Cascade Catalysis in Synthesis. An Enantioselective Route to Sch 38516 (and Fluvirucin B_1) Aglycon Macrolactam

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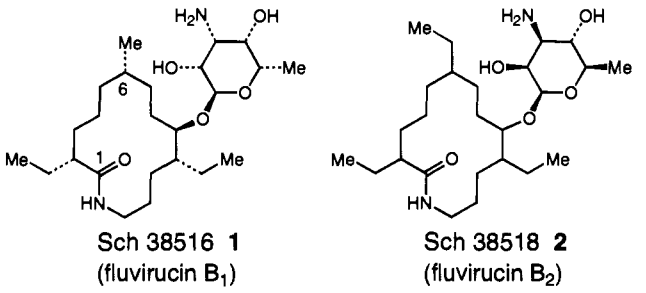
Organic chemistry has witnessed the development of a variety of selective and efficient transformations that are catalyzed by transition metal complexes. Since a number of these reactions effect bond formation enantioselectively, and because several of these processes are not feasible in the absence of metal catalysis, the ability of chemists to execute multistep synthesis schemes may now be significantly more sophisticated. Herein, we report the synthesis of Sch 38516[1] aglycon, where various catalytic reactions which are often carried out in tandem play a pivotal role in the efficient implementation of the synthesis plan.

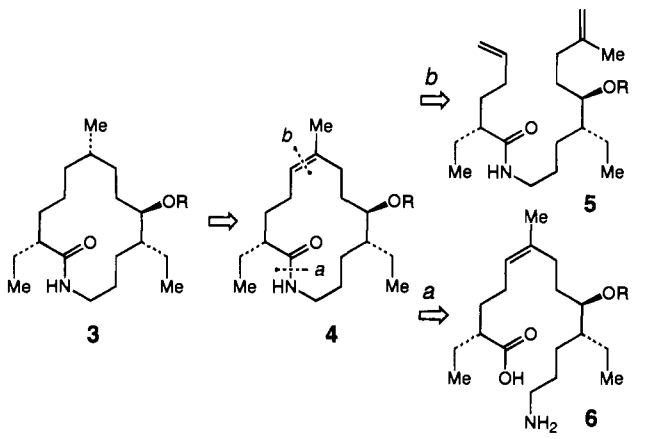
We are interested in a novel family of naturally occurring macrolactams, exemplified by **1** and **2** in Chart 1, because of their important and varied biological activity. Sch 38516 (**1**), an antifungal agent, was discovered by researchers at Schering-Plough and is likely the same as fluvirucin B_1,[2] reported by Bristol-Myers to be active against influenza A virus. The stereochemical identity of the macrolactam portion of the latter is yet to be rigorously established. Sch 38518[3] (**2**) is another antifungal agent, which may be the same as fluvirucin B_2; the stereochemistry of the macrocycle has not been established in either case. Thus, a selective, flexible, and efficient synthesis of the macrolactam segment of this class of compounds constitutes a critical first step in the development of this class of medicinally important agents.

In designing a synthesis plan, we searched for an intermediate which would afford **3** and serve as the starting point for a number of analogues. We opted for *Z*-trisubstituted alkene **4** (Scheme 1), because (1) examination of molecular models indicated that catalytic hydrogenation of **4** would establish the desired remote stereochemistry at C6 (peripheral attack)[4] and (2) the resident alkene could be selectively functionalized by a variety of procedures. The above requirements, however, posed a significant challenge in synthesis design: a stereoselective method for the preparation of an unfunctionalized trisubstituted alkene would have to be devised. That is, macrolactam formation by the more classical disconnection path a (*via* **6**) would have to be re-evaluated, since such a plan would likely carry a nonselective olefin synthesis step. We therefore chose to pursue disconnection path b; the requisite alkene would be assembled through a stereoselective metal-catalyzed diene metathesis protocol.[5]

Chart 1



Scheme 1



Recently, synthesis of a disubstituted olefin within an eight-membered ring with metathesis catalyst Mo(CHCMe$_2$Ph)(N(2,6-(*i*-Pr)$_2$C$_6$H$_3$))(OCMe(CF$_3$)$_2$)$_2$ (**7**)[6] has been reported.[7] However, it appears that the presence of a cyclic framework that bears the two reacting alkenes could be a critical factor in the success of ring closure.[8] Accordingly, the prospects of effecting a 14-membered synthesis through formation of a *trisubstituted* alkene with a conformationally mobile acyclic diene appeared doubtful. Nonetheless, to test the metathesis–macrocyclization approach, diene **5** (Scheme 4) was prepared in a convergent manner through coupling of amine **12** (Scheme 2) and carboxylic acid **17** (Scheme 3).

As the first step toward **12**, diene **9** was prepared in >99% enantiomeric excess[9] in three steps from commercially available **8** (Scheme 2). Treatment of **9** with EtMgBr in the presence of 5 mol % Cp$_2$ZrCl$_2$[10] followed by reaction quench with tosylaziridine and 5 mol % CuBr·Me$_2$S[11] results in the formation of

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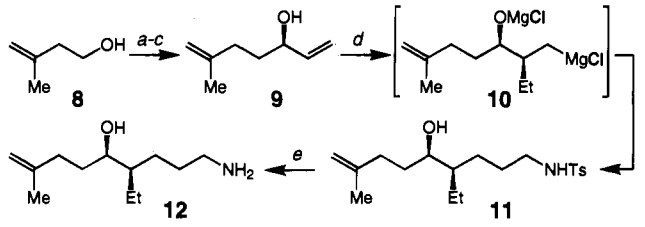
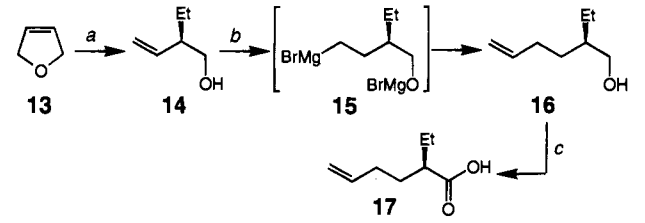
Scheme 2



[a] Ph_3P, I_2, Et_3N, CH_2Cl_2, 0 → 22 °C. [b] *t*-BuLi, $H_2CCHCHO$, THF, −78 °C, 51% overall. [c] $Ti(OiPr)_4$, *t*-BuOOH, (+)-diethyl tartrate, 4 Å molecular sieves, 66%. [d] EtMgBr, 5 mol % Cp_2ZrCl_2, Et_2O, 22 °C, 12 h; 6 equiv $TsN(CH_2CH_2)$, 5 mol % $CuBr{\cdot}Me_2S$, THF, 40%. [e] Excess Na, NH_3, −50 °C, 99%.

Scheme 3



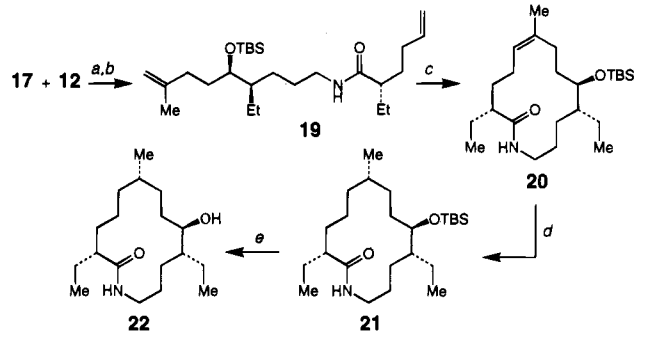
[a] 0.8 equiv of EtMgBr, 0.4 mol % (*S*)-[EBTHI]-Zr-BINOL, THF, 70 turnovers. [b] 3 equiv of *n*-PrMgBr, 3 mol % Cp_2TiCl_2, THF; then 4 equiv of CH_2CHBr, 3 mol % $(Ph_3P)_2NiCl_2$, 72%. [c] 5 mol % $(n\text{-}CH_3(CH_2)_2)_4NRuO_4$, MeCN, 3 equiv of NMO, 65%.

11 in 40% yield after silica gel chromatography. Thus, the one-pot double alkylation of the monosubstituted olefin in **9** proceeds with >99% site selectivity and 95:5 stereoselectivity (GLC). Removal of the tosyl group (Na/NH_3) delivers **12** in 99% isolated yield.

The enantioselective synthesis of **17** was carried out in three catalytic steps starting with asymmetric alkylation of **13** to afford **14** (0.4 mol % (*S*)-[EBTHI]-Zr-BINOL, ~70 turnovers).[12] Conversion of **14** to **16** requires a transformation equivalent to "hydrovinylation" of a terminal alkene. A single-flask catalytic hydrovinylation was thus designed in the following manner: Treatment of **14** with *n*-PrMgCl and 3 mol % Cp_2TiCl_2[13] affords **15**, which is subsequently treated with vinyl bromide and 3 mol % $(Ph_3P)_2NiCl_2$[14] to deliver **16** (72% from **13**). Ru-catalyzed oxidation of **16** (5 mol % $n\text{-}Pr_4NRuO_4$) provides **17** (65%; >99% ee by GLC analysis).

As shown in Scheme 4, carboxylic acid **17** and amine **12** were coupled in the presence of DCC to afford the derived amide (**18**). In accord with previous reports with regard to sensitivity of metathesis catalyst **7** to unprotected hydroxyl groups, the carbinol unit was protected as its *tert*-butyldimethylsilyl (TBS) derivative. *When **19** is subjected to 25 mol % **7** in a 0.01 M THF solution, macrolactam **20** is obtained in 60%*

Scheme 4



[a] 1 equiv of DCC, 3 equiv of *N*-methylmorpholine, 1.2 equiv HOBT, 22 °C, 12 h, 60%. [b] 3 equiv of TBSOTf, 4 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 90%. [c] 25 mol % **7**, C_6H_6, 50 °C, 60%. [d] H_2 (1 atm), 10% Pd(C), 75%. [e] HF, MeCN, 80%.

yield as a single olefin stereoisomer after silica gel chromatography (>98% *Z*, 500 MHz ^1H NMR).[15] Hydrogenation of **20** in the presence of 10% Pd(C) affords **21** with >95% diastereoselectivity (^1H NMR analysis, 75%). Removal of the silyl group provides aglycon **22**; subsequent acylation (Ac_2O, Et_3N, cat. DMAP) affords material identical (^1H NMR, IR, and TLC) to that provided by Dr. Vincent Gullo of the Schering-Plough Company.

In summary, the Sch 38516 (fluvirucin B_1) aglycon has been synthesized efficiently and enantioselectively by a general scheme that can be easily modified for the preparation of the other members of this class of natural products. All issues of carbon−carbon bond formation and stereochemistry are addressed by metal-catalyzed processes. The Zr-catalyzed regio-, diastereo-, and enantioselective alkylations readily provide intermediates **11** and **14.** In addition, the synthesis scheme contains two critical steps (**9** → **11** and **14** → **16**) where multiple operations are carried out in a single vessel, a strategy that is economically and environmentally attractive. We demonstrate that the Mo-catalyzed diene metathesis can be used in the synthesis of macrocycles in the *absence* of a rigid molecular framework, providing a powerful route to the stereoselective formation of unsaturated large rings. Studies in connection with the development of metal-catalyzed bond forming reactions and Sch 38516, including its total synthesis and preparation of various analogues, are in progress.

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Supplementary Material Available: Experimental procedures and spectral and analytical data for all reaction products (11 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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