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A Novel Enantioselective Synthesis of (+)-Myriocin Based on the Chemistry of 1-Trimethylsilylbuta-2,3-dienes

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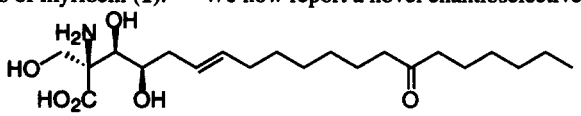
Abstract: A synthesis of (+)-myriocin has been achieved in a highly stereoselective manner employing $TiCl_4$ catalyzed addition of 1-trimethylsilylbuta-2,3-diene to an aldehyde and Et_2AlCl catalysed cyclization of an epoxytrichloroacetimidate for the construction of its α-substituted serine structure having three contiguous asymmetric centers. © 1997 Elsevier Science Ltd.

Myriocin (**1**) was first isolated as an antifungal principle from the fermentation broth of thermophilic fungi, *Myriococcus albomyces*[1] and *Mycelia sterila*.[2] Recently this compound was also found in the culture broth of *Isalia sinclairii* after screening for substances that exhibit potent immunosuppressive activity.[3] Myriocin (**1**) was found to suppress lymphocyte proliferation in mouse allogeneic mixed lymphocyte reaction *in vitro* and allo-reactive cytotoxic T lymphocyte generation *in vivo* with potency 10 to 100 times greater than that of cyclosporin A, suggesting its potential utility as a new type of immunosuppressive drug.[3,4] In connection with our recent project concerning the synthesis of α,α-disubstituted α-amino acids,[5,6] the unique structure having α-substituted serine unit as well as the intriguing biological properties prompted us to investigate a total synthesis of myriocin (**1**).[7,8] We now report a novel enantioselective synthesis of (+)-myriocin (**1**).



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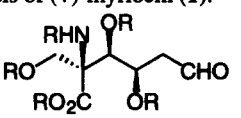

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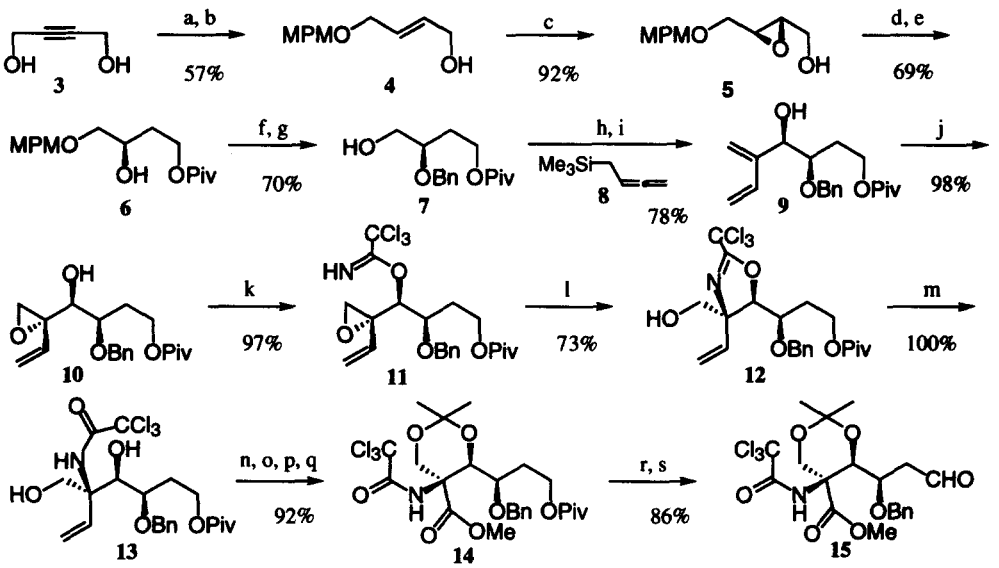
Retrosynthetic analysis of **1** led to an aldehyde **2** as a key synthetic precursor. The strategy we have employed to construct **2** having a characteristic α-substituted serine structure with three contiguous asymmetric centers relies upon the chemistry of 1-trimethylsilylbuta-2,3-dienes[9] and Lewis acid catalyzed cyclization[6] of an epoxytrichloroacetimidate both of which we have recently established.

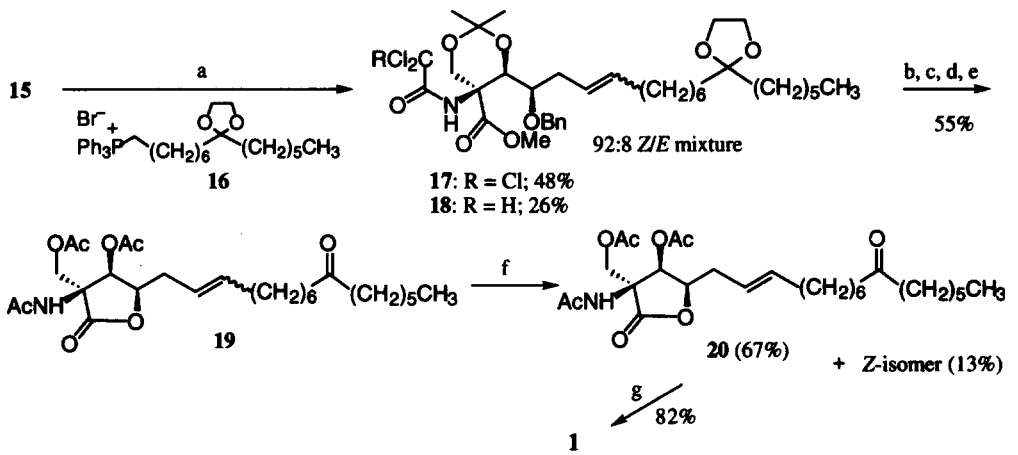
p-Methoxybenzylation[10] of 2-butyn-1,4-diol (**3**) followed by sodium bis(methoxyethoxy)aluminum hydride (Red-Al®) reduction gave the *E*-allylic alcohol **4**.[11] Katsuki-Sharpless catalytic asymmetric epoxidation[12] of **4** led to the enantiomerically pure epoxide **5**, mp 67-68 °C; $[\alpha]^{17}_D$ −17.3° (*c* 0.66, $CHCl_3$), which, upon Red-Al® reduction followed by pivaloylation, gave the monopivalate **6**, $[\alpha]^{20}_D$ +4.3° (*c* 1.00, $CHCl_3$). After silylation of **6**, the corresponding trimethylsilyl ether was subjected to TMSOTf catalyzed reductive etherification with benzaldehyde in the presence of triethylsilane according to the method which we have recently developed.[13] In this case, concomitant cleavage of the *p*-methoxybenzyl protecting group also

occurred along with the reductive benzylation and the alcohol **7**, $[\alpha]^{16}_D$ +14.7° (*c* 1.02, $CHCl_3$), was obtained directly. After Swern oxidation of **7**, the corresponding aldehyde was then allowed to react with 1-trimethylsilylbuta-2,3-diene (**8**) using $TiCl_4$ as catalyst in CH_2Cl_2 at –78 °C.[9] The reaction turned out to take place with excellent diastereoselectivity (94% de)[14] to give the dienol **9**, $[\alpha]^{27}_D$ +29.4° (*c* 1.00, $CHCl_3$). $VO(acac)_2$ mediated epoxidation[15] of **9** was also found to proceed with high diastereoselectivity (98% de)[14] to give the epoxy alcohol **10**, $[\alpha]^{25}_D$ –11.5° (*c* 1.00, $CHCl_3$). At this stage stereoselective introduction of a nitrogen atom at the quaternary center was achieved by taking advantage of Lewis acid catalyzed cyclization of an epoxytrichloroacetimidate.[6] Thus, the epoxy alcohol **10** was converted into the epoxytrichloroacetimidate **11**, $[\alpha]^{24}_D$ –10.7° (*c* 1.00, $CHCl_3$), by the reaction with trichloroacetonitrile in the presence of a catalytic amount of DBU.[16] Upon treatment of **11** with 0.5 equivalent of Et_2AlCl[17] in CH_2Cl_2 at room temperature, the cyclization took place at the quaternary center of the epoxide with complete inversion of the stereochemistry to produce the oxazoline **12**,[18] $[\alpha]^{21}_D$ –21.5° (*c* 1.00, $CHCl_3$), exclusively. Acid hydrolysis of **12** gave the trichloroacetamide **13**, $[\alpha]^{25}_D$ –14.5° (*c* 0.99, $CHCl_3$), quantitatively. Sequential acetonide formation, ozonolysis, $NaClO_2$ oxidation,[19] and esterification allowed conversion of **13** into the methyl ester **14**, $[\alpha]^{26}_D$ +19.9° (*c* 1.00, $CHCl_3$), in excellent overall yield. Selective removal of the pivaloyl group of **14** under basic methanolytic conditions followed by Swern oxidation afforded the aldehyde **15**.



Scheme 1. (a) *p*-(MeO)$C_6H_4CH_2Cl$, pulverised KOH, DMSO; (b) Red-Al®, Et_2O, –25 °C; (c) diisopropyl L-tartrate (0.09 equiv), $Ti(O\text{-}i\text{-}Pr)_4$ (0.07 equiv), *t*-BuOOH (2 equiv), 4 Å molecular sieves, CH_2Cl_2, –30 °C; (d) Red-Al®, THF, –30 °C; (e) *t*-BuCOCl, pyridine, CH_2Cl_2; (f) Me_3SiCl, Et_3N, THF; (g) PhCHO (1.1 equiv), Et_3SiH (1.1 equiv), TMSOTf (0.5 equiv), CH_2Cl_2, –35 °C; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 to 25 °C; (i) **8** (2.5 equiv), $TiCl_4$ (1.2 equiv), CH_2Cl_2, –78 °C; (j) $VO(acac)_2$ (0.08 equiv), *t*-BuOOH (2 equiv), CH_2Cl_2, –25 °C; (k) CCl_3CN, DBU (catalyst), 4 Å molecular sieves, CH_2Cl_2, –20 °C; (l) 1M Et_2AlCl in *n*-hexane (0.5 equiv), CH_2Cl_2; (m) 1M HCl, THF; (n) $(MeO)_2CMe_2$, *p*-TsOH·H_2O (catalyst), CH_2Cl_2; (o) O_3, CH_2Cl_2, –78 °C, then Me_2S; (p) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH-H_2O (4:1); (q) CH_2N_2, Et_2O, (r) NaOMe , MeOH; (s) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –60 to 25 °C.

With the required key synthetic precursor **15** in hand, we then investigated its union to the C-14 long chain. Thus, Wittig reaction of **15** with the ylide, generated from **16**[7c] by the action of *n*-butyllithium, was conducted in THF at –78 °C to give the olefin **17** and **18** each as an inseparable 92:8 *Z/E*-mixture.[14] Unexpected dechlorination giving **18** possibly occurred through nucleophilic attack of the yilide to the chlorine atom of the trichloroacetyl group of **17**. The production of **18** was not serious problem, however, because both **17** and **18** were converted into the lactone **19** respectively in the same overall yield by a four-step sequence involving saponification,[20] Birch reduction, acid hydrolysis, and acetylation. Photo-isomerization of the olefinic double bond of **19** was carried out at this stage leading to a 16:84 *Z/E*-mixture[14] and the desired *E*-isomer **20**, $[\alpha]^{23}_D$ +52.5° (*c* 0.85, $CHCl_3$){lit.[2] $[\alpha]^{24}_D$ +57° (*c* 1, $CHCl_3$)}, was obtained in a pure form[21] after purification by $AgNO_3$-SiO_2 column chromatography. Finally, saponification of **20** followed by neutralization using Amberlite® IRC-76 furnished (+)-myriocin (**1**). The synthetic substance, mp 176-178 °C (lit.[1] mp 180-181 °C); $[\alpha]^{20}_D$ +6.1° (*c* 0.26, DMSO) {lit.[3] $[\alpha]_D$ +4.7° (*c* 0.60, DMSO)}, was identical with natural myriocin by spectroscopic (^1H and ^{13}C NMR,[22] IR, MS) and chromatographic comparisons.



Scheme 2. (a) **16**, 1.57M *n*-BuLi in *n*-hexane, THF, –78 °C; (b) 3% NaOH-MeOH (1:1), reflux; (c) Li, THF, liq. NH_3, –33 °C; (d) 2M HCl-MeOH (3:2); (e) Ac_2O, DMAP (catalyst), pyridine; (f) hν, PhSSPh, benzene; (g) 10% NaOH-MeOH (1:1), reflux, then neutralized with Amberlite® IRC-76.

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(17) Upon treatment of **11** with 0.5 equivalent of $BF_3{\cdot}Et_2O$ at –20 °C in CH_2Cl_2, an 1:1 mixture of **12** and **13** was obtained in 81% yield.

(18) The stereochemistry was confirmed by NOE experiments (500 MHz ^{1}H NMR). Significant NOEs were observed between the olefinic methine proton and the proton of CH bearing the benzyloxy group and between the methylene protons of the hydroxymethyl group and the methine proton of the oxazole ring.

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(20) Birch reduction without saponification caused also reduction of the methyl ester.

(21) ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7 (s), 172.4 (s), 170.2 (s), 169.5 (s), 169.0 (s), 135.1 (d), 123.2 (d), 81.5 (d), 72.0 (d), 62.8 (t), 62.6 (s), 42.9 (t), 42.8 (t), 32.5 (t), 32.2 (t), 31.6 (t), 29.1 (t), 29.0 (t), 29.0 (t), 28.9 (t), 23.9 (t), 23.8 (t), 22.8 (q), 22.5 (t), 20.6 (q), 20.4 (q), 14.1 (q).

(22) ^{13}C NMR (125 MHz, CD_3OD) δ 214.4 (s), 173.4 (s), 134.7 (d), 126.8 (d), 73.7 (d), 71.3 (s), 70.4 (d), 65.1 (t), 43.5 (t), 43.5 (t), 38.7 (t), 33.7 (t), 32.8 (t), 30.4 (t), 30.2 (t), 30.1 (t), 30.0 (t), 24.9 (t), 23.6 (t), 14.4 (q).

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