portions of anhydrous THF, which was also transferred to the original reaction flask. CuBr·Me_2S (26 mg, 0.13 mmol; 5.0 mol %) was placed in a 10 mL round bottom flask in a dry box; to this was added 0.5 mL of anhydrous THF and 0.5 mL of Me_2S. Slight agitation facilitated solvation of CuBr·Me_2S, at which point the solution was transferred to the cooled reaction flask (−20 °C). The CuBr·Me_2S flask was rinsed once with 0.5 mL of anhydrous THF and 0.5 mL of Me_2S, and the solution resulting from the wash was transferred to the original reaction flask. The mixture was allowed to warm to 22 °C over 2 h (the yellow-white slurry turned dark brown as the temperature rose). After the solution was allowed to stir for 30 h in a cold room (−4 °C), the reaction was judged complete by ^{1}H NMR analysis of the aliquots removed from the reaction mixture. After the addition of a 10 mL solution of saturated aqueous ammonium chloride, the mixture was washed three times with 30 mL portions of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford a dark oil. Purification by silica gel chromatography (1:5:0.3 hexane:CH_2Cl_2:EtOAc) afforded the desired product as a yellow oil (347 mg, 1.0 mmol, 42% yield) (although the product after chromatography in some cases still had some impurity, it could be submitted to the next step). IR (NaCl): 3523 (br m), 3278 (br s), 3071 (w), 2961 (s), 2934 (s), 2874 (s), 1648 (w), 1598 (w), 1449 (s), 1376 (w), 1324 (s), 1158 (s), 1094 (s), 888 (m), 814 (s), 736 (s), 663 (s) cm^{-1}. ^{1}H NMR (400 MHz in $CDCl_3$): δ 7.74 (d, 2H, J = 8.1 Hz, C*H*CSO$_2$), 7.30 (d, 2H, J = 8.1 Hz, C*H*CCH$_3$), 4.73 (s, 1H, CHHCCH$_3$), 4.71 (s, 1H, CH*H*CCH$_3$), 3.58 (m, 1H, C*H*OH), 2.94 (q, 2H, J = 6.6 Hz, CH_2NH), 2.42 (s, 3H, CH_3-Ar), 2.17 (m, 1H, C*H*HCCH$_2$), 2.04 (m, 1H, CH*H*CCH$_2$), 1.73 (s, 3H, CH_3CCH$_2$), 1.6−1.1 (m, 9H, alkyl-*H*), 0.86 (t, 3H, J = 7.2 Hz, CH_3CH$_2$). ^{13}C NMR (75 MHz in $CDCl_3$): δ 145.7, 143.1, 137.0, 129.5, 127.0, 110.0, 72.7, 44.7, 43.3, 34.5, 31.1, 27.4, 26.3, 22.3, 21.8, 21.3, 11.8. HRMS Calcd for $C_{19}H_{31}O_3SN$ (M + H): 354.2106. Found: 354.2103.

2-Methyl-6-(*R*)-ethyl-1-nonen-5-(*R*)-[(*tert*-butyldimethylsilyl)oxy]-9-amine (17). Tosyl amide **22** (165.0 mg, 0.35 mmol) was dissolved in 1.0 mL of anhydrous THF, and the reaction mixture was cooled to −40 °C (acetone, CO_2). Ammonia (∼10 mL) was condensed into the reaction vessel, and the solution was allowed to stir at −40 °C for approximately 1 h. Sodium (48.3 mg, 2.11 mmol), washed initially with anhydrous pentane three times, was added to the reaction mixture, which immediately turned blue; this color persisted for 45 min. The reaction was quenched *carefully and slowly* by the addition of 5 mL of CH_2Cl_2, causing the blue color to disappear. After half the volume of the ammonia evaporated, the resulting mixture was poured in a separatory funnel containing 10 mL of brine. Organic and aqueous layers were separated, and the aqeuous layer was washed four times with 15 mL portions of CH_2Cl_2. Organic layers were dried over anhydrous $MgSO_4$, filtered through a fritted glass funnel, and concentrated *in vacuo* to afford a pale yellow oil. Purification by silica gel chromatography (Et_2O, 1:5 Et_2O/MeOH) gave 107 mg (0.34 mmol) of **17** (95% yield) as a colorless oil. $[\alpha]_D$ +14.13 (*c* 0.29, CH_2Cl_2). IR (NaCl): 3087 (w), 3077 (w), 2955 (s), 2857 (s), 2176 (w), 1649 (m), 1583 (m), 1471 (s), 1380 (m), 1254 (s), 1082 (s), 886 (m), 835 (s) cm^{-1}. ^{1}H NMR (400 MHz in $CDCl_3$): δ 4.66 (br d, 2H, J = 11.4 Hz, CH_2CHCH_2), 3.65 (m, 1H, SiOC*H*), 2.66 (m, 2H, CH_2NH$_2$), 2.07 (m, 1H, C*H*HCCH$_2$), 1.90 (m, 1H, CH*H*CCH$_2$), 1.70 (s, 3H, CCH_3), 1.6−0.8 (9H, alkyl-*H*), 0.86 (s, 12H, C(CH_3)$_4$), 0.03 (s, 3H, SiCH_3), 0.01 (s, 3H, SiCH_3). ^{13}C NMR (100 MHz in $CDCl_3$): δ 146.2, 109.5, 73.4, 45.3, 42.7, 34.4, 32.2, 30.6, 26.4, 25.8, 22.6. 18.1, 12.4, -4.39, −4.35. HRMS Calcd for $C_{18}H_{44}NOSi$ (M + H): 314.2879. Found: 314.2886.

(*S*)-2-Ethyl-3-buten-1-ol (26). 2,5-Dihydrofuran **25** (7.30 mL, 96.67 mmol) was dissolved in 30 mL of anhydrous THF in a 100 mL round bottom flask, and the solution was cooled to 0 °C. Ethylmagnesium chloride (35.0 mL, 2.07 M in THF, 72.8 mmol) was added, and the resulting mixture was allowed to stir at 22 °C for 10 min, after which it was treated with (*S*)-(EBTHI)Zr-binol (184 mg, 0.36 mmol, 0.4 mol % relative to the Grignard reagent). The mixture was allowed to stir under N_2 for 40 h. Subsequent addition of water and aqueous workup with three 20 mL portions of CH_2Cl_2, followed by careful solvent evaporation afforded the crude product as a dark oil. Vacuum distillation afforded 2.42 g (24.2 mmol) of **26** as a colorless oil. GLC analysis of the derived epoxides indicated the product to be >99% enantiomerically pure. The reaction could alternatively be performed with 10 mol % catalyst to afford 70% yield but with seven catalyst turnovers. Enantioselectivity was determined by GLC of the derived epoxide. IR (NaCl): 3440 (br, s), 3270 (m), 3245 (m), 3210 (m), 1640 (w) cm^{-1}; ^{1}H NMR (300 MHz in $CDCl_3$): δ 5.57 (ddd, 1H, J = 16.8, 10.5, 8.5 Hz, vinylic C*H*), 5.15 (m, 2H, vinylic CH_2), 3.57 (dd, 1H, J = 10.3, 5.3 Hz, CH_2OH), 3.41 (dd, 1H, J = 10.6, 8.2 Hz, CH_2OH), 2.11 (1H, m, C*H*CH$_2$OH), 1.45 (m, 1H, CH_2CH$_3$), 1.26 (m, 1H, CH_2CH$_3$), 0.89 (t, 3H, J = 7.4 Hz, CH_3); ^{13}C NMR (75 MHz in $CDCl_3$): δ 139.7, 117.2, 65.3, 48.6, 23.5, 11.4. (Due to substrate volatility, the derived (*S*)-MTPA esters were subjected to combustion analysis.) Anal. Calcd for $C_{16}H_{19}F_3O_3$: C, 60.75; H, 6.05. Found: C, 60.63; H, 6.21.

(*R*)-2-Ethyl-5-hexen-1-ol (28). Homoallylic alcohol **26** (230 mg, 2.3 mmol) was added to a solution of Cp_2TiCl_2 (16 mg, 0.06 mmol, 2.8 mol %) in 5.2 mL of anhydrous THF. The mixture was cooled to 5 °C (ice bath), and *n*-PrMgBr (2.4 mL, 2.9 M in Et_2O, 6.90 mmol) was added slowly, at which time the solution changed color from red to dark green accompanied by gas evolution. The reaction was then allowed to warm to 22 °C, after which the reaction vessel was placed in an oil bath and the mixture was heated to reflux for 36 h. The reaction flask was then cooled to −78 °C (acetone, dry ice), and $(Ph_3P)_2$-$NiCl_2$ (34 mg, 0.05 mmol, 2.2 mol %) was added as a solution in 3.0 mL of THF. A previously prepared solution of vinyl bromide (2.6 mL) in THF (3.0 mL) at −78 °C was then added slowly, resulting in vigorous gas evolution. The mixture was allowed to stir for 12 h at 22 °C, after which it was treated with 20 mL of a 2.0 M solution of HCl and washed with three 15 mL portions of Et_2O to afford a dark oil as the crude residue. Purification by silica gel (containing 10% $AgNO_3$) chromatography (6:1 pentanes:Et_2O) afforded 213 mg of **28** as a colorless oil (1.66 mmol, 72% yield). IR (NaCl): 3342 (brs), 3077 (w), 2964 (s), 2930 (s), 2874 (s), 1640 (m), 1462 (m), 1382 (m), 1044 (s), 999 (m), 909 (s) cm^{-1}. ^{1}H NMR (300 MHz in $CDCl_3$): δ 5.76 (ddt, 1H, J = 16.8, 10.2, 6.6 Hz, CH_2CH), 4.94 (dq, 1H, J = 18.0, 1.8 Hz, CH*H*CH), 4.85 (dm, 1H, J = 10.2 Hz, C*H*HCH), 3.49 (d, 2H, J = 4.8 Hz, CH_2OH), 2.03 (q, 2H, J = 7.8 Hz, CH_2CHCH$_2$), 1.35 (m, 5H, alkyl), 0.84 (t, 3H, J = 7.2 Hz, CH_3). ^{13}C NMR (75 MHz in $CDCl_3$): δ 139.0, 114.3, 64.9, 41.3, 31.0, 29.6, 23.2, 11.0. HRMS Calcd for $C_8H_{16}O$: 128.1201. Found: 128.1200.

2-(*R*)-Ethyl-5-hexenoic Acid (18). *N*-Methylmorpholine oxide (NMO, 316 mg, 2.70 mmol) was added to a solution of **28** (90 mg, 0.70 mmol) in 7 mL of anhydrous CH_3CN at 22 °C. To this mixture was added tetrapropylammonium perruthenate (TPAP, 16 mg, 0.045 mmol) as a solution in CH_3CN (2.0 mL) and the solution stirred for 5 h. The solvent was evaporated *in vacuo* and the black residue passed through a short column of silica gel (2 cm) and eluted with EtOAc to afford 64 mg of **18** as a colorless oil (0.44 mmol, 77% yield). IR (NaCl): 2900 (brs), 1702 (s), 1642 (m), 1460 (s), 1416 (s), 1289 (s), 1274 (s), 1228 (s), 938 (m), 913 (s) cm^{-1}. ^{1}H NMR (300 MHz in $CDCl_3$): δ 5.78 (ddt, 1H, J = 17.1, 10.2, 6.6 Hz, C*H*CH$_2$), 5.02 (d, 1H, J = 19.2 Hz, CHC*H*H), 4.96 (d, 1H, J = 10.2 Hz, CHCH*H*), 2.33 (m, 1H, C*H*COOH), 2.09 (m, 2H, CH_2CHCH$_2$), 1.8−1.5 (m, 4H, CH_2CH$_3$ and CH_2CHCOOH), 0.94 (t, 3H, J = 7.5 Hz, CH_3). ^{13}C NMR (75 MHz in $CDCl_3$): δ 183.4, 137.7, 115.1, 46.4, 31.4, 30.7, 25.1, 11.6. HRMS Calcd for $C_8H_{14}O_2$: 142.0993. Found: 142.0993.

***N*-(4-(*R*)-Ethyl-5-(*R*)-((*tert*-butylmethylsilyl)oxy)-8-methyl-8-nonenyl)-2-(*R*)-ethyl-5-hexenamide (29).** Carboxylic acid **18** (107 mg, 0.34 mmol) was dissolved in 3.0 mL of anhydrous CH_2Cl_2 in a 25 mL round bottom flask. The solution was cooled to 0 °C (ice bath), followed by addition of dicyclohexylcarbodiimide (76 mg, 0.37 mmol) and hydroxybenzotriazole (55 mg, 0.41 mmol). After 5 min amine **17** (48.2 mg, 0.34 mmol), dissolved in 1.0 mL of CH_2Cl_2, was added to the original mixture. The reaction mixture was allowed to warm to 22 °C and stirred at this temperature for 12 h. White solid formation was

observed as soon as the reaction temperature reached 22 °C. The reaction was treated with 15 mL of saturated aqeuous sodium bicarbonate solution. The layers were separated and the aqeuous layer was washed four times with 25 mL portions of CH_2Cl_2. The organic layers were combined and dried over anhydrous $MgSO_4$ and filtered through a fritted funnel. Solvent removal *in vacuo* afforded a yellow oil, which was purified by silica gel (containing 5% $AgNO_3$) chromatography (3:1 hexanes:EtOAc) to afford 125 mg of the desired amide **29** (0.33 mmol, 85% yield) as a clear oil. IR (NaCl): 3291 (s), 3080 (m), 2960 (s), 2932 (s), 2858 (s), 1643 (s), 1554 (s), 1462 (s), 1378 (m), 1256 (s), 1085 (s), 1064 (s), 1006 (m), 911 (m), 886 (s), 836 (s), 774 (s) cm^{-1}. ^1H NMR (400 MHz): δ 5.81 (ddt, 1H, J = 17.1, 10.2, 6.8 Hz, C*H*CH_2), 5.45 (br, s, 1H, N*H*), 5.03 (d, 1H, J = 17.5 Hz, CHC*H*H), 5.00 (d, 1H, J = 11.1 Hz, CHCH*H*), 4.74 (s, 1H, CCH*H*), 4.70 (s, 1H, CC*H*H), 3.71 (m, 1H, C*H*OTBS), 3.29 (q, 2H, J = 6.3 Hz, CH_2NH), 2.13 (m, 2H, CH_2CHCH_2), 2.03 (p, 1H, J = 8.0 Hz, C*H*CONH), 1.94 (m, 2H, $CH_2C(CH_3)CH_2$), 1.76 (s, 1H, CH_3CCH_2), 1.70−1.20 (m, 13H, alkyl C*H*), 0.92 (br, s, 15H, $(CH_3)_3$Si and CH_3), 0.08 (s, 3H, CH_3Si), 0.07 (s, 3H, CH_3Si). ^{13}C NMR (100 MHz, in C_6D_6): δ 176.2, 146.1, 138.3, 114.9, 109.5, 94.4, 73.4, 49.0, 45.2, 39.8, 34.4 31.7, 31.7, 30.4, 28.4, 26.6, 26.0, 25.9, 22.9, 22.6, 18.1, 12.4, 12.1, −4.2, −4.4. HRMS Calcd for $C_{26}H_{51}O_2NSi$ (M − (*t*-Bu)): 380.2988. Found: 380.2984.

Ethyl 4,5-Dihydroxy-2-*trans*-hexenoate (43). Ethyl sorbate (24.0 g, 0.17 mol) was placed in a 3 L round bottom flask, after which was added a 1:1 mixture of *t*-butyl alcohol (860 mL) and H_2O (860 mL) at 0 °C, followed by the addition of 249.0 g of AD-mix-α and methanesulfonamide (16.3 g, 0.17 mol). This mixture was allowed to stir at 0 °C while the reaction was monitored by TLC (R_f = 0.05 and 0.95 for ethyl sorbate, 3:1 hexanes/EtOAc) and 400 MHz ^1H NMR analysis. After 20 h, the reaction was quenched by the addition of a saturated aqueous solution of sodium thiosulfite pentahydrate (24.0 g, 96.7 mmol). The resulting solid was subsequently removed by filtration. Organic and aqueous layers were separated, and the aqueous layer was washed four times with 200 mL portions of EtOAc. The combined organic layers were washed with 200 mL of a 2.0 M KOH solution, followed by 400 mL of brine. Organic layers were dried over anhydrous magnesium sulfate, filtered through a fritted funnel, and concentrated *in vacuo* to afford a dark yellow oil. The unpurified product was passed through a short column of silica gel to remove excess salts. This material was used directly for conversion to acetonide. IR (NaCl): 3431 (br, s), 2980 (m), 2934 (w), 2908 (w), 1711 (s), 1662 (m), 1447 (w), 1370 (m), 1278 (m) cm^{-1}. ^1H NMR (400 MHz in $CDCl_3$): δ 6.92 (dd, 1H, J = 15.6, 5.2 Hz, C*H*CHCOO), 6.15 (dd, 1H, J = 15.6, 2.5 Hz, CHC*H*COO), 4.22 (q, 2H, J = 7.1 Hz, OCH_2CH_3), 4.05 (qd, 1H, J = 5.2, 1.6 Hz, CH_3CHO), 3.74 (dq, 1H, J = 6.0, 4.0 Hz, CHCHC*H*O), 2.54 (m, 1H, O*H*), 2.16 (m, 1H, O*H*), 1.29 (t, 3H, J = 7.0 Hz, CH_3CH_2), 1.25 (d, 3H, J = 6.4 Hz, CH_3CHO). ^{13}C NMR (100 MHz in $CDCl_3$): δ 166.4, 146.5, 122.5, 75.6, 70.3, 60.5, 18.9, 14.8.

Nitrone 47. Aldehyde **45** (55.0 mg, 0.38 mmol) was dissolved in 4 mL of benzene, and (*R*)-*N*-hydroxy-α-methylbenzylamine (60.0 mg, 0.43 mmol) was added to this solution. The resulting mixture was allowed to reflux for 5 h. The reaction mixture was cooled to 22 °C, and solvent was removed *in vacuo* to give a yellow oil. Purification by silica gel chromatography (1:1 hexanes:EtOAc) afforded 84.0 mg of the desired nitrone as a colorless oil (0.32 mmol, 74% yield). IR (NaCl): 3069 (m), 2987 (s), 2924 (S), 2867 (m), 1734 (w), 1590 (s), 1457 (s), 1388 (s), 1250 (s), 1168 (s), 1086 (s), 859.4 (s). ^1H NMR (400 MHz in $CDCl_3$): δ 7.4 (m, 5H, aromatic-*H*), 6.88 (d, 1H, J = 5.6 Hz, OCHC*H*N), 5.02 (q, 1H, J = 6.8 Hz, NC*H*CH_3), 4.87 (dd, 1H, J = 7.3, 5.6 Hz, NCHC*H*), 3.97 (qd, 1H, J = 6.0, 1.2 Hz, MeC*H*O), 1.80 (d, 3H, J = 6.9 Hz, PhCHC*H*$_3$), 1.45 (d, 1H, J = 6.4 Hz, C*H*$_3$-CHOCH), 1.44 (s, 3H, C*H*$_3$CCH$_3$), 1.35 (s, 3H, CHCC*H*$_3$). ^{13}C NMR (100 MHz in $CDCl_3$): δ 138.1, 135.4, 128.8, 128.7, 127.2, 126.9, 109.5 77.3, 76.3, 73.5, 53.6, 27.1, 26.3, 19.4, 18.9. HRMS Calcd for $C_{15}H_{22}NO_3$ (M + H): 264.1599. Found: 264.1600.

Isoxazolidine 48. Nitrone **47** (106 mg, 0.40 mmol) was placed in a flame-dried round bottom flask equipped with a reflux condenser (under argon). Vinylene carbonate (102 mL, 1.6 mmol), freshly distilled over calcium hydride under vacuum (15 mmHg), was added to the nitrone substrate. The resulting mixture was heated at 85 °C for 19 h to afford a dark brown oil. Purification by silica gel chromatography with 5:1 hexanes/EtOAc afforded 96.4 mg (0.28 mmol) of desired product **48** as a white solid (69% yield). IR (NaCl): 2986 (m), 2936 (w), 2886 (w), 1822 (s), 1463 (w), 1381 (m), 1262 (w), 1168 (m), 1067 (m), 992 (m), 859 (w), 702 (w) cm^{-1}. ^1H NMR (400 MHz in $CDCl_3$): δ 7.27−7.38 (m, 5H, aromatic-*H*), 6.28 (dd, 1H, J = 5.2, 0.4 Hz, OC*H*O), 5.48 (d, 1H, J = 5.2 Hz, CHC*H*OCO), 4.02 (q, 1H, J = 6.0 Hz, PhC*H*Me), 3.45 (d, 1H, J = 7.6 Hz, NC*H*), 3.29 (t, 1H, J = 7.6 Hz, NC*H*CH), 3.24 (dq, 1H, J = 7.6, 6.0 Hz, MeC*H*OCH), 1.57 (d, 3H, J = 6.0 Hz, PhCHC*H*$_3$), 1.31 (s, 3H, C*H*$_3$CCH$_3$), 1.23 (s, 3H, CH$_3$-CC*H*$_3$), 1.22 (d, 3H, J = 6.0 Hz, C*H*$_3$CO). ^{13}C NMR (100 MHz in $CDCl_3$): δ 152.6, 140.7, 128.9, 128.7, 128.1, 109.0, 105.1, 87.2, 79.4, 76.0, 68.4, 67.5, 27.1, 26.5, 21.2, 19.1. HMRS Calcd for $C_{18}H_{23}NO_6$: 349.1525. Found: 349.1527.

Diol Isoxazolidine 52. Tricycle **48** (931 mg, 2.66 mmol) was dissolved in 13.3 mL of a 4:1 THF/1 M aqueous hydrochloric acid solution. The resulting mixture was heated to 65 °C. Reaction progress was monitored by TLC (1:1 hexane/EtOAc, R_f = 0.75 for starting material, 0.30 for product), which indicated complete consumption of starting material after 4 h . Reaction was quenched by the addition of 50 mL of a saturated solution of sodium bicarbonate. Aqueous and organic layers were separated, and the aqueous layer was washed four times with 50 mL portions of EtOAc. The combined organic layers were washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered through a fritted funnel, and concentrated *in vacuo* to afford a pale yellow oil, which could be used for next step without purification. When necessary, purification by silica gel chromatography (2:1 hexanes/EtOAc) provides 733 mg (2.50 mmol) of diol **52** as a colorless oil (94% yield). IR (NaCl): 3459 (br), 3069 (w), 3032 (w), 2980 (m), 2936 (w), 1822 (s), 1734 (m), 1495 (m), 1451 (s), 1376 (s), 1313 (m), 1168 (s), 1080 (s), 985 (s) cm^{-1}. ^1H NMR (400 MHz in $CDCl_3$): δ 7.42−7.30 (m, 5H, aromatic-*H*), 6.62 (dd, 1H, J = 5.6, 0.8 Hz, OC*H*O), 5.64 (d, 1H, J = 5.6 Hz, CHC*H*OCO), 4.02 (q, 1H, J = 6.4 Hz, PhC*H*), 3.78 (qd, 1H, J = 6.4, 2.0 Hz, CH_3CHOH), 3.43 (d, 1H, J = 8.8 Hz, NC*H*), 2.95 (dd, 1H, J = 8.8, 2.0 Hz MeCHOHC*H*O), 1.40 (d, 3H, J = 8.8 Hz, PhCHC*H*$_3$), 1.10 (d, 3H, J = 6.4 Hz, C*H*$_3$CHO). ^{13}C NMR (100 MHz in $CDCl_3$): δ 152.8, 141.0, 129.1, 128.7, 128.1, 105.3, 87.2, 72.6, 67.6, 67.57 , 65.6, 21.0, 19.0. HRMS Calcd for $C_{14}H_{17}O_6N$ (M + H): 296.1134 . Found: 296.1129.

3-Amino-3,6-dideoxy-α-L-talopyranose (38). Diol **52** (0.737 mmol) was dissolved in 36 mL of MeOH and brought into a glove box, at which time 50% (by weight) $Pd(OH)_2$ was added. The reaction flask was removed from the glove box and charged with acetyl chloride (143 mL, 2.01 mmol). The resulting mixture was placed in a high pressure bomb which was subsequently purged with hydrogen three times. Hydrogenation was allowed to proceed under 300 psi of hydrogen at 22 °C. After 14 h, the reaction mixture was filtered through Celite and concentrated *in vacuo* to provide a light yellow solid, which could be directly submitted to the next step. When necessary, purification by silica gel chromatography (4:1 CH_2Cl_2/MeOH) afforded 120 mg (0.70 mmol) of **38** (7:1 ratio of α/β anomers, 95% yield), the ratio of both anomers varied upon silica gel chromatography. The mixture is a white solid. IR (NaCl): 3312 (brs), 2985 (s), 2938 (s), 1606 (w), 1505 (m), 1380 (w), 1054 (s), 1016 (m), 975 (w), 860 (w) cm^{-1}. ^1H NMR (400 MHz in CD_3OD): δ (α-anomer): 5.20 (s, 1H, C_1-*H*), 4.17 (q, 1H, J = 6.2 Hz, C_5-*H*), 3.75 (br, m, 1H, C_2-*H*), 3.69 (br, m, 1H, C_4-*H*), 3.56 (br, m, 1H, C_3-*H*), 1.24 (d, 3H, J = 6.5 Hz, C_6-*H*$_3$). (β-anomer): 4.75 (s, 1H, C_1-*H*), 3.85 (br, s, 1H, C_2-*H*), 3.71 (br, 1H, C_4-*H*), 3.65 (br, m, 1H, C_3-*H*), 1.28 (d, 3H, J = 6.0 Hz, C_6-*H*$_3$), C_5-*H* buried underneath one peak of β-anomer. ^{13}C NMR (100 Hz in CD_3OD): δ (α-anomer) 95.6, 70.0, 68.9, 66.8, 50.21, 17.1. HRMS Calcd for $C_6H_{13}O_4N$ (M − Cl): 164.0928. Found: 164.0928.

Methoxy-3-amino-3,6-dideoxy-α-L-talopyranose (69). Hydroxy glycoside **38** (128 mg, 0.76 mmol) was placed in a 100 mL round bottom flask, to which was added 36 mL of 10% (by weight) anhydrous methanolic hydrochloric acid solution. Stirring was allowed to continue for 70 h at 22 °C. The resulting reaction mixture was concentrated *in vacuo* to give a light yellow solid, which could be subsequently submitted to next step without purification. Purification by silica gel chromatography (4:1 CH_2Cl_2/CH_3OH) to provide 116 mg (0.63 mmol) of the α-methoxy glycoside **69** (84% yield from the diol). Note: If reaction time is too brief (*e.g.*, 20 h), the product will be contaminated

with the β-anomer. IR (NaCl): 3339 (brs), 2949 (s), 2829 (s), 2363 (w), 1621 (w), 1507 (m), 1444 (m), 1381 (m), 1193 (w), 1117 (s), 1067 (s), 1016 (s) cm^{-1}. ^{1}H NMR (400 MHz in CD_3OD): δ 4.68 (br, s, 1H, C_1-*H*), 3.92 (q, 1H, J = 6.5 Hz, C_5-*H*), 3.75 (dd, 1H, J = 3.3, 1.6 Hz C_2-*H*), 3.66 (m, 1H, C_4-*H*), 3.47 (t, 1H, J = 3.3 Hz, C_3-*H*), 3.34 (s, 3H, OC*H*$_3$), 1.20 (d, 3H, J = 6.5 Hz, C_6-*H*$_3$). ^{13}C NMR (125 MHz in CD_3OD): δ 102.4, 69.7, 67.9, 67.3, 55.8, 50.4, 17.0. HRMS calcd for $C_7H_{16}O_4N$ (M − Cl): 178.1079. Found: 178.1083.

Acetoxy-2,4-di-*O*-acetyl-3-*N*-(trifluoroacetyl)-3,6-dideoxy-α-L-talopyranose (70). To a solution of methoxy glycoside **69** (133 mg, 0.63 mmol) in 10 mL of methanol were added triethylamine (0.13 mL, 0.94 mmol) and *S*-ethyl trifluorothioacetate (117 mL, 0.93 mmol). The resulting mixture was allowed to stir for 4 h at 22 °C and then concentrated to dryness *in vacuo*. Pyridine (1.0 mL, 10.6 mmol), acetic anhydride (295 mL, 6.25 mmol), and a catalytic amount of DMAP (∼10 mg) were added to the resulting solid. The reaction mixture was allowed to stir at 22 °C for 10 h, after which the reaction was quenched by the addition of 15 mL of a saturated aqueous copper sulfate solution. Organic and aqueous layers were separated; the aqueous layer was washed with 3 × 20 mL of EtOAc. Combined organic layers were virgously stirred over 50 mL of saturated aqeuous sodium bicarbonate for 40 min. Layers were once again separated and the aqueous layer was washed with 3 × 20 mL portions of EtOAc. Combined organic layers were washed with a 100 mL solution of brine, dried over anhydrous $MgSO_4$, filtered through a fritted funnel, and concentrated *in vacuo* to afford a light yellow solid, which could be directly used in the next step without purification. When necessary, purification by silica gel chromatography (2:1, hexanes/EtOAc) afforded 154 mg (0.43 mmol) of the desired peracylated methyl glycoside as a white foam (α-anomer, 92% yield). IR (NaCl): 3446 (w), 3326 (w), 3068 (w), 2943 (m), 2841 (w), 1759 (s), 1545 (m), 1381 (s), 1230 (s), 1167 (s), 1136 (s), 1073 (s), 1029 (s), 960 (m) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (bd, 1H, J = 8.0 Hz, N*H*), 5.12 (m, 1H, C_2-*H*), 4.83 (m, 1H, C_4-*H*), 4.76 (d, 1H, J = 1.1 Hz, C_1-*H*), 4.60 (dt, 1H, J = 8.0, 3.5 Hz, C_3-*H*), 4.10 (qd, 1H, J = 6.2, 1.1 Hz, C_5-*H*), 3.4 (s, 3H, OC*H*$_3$), 2.15 (s, 3H, COC*H*$_3$), 2.148 (s, 3H, COC*H*$_3$), 1.18 (d, 3H, J = 6.6 Hz, C_6-*H*$_3$). ^{13}C NMR (100 MHz in $CDCl_3$): δ 170.8, 170.6, 156.6 (q, J_{C-F} = 38 Hz), 115.4 (q, J_{C-F} = 286 Hz), 97.9, 69.0, 68.2, 64.6, 55.2, 46.3, 20.8, 20.4, 16.2. ^{19}F (in $CDCl_3$): δ 95.4. HRMS Calcd for $C_{13}H_{18}F_3NNaO_7$ (M + Na): 380.0933. Found: 380.0942. To the peracylated amine glycoside (261 mg, 0.73 mmol) was added 2.53 mL of freshly prepared 1% (by volume) H_2SO_4 acetic anhydride solution at 0 °C. After 1 h, the reaction solution was *slowly* poured into 50 mL of saturated aqeuous sodium bicarbonate solution at 0 °C and vigrously stirred for 30 min at 22 °C. Aqueous and organic layers were separated, and the aqueous layer was washed four times with 30 mL portions of CH_2Cl_2. Combined organic layers were dried over anhydrous $MgSO_4$, filtered through a fritted funnel, and concentrated *in vacuo* to afford a white foam, which was virtually pure and could be submitted to the next step without purification. When necessary, purification by silica gel chromatography (3:1 hexanes/EtOAc) gave 240 mg (0.67 mmol) of **70** as a white foam (92% yield). IR (NaCl) 3327 (w), 2993 (w), 1747 (s), 1539 (m), 1372 (m), 1224 (s), 1151 (m), 1021 (m) cm^{-1}. ^{1}H NMR (400 MHz in $CDCl_3$): δ 6.90 (br, d, 1H, J = 7.3 Hz N*H*), 5.18 (m, 1H, C_1-*H*), 4.88 (m, 1H, C_4-*H*) 4.65 (dt, 1H, J = 6.8, 3.4 Hz, C_3-*H*), 4.21 (qd, 1H, J = 6.6, 1.5 Hz, C_5-*H*), 2.17 (br, 6H, COC*H*$_3$, COC*H*$_3$), 2.14 (s, 3H, COC*H*$_3$), 1.17 (d, 1H, J = 6.6 Hz, C_6-*H*$_3$). ^{13}C NMR (100 Hz in $CDCl_3$): δ 170.8, 170.4, 168.2, 157.0 (q, J_{C-F} = 38 Hz), 115.3 (q, J_{C-F} = 286 Hz), 90.3, 68.6, 67.3, 67.1, 64.4, 20.8, 20.7, 20.4, 16.3. HRMS Calcd for $C_{20}H_{25}O_9N$ (M + H): 370.1114. Found: 370.1114.

Fluoro-2,4-di-*O*-acetyl-3-*N*-(trifluoroacetyl)-3,6-dideoxy-α-L-talopyranose (71). To a benzene (8.9 mL) solution of acetoxy glycoside **70** (230 mg, 0.62 mmol) was added thiophenol (76.6 mL, 0.75 mmol), followed by $SnCl_4$ (51.1 mL, 0.44 mmol). The mixture was placed in an oil bath preheated to 50 °C; reaction progress was monitored carefully by thin layer chromatographic analysis (1:1 hexane/EtOAc, R_f = 0.50 for starting material, 0.60 for the product). After 45 min, the reaction was quenched by the addition of a 20 mL portion of a saturated aqueous sodium bicarbonate solution. Organic and aqueous layers were separated, and the aqueous layer was washed with CH_2Cl_2 (three 20 mL portions). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (2:1 Et_2O/pentane) gave 213 mg (0.58 mmol, 80% yield) of the thiophenyl glycoside as a pale yellow oil. IR (NaCl): 3320 (w), 3049 (w), 2987 (w), 1740 (s), 1539 (m), 1444 (w), 1375 (m), 1218 (s), 1155 (s), 1098 (m) cm^{-1}. ^{1}H NMR (400 MHz in $CDCl_3$): δ 7.4−7.26 (m, 5H, aromatic-*H*), 6.83 (br, 1H, N*H*), 5.60 (s, 1H, C_1-*H*), 5.20 (m, 1H, C_2-*H*), 5.13 (d, 1H J = 3.7 Hz, C_4-*H*), 4.60 (m, 2H, C_3-*H*, C_5-*H*), 2.18 (s, 3H, COC*H*$_3$), 2.16 (s, 3H, COC*H*$_3$), 1.19 (d, 3H, J = 6.6 Hz, C_6-*H*$_3$). ^{13}C NMR (100 MHz in $CDCl_3$): δ 170.8, 170.3, 156.8 (q, J_{C-F} = 38 Hz), 132.5, 131.7, 129.0, 127.8, 115.2 (q, J_{C-F} = 286 Hz), 83.3, 69.4, 69.0, 66.2, 47.2, 20.7, 20.3, 16.4. The resulting thioglycoside (192 mg, 0.44 mmol), dried by azeotropic distillation with benzene, was dissolved in 8.8 mL of CH_2Cl_2. The resulting solution was subsequently treated with DAST (70.2 mL, 0.58 mmol), and the resulting mixture was allowed to stir for 2 min before NBS (118 mg, 0.67 mmol) was added at −15 °C (dry ice and acetone bath). The reaction mixture was allowed to stir at this temperature for 1 h and at 0 °C for 2 h, after which the reaction was quenched by the addition of a 15 mL solution of a saturated solution of sodium bicarbonate. Aqueous and organic layers were separated, and the aqueous layer was washed with CH_2Cl_2 (3 × 20 mL portions). Organic layers were dried over anhydrous $MgSO_4$, filtered through a fritted glass funnel, and concentrated *in vacuo* to provide a pale yellow oil. Purification by silica gel chromatography (2:1 Et_2O/pentane) afforded a partial separable 3:2 mixture of both α and β anomers of **71** (129 mg, 0.36 mmol, 81% yield); the product was a white foam. For α-anomer of **71**: IR (NaCl): 3339 (w), 1734 (s), 1539 (m), 1382 (m), 1224 (s), 1162 (s), 1036 (m), 966 (m) cm^{-1}. ^{1}H NMR (300 MHz in $CDCl_3$): δ 6.83 (br, s, 1H, N*H*), 5.68 (d, 1H, J_{H-F} = 48.0 Hz, C_1-*H*), 5.20 (m, 1H, C_2-*H*), 5.03 (m, 1H, C_4-*H*), 4.66 (dt, 1H, J = 7.9, 3.3 Hz, C_3-*H*), 4.35 (qd, 1H, J = 6.6, 1.2 Hz, C_5-*H*), 2.18 (s, 3H, COC*H*$_3$), 2.17 (s, 3H, COC*H*$_3$), 1.2 (d, 3H, C_5-C*H*$_3$, J = 6.6 Hz). ^{13}C NMR (100 MHz in $CDCl_3$): δ 170.8, 170.2, 156.8 (q, J_{C-F} = 40.0 Hz), 115.5 (q, J_{C-F} = 280.0 Hz, 104.3 (d, J_{C-F} = 221.0 Hz), 68.4, 67.6, 67.59, 66.2 (d, J_{C-F} = 41.0 Hz), 45.9, 20.7, 20.5, 16.2. For β-anomer of **71**: IR (NaCl): 3333 (w), 2955 (w), 2351 (w), 1750 (s), 1533 (m), 1376 (m), 1220 (s), 1164 (s), 1099 (m), 1029 (m). ^{1}H NMR (400 MHz in $CDCl_3$): δ 7.00 (br, d, 1H, J = 6.8 Hz , 1H, N*H*), 5.50 (dd, 1H, J_{H-F} = 50.0, 1.6 Hz, C_1-*H*), 5.30 (ddd, 1H, J = 8.2, 3.8, 1.6 Hz C_2-*H*), 5.16 (m, 1H, C_4-*H*), 4.54 (dt, 1H, J = 8.0, 3.8 Hz, C_3-*H*), 4.03 (qd, 1H, J = 6.6, 3.0 Hz,C_5-*H*), 2.18 (s, 3H, COC*H*$_3$), 2.15 (s, 3H, COC*H*$_3$), 1.34 (d, 3H, J = 6.6 Hz, C_6-*H*). ^{13}C NMR (100 MHz in $CDCl_3$): δ 170.42, 170.40, 157.1 (q, J_{C-F} = 38.0 Hz), 115.4 (q, J_{C-F} = 288.0 Hz) 105.1 (d, J_{C-F} = 217.0 Hz), 70.8, 67.2, 66.1 (d, J_{C-F} = 20.0 Hz), 48.5, 48.48, 20.6, 20.4, 16.7.

***N*-(4-(*R*)-Ethyl-5-(*R*)-((2′,4′-di-*O*-acetyl-3′-*N*-(trifluoroacetyl)-3′,6′-dideoxy-α-L-talopyranosyl)oxy)-8-methyl-8-nonenyl)-2-(*R*)-ethyl-5-hexenamide (72).** In a 25 mL flame-dried round bottom flask diene **62** (35.0 mg, 0.11 mmol) was dried by azeotropic distillation with benzene (3 × 5 mL). $AgClO_4$ (49.3 mg, 0.24 mmol), $SnCl_4$ (45.1 mg, 0.24 mmol), and flame dried 4 Å molecular sieves were then added in a glove box. The mixture was subsequently charged with 2.0 mL of anhydrous diethyl ether. This resulting slurry was cooled to −15 °C, and after 2 min the glycosyl fluoride **71** (50.3 mg, 0.14 mmol dried by azeotrope distillation with benzene) solution in 3.0 mL of Et_2O was transferred to the slurry *via* cannula. The resulting mixture was allowed to stir for 1 h at −15 °C, at 0 °C for 1 h, and finally to 22 °C for 1−2 h. When thin layer chromatography (1:1 hexane/EtOAc, R_f = 0.54 for **62**, 0.63 for **71**, 0.60 for **72**) indicated complete consumption of the starting material, the reaction solution was diluted with 10 mL of CH_2Cl_2, and the solid was filtered and washed with an additional 10 mL of CH_2Cl_2. The filtrate was washed with 15 mL of aqueous $NaHCO_3$ solution, and the layers were separated. The aqueous layer was washed with 3 × 30 mL portions of CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to give a yellow oil. Purification by silica gel chromatography (3:1 hexanes/EtOAc) afforded 66 mg (0.10 mmol, 92% yield) of the desired compound as a colorless oil. IR (NaCl): 3288 (m), 2961 (m), 2935 (m), 2867 (m), 2363 (w), 2332 (w), 1744 (s), 1646 (m), 1539 (m), 1375 (m), 1369 (m), 1224 (s) cm^{-1}. ^{1}H NMR (400 MHz in $CDCl_3$): δ 6.95 (bd, 1H, J = 7.3 Hz, CH_2CON*H*), 5.76 (dddd, 1H J = 17.2, 10.3, 7.1, 6.2 Hz, CH_2CH*C*H_2), 5.62 (br, t, J =

6.3 Hz, 1H, N*H*COCF), 5.12 (m, 1H,$C_{2'}$-*H*), 4.97 (d, 1H, J = 17.3 Hz, CH_2CHCH_2), 4.96 (br, s, 1H, $C_{1'}$-*H*), 4.94 (m, 1H, CH_2CHCH*H*), 4.82 (m, 1H, $C_{4'}$-*H*), 4.71 (d, 2H, J = 14.1 Hz, $CH_2CH_2CHCH_2$), 4.60 (dt, 1H, J = 7.9, 2.5 Hz, $C_{3'}$-*H*), 4.20 (qd, 1H, J = 6.6, 1.4 Hz, $C_{5'}$-*H*), 3.65 (m, 1H, EtCHC*H*O), 3.25 (q, 2H, J = 5.9 Hz, NCH_2), 2.17 (s, 3H, $COCH_3$), 2.16 (s, 3H, $COCH_3$), 2.16−1.20 (15H, alkyl-*H*), 1.71 (s, 3H, CH_3CCH_2), 1.16 (d, 2H, J = 6.6 Hz, $C_{6'}$-H_3), 0.90 (t, 3H, J = 7.3 Hz, CH_2CH_3), 0.87 (t, 3H, J = 7.3 Hz, CH_2CH_3). ^{13}C NMR (100 MHz in $CDCl_3$): δ 175.4, 170.9, 170.6, 157.3 (q, J_{C-F} = 38 Hz), 145.0, 138,3, 116.1 (q, J_{C-F} = 287.0 Hz), 114.7, 110.5, 97.3, 81.5, 69.0, 65.4, 48.7, 46.6, 43.6, 39.7, 33.8, 31.66, 31.64, 28.4, 27.6, 27.0, 25.9, 23.1, 22.3, 20.9, 20.5, 16.3, 12.2, 12.0. HRMS Calcd for $C_{30}H_{47}N_2O_8F_3Na$ (M + Na): 671.3495. Found: 671.3516.

2,10-(*R*,*R*)-Diethyl-6-methyl-9-(*R*)-((2′,4′-di-*O*-acetyl,3′-*N*-(trifluoroacetyl)-3′,6′-dideoxy-α-L-talopyranosyl)oxy)-13-trideca-5-ene Lactam (73). Freshly prepared Mo catalyst **14** (5.3 mg, 7×10^{-3} mmol) was weighed in a glove box in a 10 mL pear shaped flask containing 15.0 mg (0.023 mmol) of diene **72** dried by azeotropic distillation with benzene (3 × 3 mL) . The reaction flask was then equipped with a reflux condenser and removed from the glove box; the reaction mixture was diluted with 1.9 mL of anhydrous benzene. The resulting mixture was allowed to stir at 22 °C under an atmosphere of argon for 4 h. At this time, the solvent was removed *in vacuo* to leave behind a dark brown oil. Purification by silica gel chromatography (2:3 hexanes/EtOAc) afforded 13 mg of **73** (0.022 mmol, 91% yield) as a white solid. IR (NaCl): 3314 (w), 2961 (m), 2930 (m), 2880 (m), 2351 (w), 1746 (s), 1532 (m), 1174 (s) cm^{-1}. ^{1}H NMR (400 Hz in $CDCl_3$): δ 6.76 (br, d, 1H, J = 7.0 Hz, CHCON*H*), 5.47 (br, t, 1H, J = 7.0 Hz, N*H*$COCF_3$), 5.14 (m, 1H, $C_{2'}$-*H*), 5.07 (m, 1H, CH_2CHCMe), 5.04 (s, 1H, $C_{1'}$-*H*), 4.75 (br, d, 1H, J = 3.7 Hz, $C_{4'}$-*H*), 4.62 (dt, 1H, J = 8.2, 3.5 Hz, $C_{3'}$-*H*), 4.20 (qd, 1H, J = 6.6, 1.1 Hz,$C_{5'}$-*H*), 3.60 (br d, 1H, HNCH*H*), 3.57 (m, 1H, EtCHC*H*O), 3.14 (m, 1H, CH*H*NH), 2.17 (s, 3H, $OCOH_3$), 2.16 (s, 3H, $OCOCH_3$), 2.00−1.20 (15H alkyl-*H*), 1.69 (s, 3H, $CHCCH_3$), 1.16 (d, 3H, J = 6.4 Hz, $C_{6'}$-H_3), 0.89 (t, 3H, J = 7.3 Hz, CH_2CH_3), 0.84 (t, 3H, J = 7.5 Hz, CH_2CH_3). ^{13}C NMR (100 MHz in $CDCl_3$): δ 175.8, 170.9, 170.3, 156.6 (q, J_{C-F} = 38.0 Hz), 135.7, 124.2, 115.5 (q, J_{C-F} = 268.7), 94.1, 77.7, 69.2, 65.3, 50.6, 46.2, 40.0, 38.7, 34.0, 27.8,27.3, 27.2, 26.5, 24.9, 24.6, 23.5, 20.9, 20.5, 16.0, 12.2, 8.8. HRMS Calcd for $C_{30}H_{47}N_2O_8Na$ (M + Na): 643.3182. Found: 643.3186.

2,10-(*R*,*R*)-Diethyl-6-(*S*)-methyl-9-(*R*)-((2′,4′-di-*O*-acetyl,3′-*N*-(trifluoroacetyl)-3′,6′-dideoxy-β-L-talopyranosyl)oxy)-13-tridecane Lactam (Sch 38516; 1). Into a solution of 2.5 mg (4×10^{-3} mmol) of hydrogenation product **73** in 0.7 mL of CH_3OH, 3.9 mL of hydrazine was added. After 24 h, ^{1}H NMR analysis indicated complete consumption of the starting material. The reaction solution was concentrated to dryness to give 1.6 mg of product as a white solid (96%). This compound was determined to be indentical to the natural product by the comprarison with ^{1}H NMR of natural product. For further proof, the product was converted to the corresponding hydrochloric acid salt, which was accomplished simply by dissolving the product in 5 mL of acetyl chloride in 1 mL of EtOH solution, followed by concentration *in vacuo* to dryness to afford synthetic **1**. ^{1}H, ^{13}C NMR and IR spectra of synthetic and natural product salts proved superimposable. For authentic free base product:[61] IR (KBr): 3310 (m), 3307 (br, m), 2954 (m), 2932 (m), 1652 (s) cm^{-1}. ^{1}H NMR (400 MHz in CD_3OD): δ 3.94 (dq, 1H, J = 6.1, 1.0 Hz, $C_{5'}$-*H*), 3.65−3.55 (2H, EtCHC*H*O, NC*H*H), 3.54 (m, 1H, $C_{2'}$-*H*), 3.46 (m, 1H, $C_{4'}$-*H*), 2.95 (m, 1H, NCH*H*), 2.91 (br, t, 1H, J = 3.0 Hz, $C_{3'}$-*H*), 2.06 (m, 1H, NCOC*H*Et), 1.80−1.00 (m, 21H, alkyl-*H*), 1.21 (s, 3H, J = 6.6 Hz, $C_{5'}$-CH_3), 0.92 (d, 3H, J = 7.0 Hz, CH_2CHCH_3), 0.86 (t, 3H, J = 7.2 Hz, CH_2CH_3), 0.84 (t, 3H, J = 7.2 Hz, CH_2CH_3). For synthentic hydrochloric salt product: ^{1}H NMR (400 MHz in CD_3OD): δ 4.02 (q, 1H, J = 7.0 Hz, $C_{5'}$-*H*), 3.70 (m, 1H, $C_{2'}$-*H*), 3.64 (m, 1H, $C_{4'}$-*H*), 3.62−3.50 (m, 2H, EtCHC*H*O, NC*H*H), 3.41 (t, 1H, 3.3 Hz, $C_{3'}$-*H*), 2.97 (m, 1H, NHCH*H*), 2.09 (m, 1H, NCOC*H*Et), 1.80−1.00 (m, 21H, alkyl-*H*), 1.14 (d, 3H, J = 6.4 Hz, $C_{5'}$-C*H*), 0.93 (d, 3H, J = 7.0 Hz, CH_2CHCH_3), 0.87 (t, 3H, J = 7.3 Hz, CH_2CH_3), 0.86 (t, 3H, J = 7.2 Hz, CH_2CH_3). ^{13}C NMR (100 MHz in CD_3OD): δ 179.2, 98.7, 78.8, 69,7, 68.7, 68.0, 51.3, 50.3, 42.1, 40.0, 35.5, 34.7, 32.5, 28.6, 27.7, 26.5, 26.4, 25.9, 22.3, 22.1, 21.1, 16.9, 12.7, 9.4. HRMS Calcd for $C_{24}H_{46}N_2O_5Na$ (M + Na): 443.3485. Found: 443.3478.

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Supporting Information Available: Experimental procedures and spectral and analytical data for select reagents and reaction products (42 pages). See any current masthead page for ordering and Internet access instructions.

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(61) The sample obtained from Schering-Plough Co. was determined to be the derived hydrochloric salt of the natural product. The free base Sch 38516 (neutral amine) was obtained through treatment of this material with excess Et_3N.