Enantioselective Total Synthesis of Antifungal Agent Sch 38516

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The paucity of stereogenic centers in the macrolactam region of Sch 38516[1] demands effective control of distal asymmetric induction, rendering the stereoselective preparation of this antifungal agent a challenging problem in chemical synthesis. In addition, the target molecule, which is also known as fluvirucin B1,[2] contains a novel carbohydrate moiety that appears as part of a natural product for the first time. We envisioned that a direct approach to the enantiocontrolled assembly of Sch 38516 would involve the following: (1) the attachment of carboxylic acid **I** to the amine segment **II** (→**III**, Scheme 1; P = protecting group); (2) diastereoselective glycosidation to obtain **IV**; (3) transition metal-catalyzed 14-membered ring closing metathesis of **IV** to reach **V**; and (4) diastereoselective hydrogenation of **V**, dictated by the conformational preferences of the macrocyclic ring,[3] which would establish the remote C6 stereogenic center.

In this context, we recently disclosed the enantioselective synthesis of **I** and **II** (P = TBS),[4] wherein various metal-catalyzed reactions, particularly the diastereo- and enantioselective Zr-catalyzed carbomagnesations,[5] played a pivotal role. We report here the first total synthesis of Sch 38516. The successful implementation of the enantioselective synthesis highlights the stereoselective construction of the requisite carbohydrate unit, its efficient and diastereoselective coupling to the acyclic diene and a competent Mo-catalyzed ring-closing metathesis of the diene-carbohydrate ensemble.

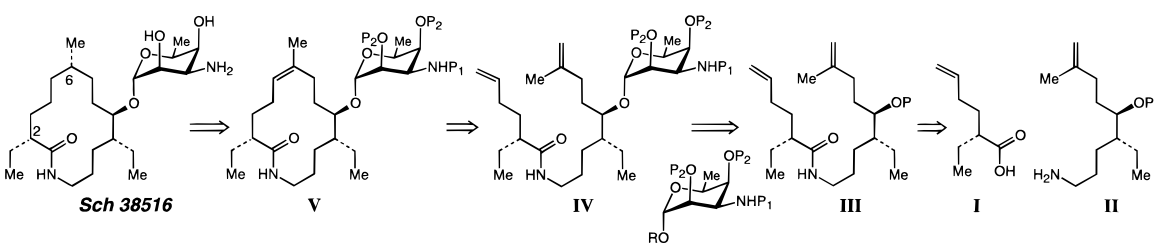
As illustrated in Scheme 2, stereocontrolled carbohydrate synthesis began with catalytic asymmetric dihydroxylation[6] of the inexpensive and commercially available ethyl sorbate **1**, followed by protection of the resulting nonracemic unsaturated ester as its derived acetonide to give **2** in 52% overall yield (80% ee, chiral GLC analysis). Subjection of **2** with O_3, reduction with dimethyl sulfide, and treatment of the chiral aldehyde with *N*-benzylhydroxylamine afforded nitrone **3a** (30% overall yield). When **3a** was heated to 85 °C in the presence of vinylene carbonate, as reported by DeShong and co-workers,[7] the [3 + 2] cycloaddition products **4a** and **5a** were formed as a 3.5:1 mixture of endo diastereomers (95:5 endo:exo, 52% yield). In addressing this shortcoming, we discovered that *when (R)-N-hydroxyl-α-methylbenzylamine derivative*[8] ***3b*** *is used instead,*[9] *the cycloaddition proceeds under identical conditions to afford* ***4b*** *with 20:1 diastereoselectivity in 69% isolated yield* (>98% endo:exo; ^{1}H NMR analysis).[10] Although the mechanistic justification for the enhancement in π-facial selectivity must await the results of ongoing studies, it is notable that with the (*S*)-antipode of the chiral auxiliary, little or no diastereofacial selectivity is observed (10:1 endo:exo selectivity).[11] Subjection of **4b** to HCl (THF) to effect the removal of the acetonide group, treatment of the resulting diol with $Pd(OH)_2$ and HCl under 300 psi H_2 (MeOH), and conversion of the product hemiacetal (7:1 ratio of α:β anomers) to methoxy acetal **6** proceeded in 79% overall yield after silica gel chromatography (>98% α-methoxy anomer).

We next outfitted the carbohydrate nucleus with the appropriate protecting and functional groups essential for stereoselective glycosylation and completion of the total synthesis. Protection of the primary amine by treatment with *S*-ethyl trifluorothioacetate,[12] acylation of the two secondary carbinols, and conversion of the methyl glycoside to the corresponding acetoxy derivative delivered the fully protected **7** (85% yield; >98% α anomer).[13] Treatment of **7** with thiophenol and $SnCl_4$,[14] followed by subjection of the resulting thioglycoside with diethylaminosulfur trifluoride and N-bromosuccinamide gave rise to the formation of fluorinated carbohydrate **8** in 65% purified overall yield.[15c]

After extensive investigation of a variety of protocols, we established that when 1 equiv of diene **11** and 1.1 equiv of fluorocarbohydrate **8** are treated with $SnCl_2$ and silver perchlorate in the presence of 4 Å molecular sieves,[15] lycosylated diene **12** is formed as a single stereoisomer (>98%) in 92% yield after silica gel chromatography. The stage was thus set for the Mo-catalyzed ring closing metathesis of the fully functionalized **12**. Heating of **12** to 60 °C in benzene in the presence of 20 mol% of freshly prepared $Mo(CHCMe_2Ph)(N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$[16] led us to macrolactam **13**,[17] which was isolated after 10 h in 90% purified yield as a single alkene isomer (>98%). It must be noted that the facile catalytic ring closure of **12** was crucial to the completion of the total synthesis, as all attempts to effect glycosylation between the hydroxyl aglycon (ring closed product of **11**) and a gamut of carbohydrate derivatives failed. This is probably due to the low solubility of the macrolactam carbinol substrate in organic solvents;[18] in contrast, acyclic diene **11** is readily dissolved in most solvents and can be easily manipulated under a variety of conditions. Stereoselective hydrogenation of the trisubstituted olefin in **13**, where H_2 addition occurs by peripheral attack,[3] delivered **14** as a single diastereomer (minor isomer not detected by ^{1}H NMR analysis). When **14** was subjected to hydrazine in MeOH, removal of the two acetoxy units and the deprotection of the amide trifluoroacetate group was effected smoothly, releasing Sch 38516 in 96% yield as a white solid. The synthetic compound proved identical by ^{1}H NMR, ^{13}C NMR, IR, HRMS, and TLC to an authentic sample of natural Sch 38516.

The present study records an efficient and enantioselective synthesis of a novel carbohydrate moiety, where a readily available chiral auxiliary is employed to render the key cycloaddition highly diastereoselective (**3b** → **4b**, Scheme 1). The remarkably efficient transition metal-catalyzed macrocyclization of **12** illustrates that the ring closing metathesis strategy

Scheme 1



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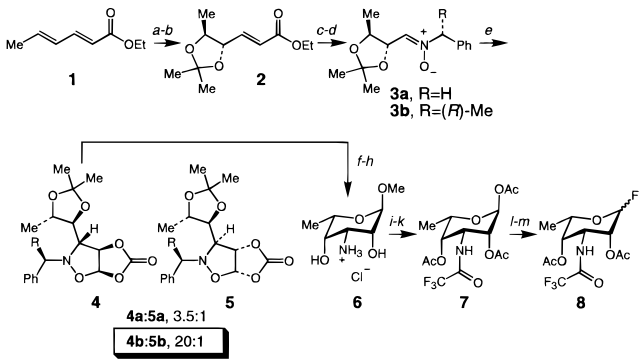
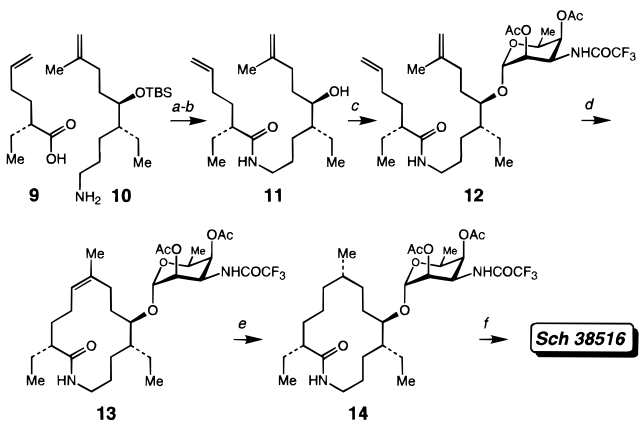
Scheme 2[a]



[a] AD mix-α, 1 equiv $MeSO_2NH_2$, *t*-BuOH, H_2O. [b] 2,2-Dimethoxypropane, 5 mol% *p*-TsOH, 52% from **1**. [c] O_3, 8:1 CH_2Cl_2:MeOH, −78 °C; Me_2S. [d] 1.0 equiv of (*R*)-*N*-hydroxy-α-methylbenzylamine, 20 h, 30% from **2**. [e] 4 equiv of vinylene carbonate, C_6H_6, 85 °C, 38% for **3a**, 69% for **3b**. [f] 4:1 THF:1.0 M HCl, 65 °C. [g] $Pd(OH)_2$ (50% by weight), 300 psi H_2, 2.5 equiv of MeCOCl, MeOH. [h] 10% anhydrous HCl in MeOH, 79% from **4b**. [i] 1.5 equiv of CF_3COSEt, 1.5 equiv of Et_3N, MeOH. [j] 10 equiv of Ac_2O, pyridine, DMAP. [k] 1% H_2SO_4 in Ac_2O, 0 °C, 1 h, 85% from **6**. [l] 1.2 equiv of PhSH, 0.7 equiv of $SnCl_4$, 50 °C, 1 h. [m] 1.3 equiv of Et_2NSF_3, 1.5 equiv of NBS, 0 °C, 65% from **7**.

Scheme 3[a]



[a] 1.1 equiv of DCC, 1.2 equiv of HOBT, 22 °C, 8 h, 85%. [b] 48% HF, MeCN, 22 °C, 20 min, 80%. [c] 2.2 equiv of $AgClO_4$, 2.2 equiv of $SnCl_2$, 4 Å molecular sieves, 1.1 equiv of **8**, −15 °C (1 h), 0 °C (1 h), 22 °C (2 h), Et_2O, 92%. [d] 20 mol% $Mo(CHCMe_2Ph)N(2,6\text{-}(i\text{-}Pr)_2C_6H_3))(OCMe(CF_3)_2)_2$, C_6H_6, 60 °C, 10 h, 90%. [e] H_2, 10% Pd(C), EtOH, 72%. [f] 20 equiv of N_2H_4, MeOH, 24 h, 96%.

represents a dependable approach for the construction of complex and highly functionalized macrocyclic structures.

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Supporting Information Available: Experimental procedures and spectral and analytical data for all reaction products (51 pages). See any masthead page for ordering and Internet access information.

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(1) (a) Hegde, V. R.; Patel, M. G.; Gullo, V. P.; Ganguly, A. K.; Sarre, O.; Puar, M. S.; McPhail, A. T. *J. Am. Chem. Soc.* **1990**, *112*, 6403−6405. (b) Hegde, V. R.; Patel, M.; Horan, A.; Gullo, V.; Marquez, J.; Gunnarsson, I.; Gentile, F.; Loebenberg, D.; King, A. *J. Antibiot.* **1992**, *45*, 624−632.

(2) (a) Naruse, N.; Tenmyo, O.; Kawano, K.; Tomita, K.; Ohgusa, N.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 733−740. (b) Naruse, N.; Tsuno, T.; Sawada, Y.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 741−755. (c) Naruse, N.; Konishi, M.; Oki, T. *J. Antibiot.* **1991**, *44*, 756−761. (d) Komita, K.; Oda, N.; Hoshino, Y.; Ohkusa, N.; Chikazawa, H. *J. Antibiot.* **1991**, *44*, 940−948.

(3) Still, W. C.; Novack, V. J. *J. Am. Chem. Soc.* **1984**, *106*, 1148−1149 and references cited therein.

(4) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943−2944.

(5) Diastereoselective carbomagnesation: (a) Hoveyda, A. H.; Xu, Z. *J. Am. Chem. Soc.* **1991**, *113*, 5079−5080. (b) Houri, A. F.; Didiuk, M. T.; Xu, Z.; Horan, N. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6614−6624. Enantioselective carbomagnesation: (c) Morken, J. P.; Didiuk, M. T.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1993**, *115*, 6697−6698. (d) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291−4298.

(6) Xu, D.; Crispino, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570−7571.

(7) DeShong, P.; Dicken, C. M.; Leginus, J. M.; Whittle, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 5598−5602.

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

(9) At this point, the diastereomer derived from minor dihydroxylation enantiomer is separated from **3b**.

(10) For the use of this chiral auxiliary in stereoselective reactions with *O*-silylketene acetals, see: Kita, Y.; Itoh, F.; Tamura, O.; Ke, Y. Y.; Tamura, Y. *Tetrahedron Lett.* **1987**, *28*, 1431−1434.

(11) This experiment was carried out by Mr. Daniel La of these laboratories.

(12) Imazawa, M.; Eckstein, F. *J. Org. Chem.* **1979**, *44*, 2039−2041.

(13) Pozsgay, V. *J. Am. Chem. Soc.* **1995**, *117*, 6673−6681. Although the secondary amine of the unmasked carbohydrate (product of hydrogenation) could be protected, attempts to acylate the two secondary carbinols and the hemiacetal hydroxyl group, under a variety of conditions, led to the formation of complex mixtures of products.

(14) Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556−5558.

(15) (a) Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.* **1981**, 431−432. (b) Mukaiyama, T.; Hashimoto, Y.; Shoda, S. *Chem. Lett.* **1983**, 935−938. (c) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L.; *J. Am. Chem. Soc.* **1984**, *106*, 4189−4192. (d) Reference 14.

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

(17) For other macrocyclic ring syntheses through catalytic ring closing metathesis, see: (a) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691−694. (b) Borer, B. C.; Deerenberg, S.; Bieraugel, H.; Pandit, U. K. *Tetrahedron Lett.* **1994**, *35*, 3191−3194. (c) Martin, S. F.; Liao, Y.; Chen, H.-J.; Patzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005−6008. (d) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856. (e) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364−12365. (f) Furstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942−3943. (g) McKervey, M. A.; Pitarch, M. *J. Chem. Soc., Chem. Commun.* **1996**, 1689−1690.

(18) Efforts to prepare more soluble derivatives of the macrolactam alcohol (*e.g.*, the derived TMS ether) which would also be suitable for glycosylation by other methods (*e.g.*, involving triacetate **7**) were not successful. For an example, see: Mukaiyama, T.; Katsurada, M.; Takashima, T. *Chem. Lett.* **1991**, 985−988.