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Methanesulfenyl Triflate Promoted Iminosulfenylation of an Allylic Trichloroacetimidate. An Efficient and Stereospecific Total Synthesis of (+) Mannostatin A.

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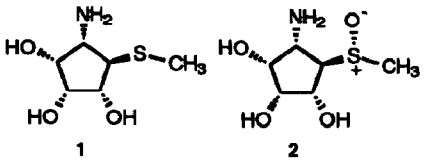
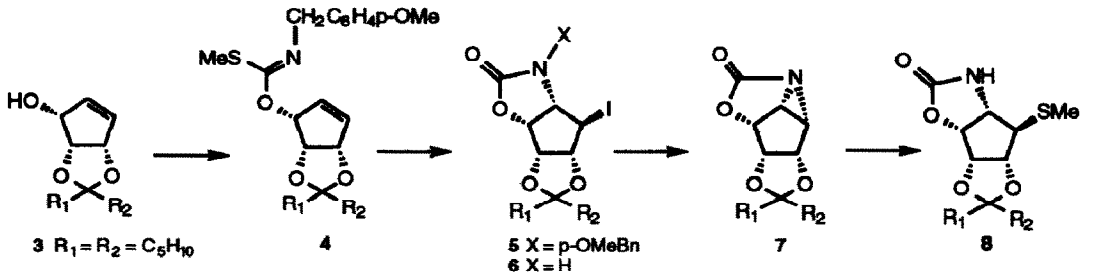
Abstract: The stereospecific synthesis of glycoprotein processing enzyme inhibitor (+) mannostatin A **1** was achieved in ten steps from D-ribonolactone **9** (~ 39% overall yield). The strategy featured methanesulfenyl triflate mediated intramolecular cyclization of allylic N-sufenylimidate **12**.

In 1989, two unusual pentasubstituted cyclopentanes **1** and **2** were isolated from the fermentation broth of the microorganism *Streptoverticillium verticillus* var. *quintum* ME3-AG3.[1] They were named mannostatin A and B, respectively, for their inhibitory activity towards rat epididymal α-mannosidase.[1] Armed with dense functionality and stereochemistry, **1** and **2** are the only carbocyclic, naturally occurring mannosidase inhibitors known to date. Among its broad spectrum of biological activities, mannostatin A **1** competitively inhibited Golgi processing mannosidase II of both plant and animal origins.[2] In cell culture, **1** successfully altered the normal processing of viral glycoproteins, resulting in increased production of hybrid types of glycoproteins at the expense of the complex types.[2] It was believed that the inhibition of mannosidase II by **1** triggered this cellular phenomenon. Most recently, **1** was shown to interfere with the development of pulmonary metastasis in mice.[3] Interest in the structure-biological activity relationship has prompted a rash of synthetic activity towards the mannostatins, resulting in four independent syntheses of **1**.[4]



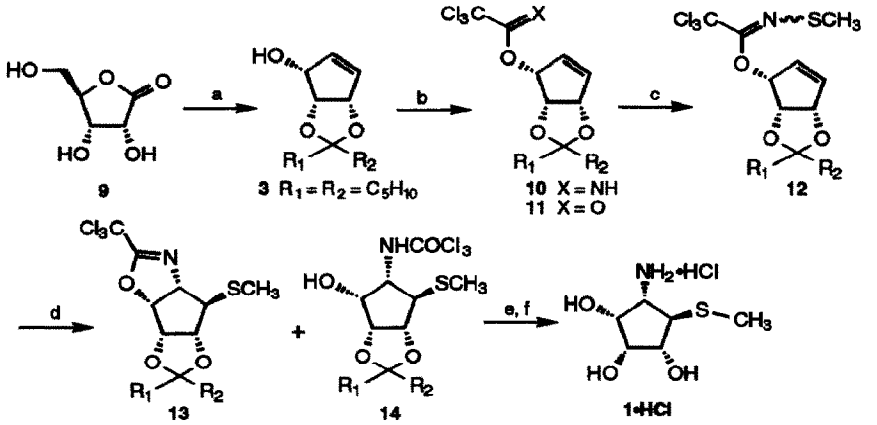
1 **2**

Our need for **1** arose in connection with an anti-AIDS project which sought to utilize glycosidase inhibitors as "recognition elements" for the delivery of a variety of suicide agents seeking to arrest development of the envelope glycoprotein. As our interest in this pseudosugar was simply one of need, we initially elected simply to adopt the best synthesis of optically active **1**, namely the method of Knapp and Dhar (32% overall).[4a] These authors converted allylic alcohol **3** to carbonimidothioate **4**, followed by iodocyclization to **5**, benzylic cleavage to **6**, and addition of methanethiol to the intermediate acylaziridine **7**. While each of these reactions was quite efficient, it is clear that strategic considerations would dictate the direct introduction of both the nitrogen and sulfur residues in a single step. The desirability of such a strategy was clearly apparent to both Trost[4c] and Knapp[5] as both authors reported sulfenylation failures using traditional sulfenylating agents with the necessarily inductively-deactivated olefinic intermediates.



Our own approach to **1** also employed allylic alcohol **3**, which was synthesized from the readily available, enantiopure D-ribonolactone **9** in 42-55% overall yield.[6] It was envisaged that a proper nitrogen nucleophile tethered through the allylic oxygen could undergo methanesulfenyl cation mediated cyclization, resulting in the incorporation of both the nitrogen and sulfur residues in a single step. To this end, allylic alcohol **3** was converted to allylic trichloroacetimidate **10** by the method of Overman.[7] The crude product was >95% pure by ^{1}H NMR and was used directly without further purification. The selection of an allylic trichloroacetimidate for the proposed cyclization stems from its proclivity to undergo electrophile initiated regiospecific cyclization reactions.[8]

Consistent with the observations of Trost and Knapp, reaction of **10** with CH_3SCl[9] in the presence of diisopropylethylamine (DIEA) produced N-sulfenylimidate **12** in 51% yield, but did not proceed further to the desired oxazoline **13** even under forcing conditions. The C=N carbon atom in **12** appears 17-18 ppm upfield of the corresponding C=O and C=NH carbon atoms, which is in agreement with the resonance effect exerted by the thiomethyl group.[10] Although N-sulfenylimines are known in the literature, **12** represents the first example of an N-sulfenylimidate.[11]

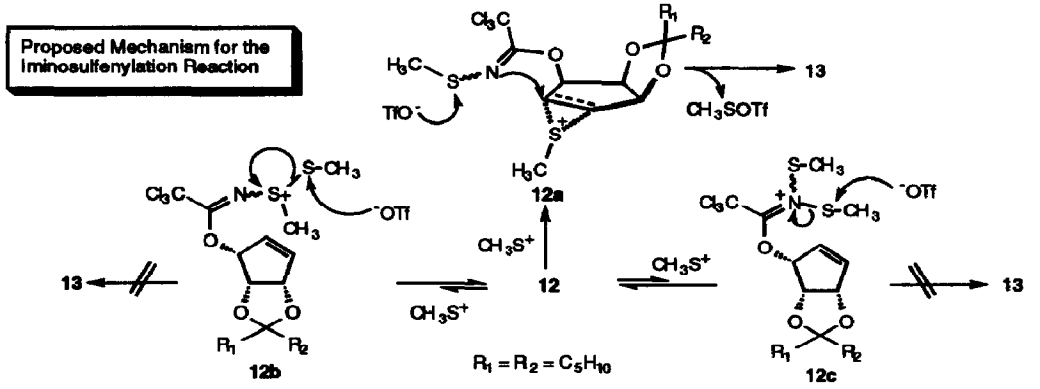


(a) 6 steps; 42-55%. (b) **3** to **10**, NaH, Cl_3CCN, CH_2Cl_2, -10 to 25°C. (c) 3.4 eq. $(i\text{-}Pr)_2NEt$, 3.3 eq. CH_3SOTf, CH_2Cl_2, -72 to 0°C; 94% overall from **3**. (d) 1.5 eq. $(i\text{-}Pr)_2NEt$, 3.5 eq. CH_3SOTf, CH_2Cl_2, -72 to 20°C; 71% **13** and 8% **14**. (e) **13** to **1•HCl**, 7 N HCl:CH_3OH (v:v = 50:50), 25°C; 97%. (f) **14** to **1•HCl**, 7 N HCl:CH_3OH (v:v = 50:50), 60-80°C; 90%.

Since insufficient electrophilicity of the conventional sulfenylating agents was likely responsible for the aforementioned sulfenylation failures, an effort was made to search for a super-electrophilic CH_3S^+ source. A

thorough literature survey revealed a 1982 paper by Effenberger and Russ which detailed the first preparation of CH_3SOTf from CH_3SCl and silver triflate (AgOTf).[12] Except a brief analysis of its stability, no synthetic application of this simplest alkyl sulfenyl triflate was described. In fact, synthetic study on CH_3SOTf had been conspicuously absent from literature until Dasgupta and Garegg unveiled its use as a powerful promoter for thioglycosides in 1988.[13a] In the ensuing years, this reagent has only been used in carbohydrate chemistry.[13b] With a superb leaving group as its non-nucleophilic counterion, CH_3SOTf is arguably the most electrophilic methanesulfenylating reagent and a perfect choice to test the iminosulfenylation strategy.

Portionwise additions of 3 to 5 equivalents of freshly prepared CH_3SOTf to **10** in the presence of 1.1 to 1.3 equivalents of diisopropylethylamine (DIEA) led to a mixture of **13** and **14** in ~ 60% overall yield. The latter compound, isolated in ~ 20% yield, was presumably formed by hydrolysis of **13** during the aqueous workup or column chromatography.[14] On prolonged exposure of a purified sample of **13** to silica gel, partial hydrolysis to **14** was indeed observed. The function of DIEA is to neutralize trifluoromethanesulfonic acid generated during the reaction, thereby avoiding potential side reactions. Monitoring the reaction by TLC while slowly warming the solution from -78°C revealed the gradual consumption of **10** with the concomitant generation of **12**. At about -30°C, a new spot corresponding to **13** emerged. At higher temperatures (0 to 20°C), **12** began to disappear at a reasonable rate and substantial conversion of **12** to **13** was noted. These observations suggested that N-sulfenylimidate **12** was the reactive intermediate in this CH_3SOTf mediated cyclization. The inefficiency associated with the *in situ* generation of **12** was likely responsible for the moderate yields. Therefore, a two-step procedure (i.e., **10** → **12**, and then **12** → **13**) was tested to see if a better yield could be achieved. Under the optimal conditions, treatment of **10** with 3.4 equivalents of DIEA and 3.3 equivalents of CH_3SOTf in three equal portions led to the isolation of **12** in a remarkable 94% yield.



Subsequent reaction of **12** with 0.3 equivalent of CH_3SOTf in the absence of DIEA led to only ~ 30% conversion to **13**. This inconclusive result does not provide unambiguous support for the proposed catalytic mechanism (**12** to **13**, see scheme above). Monitoring the reaction by TLC proved to be problematic. Significant amounts of **11** was detected even when neutral alumina or deactivated silica gel TLC was used. The observed **11** was presumably via hydrolysis of **12** and an artifact of exposure of the TLC sample to the air. After much experimentation, it was found that addition of 1 equivalent of DIEA to the reaction mixture before the first addition of CH_3SOTf, and up to 0.2 equivalent of DIEA before each of subsequent additions

of CH_3SOTf drastically reduced the appearance of **11** on TLC. In a separate experiment, treatment of **12** with 3.5 equivalents of CH_3SOTf and 1.5 equivalents of DIEA in dichloromethane provided a separable mixture of **13** and **14** in 71% and 8% yields, respectively.

Finally, treatment of **13** with acidic methanol at 25°C provided (+) mannostatin A **1** as its hydrochloride in 97% yield. In addition, the hydrolysis of trichloroacetamide **14** at 60-80°C proceeded smoothly to afford **1** as its hydrochloride in 90% yield. The physical data of the synthetic **1•HCl** were in full agreement with the reported values.[4a,15]

In conclusion, the synthesis of (+) mannostatin A hydrochloride **1•HCl** has been achieved in ~ 39% overall yield in 10 steps from the commercially available D-ribonolactone **9**. Among the several interesting features presented above, methanesulfenyl triflate was found to be a highly electrophilic activator of an inductively-deactivated olefin. Its superior electrophilicity over traditional sulfenylating reagents should find broad applications in organic synthesis.

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References and Notes

1. (a) Aoyagi, T.; Yamamoto, T.; Kojiri, K.; Morisha, H.; Nagai, M.; Hamada, M.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1989**, *42*, 883; (b) Morishima, H.; Kojiri, K.; Yamamoto, T.; Aoyagi, T.; Nakamura, H.; Iitaka, Y. *J. Antibiot.* **1989**, *42*, 1008.
2. Tropea, J. E.; Kaushal, G. P.; Pastuszak, I.; Mitchell, M.; Aoyagi, T.; Molyneux, R. J.; Elbein, A. D. *Biochemistry* **1990**, *29*, 10062.
3. Ochi, Y.; Atsumi, S.; Aoyagi, T.; Umezawa, K. *Anticancer Res.* **1993**, *13*, 1421.
4. (a) Knapp, S.; Dhar, T. G. M. *J. Org. Chem.* **1991**, *56*, 4096; (b) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1994**, *116*, 562; (c) Trost, B. M.; Van Vranken, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 444; (d) Ogawa, S.; Yuming, Y. *J. Chem. Soc., Chem. Comm.* **1991**, 890.
5. Compound **4** fails to undergo iminosulfenylation when treated with methanesulfenyl chloride (Professor S. Knapp, private communication).
6. (a) Bélanger, P.; Prasit, P. *Tetrahedron Lett.* **1988**, 5521; (b) Borcherding D. R.; Scholtz, S. A.; Borchardt, R. T. *J. Org. Chem.* **1987**, *52*, 5457; (c) Beer, D.; Meuwly, R.; Vasella, A. *Helv. Chim. Acta* **1982**, *65*, 2570. (d) We are grateful to Professor Knapp for providing us a copy of the experimental procedures for the preparation of **3**.
7. (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901; (b) Beier, B.; Schhürrle, K.; Werbitzky, O.; Pieperberg, W. *J. Chem. Soc. Perkin Trans. 1*, **1990**, 2255.
8. Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321; and references cited therein.
9. Ohishi, J. *Synthesis*, **1980**, 690.
10. **12**: $[\alpha]_D^{25}$=+184.5° (c 0.06, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.10 (1H, dt, J=5.8, 1.6 Hz); 5.97 (1H, dd, J=5.8, 1.6 Hz), 5.34 (1H, app dt, J=5.4, 1.6 Hz), 5.02 (1H, m), 4.93 (1H, app t, J=5.4 Hz), 2.68 (s, 3H, SCH_3), 1.68-1.22 (10H, m, 5 CH_2's); ^{13}C NMR ($CDCl_3$) δ 144.18 (e, C=N-SMe), 135.30 (o), 131.94 (o), 113.50 (e), 90.33 (e), 83.07 (o), 79.92 (o), 76.47 (o), 37.17 (e), 36.45 (e), 25.29 (o), 25.02 (e), 23.96 (e), 23.77 (e); HRMS (EI): calcd for $C_{14}H_{18}Cl_3NO_3S$ 385.0073, found 385.0068.
11. Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 702.
12. Effenberger, F.; Russ, W. *Chem. Ber.* **1982**, *115*, 3719.
13. (a) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1988**, *177*, c13; (b) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.* **1990**, *202*, 225.
14. Bongini, A.; Cardillo, G.; Orena, M.; Sandri, S.; Tomasini, C. *J. Chem. Soc. Perkin Trans. 1*, **1986**, 1339 and 1345.
15. **1•HCl**: $[\alpha]_D^{26}$=+5.6° (c 0.01, CH_3OH); ^1H NMR (D_2O) δ 4.14 (1H, dd, J=6.5, 3.9 Hz, H-3), 3.96 (1H, app t, J=4.3 Hz, H-2), 3.86 (1H, dd, J=7.7, 4.8 Hz, H-1), 3.40 (1H, app t, J=6.7, H-4), 2.97 (1H, app t, J=7.3 Hz, H-5), 2.01 (s, 3H, SCH_3); ^{13}C NMR (D_2O) δ 73.89, 72.19, 68.37, 55.12, 51.84, 12.09; HRMS (EI): calcd for $C_6H_{13}NO_3S$ 179.0616, found 179.0618.

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