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Total Synthesis of (-)-Verrucarol, a Component of Naturally Occurring Verrucarin A

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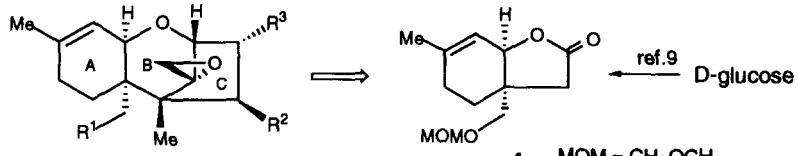
This paper is dedicated to Professor Dieter Seebach on the occasion of his 60th birthday.

Abstract: Total synthesis of (-)-verrucarol (**1**) was achieved starting from D-glucose-derived bicyclic lactone **4** through 1) a stereoselective asymmetric quaternization of the α-carbon of the lactone, 2) Dieckmann cyclization for access to the C-ring equivalent, 3) a skeletal rearrangement for the trichothecene ring system, and 4) the final stereoselective epoxidation of an *exo*-methylene group.

During the past two decades, the trichothecene family of sesquiterpenoid natural products has attracted the attention of synthetic chemists owing to their unique structure and significant biological activity.[2] (-)-Verrucarol (**1**) (Figure 1) was characterized as an alkaline hydrolyzate of natural antifungal and cytostatic antibiotic verrucarin A by Tamm and co-workers more than thirty years ago.[3,4] As other structurally related natural products, calonectrin (**2**) and anguidine (**3**) are known. Because of their potent biological properties and highly functionalized tricyclic skeletons, synthetic methods for these three sesquiterpenoids have been extensively explored so far.[5] Most total syntheses and synthetic endeavors were achieved in racemic fashion for **1**[6] and **2**,[7] although a few enantioselective total syntheses exemplified by that of **3** were reported.[8] Here we disclose a total synthesis of **1** as the naturally derived enantiomer. We have accomplished our total synthesis of **1** starting from the previously reported bicyclic γ-lactone **4**, which was prepared from D-glucose.[9]



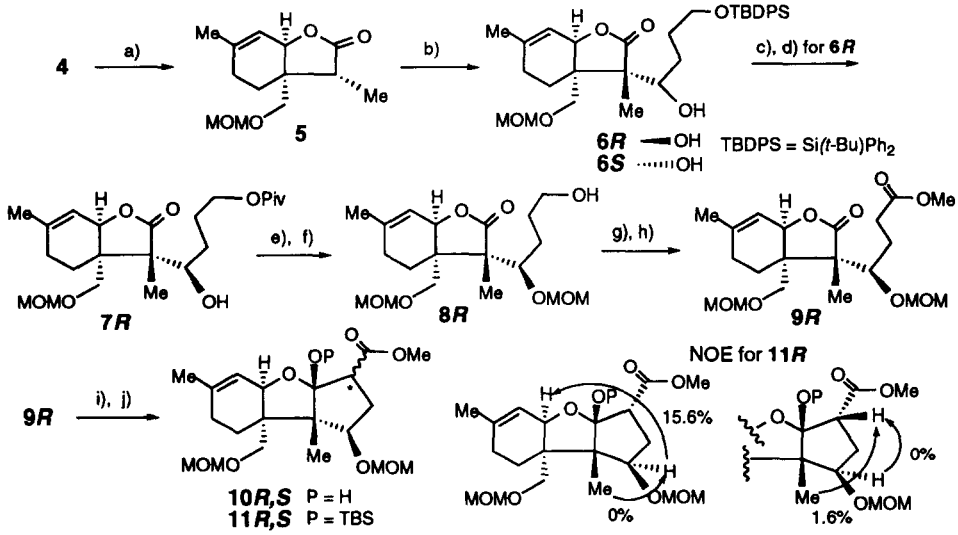
verrucarol (1) : R^1 = OH, R^2 = OH, R^3 = H
calonectrin (2) : R^1 = OAc, R^2 = H, R^3 = OAc
anguidine (3) : R^1 = OAc, R^2 = OAc, R^3 = OH

Figure 1

At the outset, the highly stereoselective asymmetric quaternization of the α-carbon of the γ-lactone **4**, a crucial issue of the C-ring construction, was achieved as follows (Scheme 1). Deprotonation of **4** with LDA which, followed by addition of MeI, provided the α-methylated product **5**[10] essentially as a single product. The second carbon-carbon bond formation was carried out using 4-*O*-(*tert*-butyldiphenylsilyloxy)butanal as an electrophile, providing **6*S*** and **6*R*** as a separable mixture (ca. 1:1) quantitatively. Although the attacks of both electrophiles occurred exclusively from the less hindered convex face of the generated bicyclic enolate as

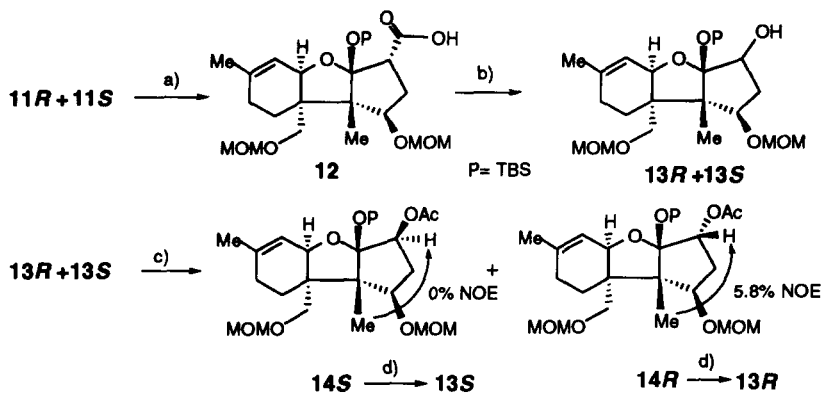
anticipated, we were not able to optimize reaction conditions for the stereocontrolled introduction of the carbinol center in the side chain.[11] Of the two diastereomers, the **6*R*** isomer was required for the verrucarol synthesis.[12,13] The following conventional six-reaction sequence to modify the side chain in the separated **6*R*** provided ester-lactone **9*R*** via **7*R*** and **8*R***. The directed Dieckmann cyclization of **9*R*** was only achieved when potassium bis(trimethylsily)amide (KHMDS) was used as a base. The desired cyclized product **10** was obtained as an inseparable diastermeric mixture (**10*R*:10*S*** = ca. 5:4, ^{1}H NMR analysis) regarding the α-carbon of the ester group.[14] The hemiketal hydroxyl groups in the mixture **10** were protected as the *tert*-butyldimethylsilyl (TBS) ethers **11**. These silyl ethers could be cleanly separated by silica-gel chromatography, and the structure of the (*R*)-isomer **11*R*** was confirmed based on the difference NOE experiments as depicted in Scheme 1. Both **11*R*** and **11*S*** (or the mixture of them) were saponified separately to the same diastereomerically homogeneous carboxylic acid **12** (Scheme 2). The structure of **12** was tentatively assigned as the α-oriented isomer, but was not confirmed. Subjection of **12** to the Barton-Crich's radically induced decarboxylative oxygenation reaction[15] provided two hydroxylated products **13*R*** and **13*S*** as an inseparable 1:1 mixture.[16] Acetylation of the mixture gave readily separable **14*S*** and **14*R***, whose stereochemistries were determined based on their difference NOE experiments. Diastereomerically homogeneous **13*S*** and **14*S*** were obtained by respective Dibal-H reduction of the separated acetates **14*S*** and **14*R***.

For the construction of the B/C ring system of the trichothecene framework, we expected that the ring enlargement strategy, originally disclosed by Trost and McDougal,[6b] could be workable in our case. In fact, when the mesylate **15** from the β-isomer **13*S*** was subjected to usual desilylation conditions with tetrabutylammonium fluoride (TBAF), ring enlargement occurred spontaneously to afford **16** exclusively as depicted in Scheme 3. On the contrary, the TBAF treatment of the α-mesylate, prepared from **13*R***, did not undergo



Reagents and conditions: a) LDA, MeI-THF, -78 °C (96%); b) LDA, 4-*O*-(*tert*-butyldiphenylsilyloxy)butanal-THF:toluene (1:1), -78 °C, then separation (**6*S*:6*R*** = 1:1, each 50%); c) Bu_4NF-THF; d) PivCl-pyr.; e) MOMCl, *i*-Pr_2NEt-$CHCl_3$, reflux; f) NaOMe-MeOH (for **8*R***, 58% from **6*R***); g) Jones' reagent-acetone, 0 °C; h) CH_2N_2-Et_2O/$CHCl_3$, 0 °C (72%); i) KHMDS-THF, -78 °C (**10*R*:10*S*** = ca. 5:4, 82% combined yield); j) TBSOTf, 2,6-lutidine-CH_2Cl_2, 0 °C (75% combined yield of **11*R*** and **11*S***).

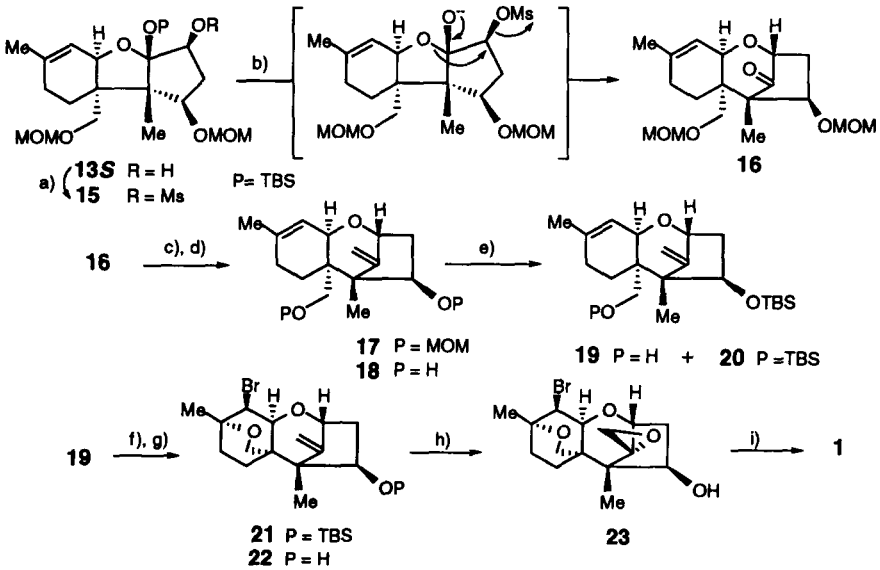
Scheme 1



Reagents and conditions: a) 4M KOH- aq. MeOH, 80 °C (81%); b) WSC, 4-DMAP, N-hydroxypyridine-2-thione, *tert*-BuSH, O_2-CH_2Cl_2 (84% as a 1:1 mixture of **13*R*** and **13*S***) ; c) Ac_2O-pyr., and separation (43% for **14*S*** and 54% for **14*R***) ; d) Dibal-H-CH_2Cl_2, -78 °C (quant. for **13*S*** and 99% for **13*R***).

Scheme 2

the ring enlargement reaction. For this skeletal transformation, the antiperiplanar alignment of the mesyloxy group and the migrated C-O bond is crucial.[17] The remaining task for the total synthesis of **1** was the stereoselective epoxidation of the *exo*-methylene derivative **17**, which was prepared by the usual Wittig methylenation of **16**. Thus, the MOM groups in **17** were deprotected with bromotrimethylsilane. The resulting diol **18** was known to be 12,13-deoxyverrucarol, an alkaline hydrolyzate of naturally occurring verrucarin K,[18] and the spectral comparison of **18** to those of the reported data verified their identity [$[\alpha]_D$ -93 for **18** and $[\alpha]_D$ -98 for the reported product]. The hydroxy groups in **18** were then silylated to give



Reagents and conditions: a) MsCl-pyr. (99%); b) Bu_4NF-THF (98%); c) $Ph_3P{=}CH_2$-THF, 60 °C (73%); d) TMSBr, MS4A-CH_2Cl_2, -30 °C (78%); e) TBSOTf, 2,6-lutidine-CH_2Cl_2, -78 °C to rt (40% for **19** and 39% for **20**); f) NBS-wet acetone, 0 °C (94%); g) Bu_4NF-THF (96%); h) *m*-CPBA, $NaHCO_3$-CH_2Cl_2 (91%); i) Zn-Ag-THF:EtOH=5:1, reflux (81%).

Scheme 3

a mixture of mono- **19** and di-*O*-silyl ethers **20**. We could not find a practical procedure for the preferential protection of the primary hydroxyl group. Thus, the primary hydroxyl group and the double bond in the A ring were simultaneously protected as the bromo-ether **21**.[6a,c] The silyl group in **21** was deprotected to give **22**.[19] The hydroxyl-directed epoxidation of **22** with *m*-CPBA afforded **23** as a single product.[6a,c] Finally, the double bond in the A-ring was regenerated by the Zn-Ag reduction of the bromo-ether part in **23**, providing (-)-verrucarol **1**. The synthetic **1** was completely identical to a naturally derived specimen [mp, TLC, IR, ^{1}H and ^{13}C NMR) [$[\alpha]_D$ -40.6 for the synthetic **1**, and $[\alpha]_D$ -39.2 for the naturally derived product].

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10. All new compounds shown in Schemes 1-3 were fully characterized by spectroscopic means (IR, ^{1}H and ^{13}C NMR), and their elemental compositions were confirmed by high-resolution mass spectra except some nonvolatile intermediates.
11. We expected that this aldol-type reaction would proceed favorably through the attack of the enolate to *Si*-face of the aldehyde group leading to the desired **6*R*** predominantly because of its less steric interaction between aldehyde and the bridgehaed $MOMCH_2$ group.
12. We could not determine the stereochemistries of the carbiol carbons in **6*R*** and **6*S*** unambiguously at this stage. That of the desired isomer **6*R*** was determined by the NOE experiments of **11*R***.
13. The undesired **6*S*** was converted into **6*R*** by means of an oxidation-reduction strategy, i.e., 1) PCC, then 2) $NaBH_4$-MeOH, in an overall yield of 74% (13% of **6*S*** was also obtained).
14. We examined the Dieckmann cyclization of **9*S*** (not shown), which was prepared from **6*S*** by the same reaction sequence used for **6*R*** in an overall yield of 48%. Under the same reaction conditions used for **9*R***, **9*S*** was recovered intact. We do not have any explanation for this difference in the reactivity between **9*R*** and **9*S***.
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16. By the nature of the *cis*-fused right-hand bicyclic ring system in **12**, we hoped the attack of O_2 to the methylene radical would proceed from the convex face leading to **13*S*** favorably.
17. On the other hand, we found the stereoselective inversion at the hydroxy bearing carbon of **13*R*** to the required **13*S***. Thus, PDC oxidation of **13*R*** gave ketone, which was stereoselectively reduced with Dibal-H in CH_2Cl_2 at -78 °C. More than 10:1 diastereomeric mixture (^{1}H NMR analysis) of **13*S*** and **13*R*** was obtained in 68% combined yield. This mixture was separated as the corresponding acetates.
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19. One-step derivatization of **18** to the bromo-ether **22** was also achieved in 58% yield using the NBS-wet acetone conditions.

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