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Synthetic Study on Antitumor Antibiotic Terpentecin: Construction of the Carbobicyclic Decalin Moiety

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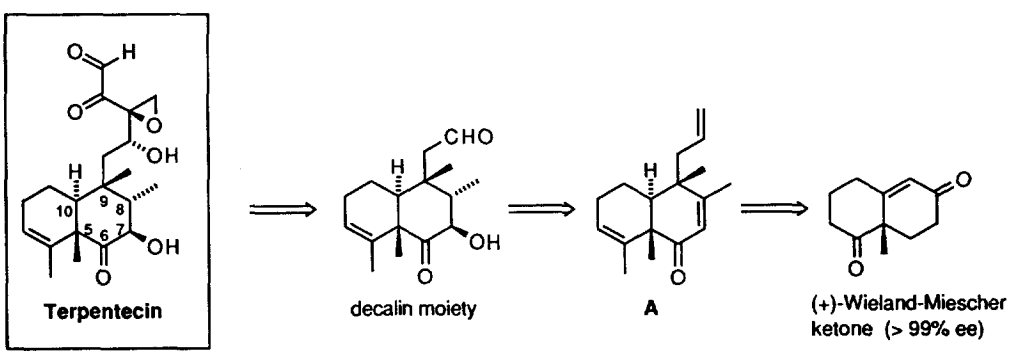
Abstract: Carbobicyclic decalin moiety of antitumor terpentecin is prepared in a stereoselective manner from (+)-Wieland-Miescher ketone *via* reductive alkylation and Birch reduction. © 1997 Elsevier Science Ltd.

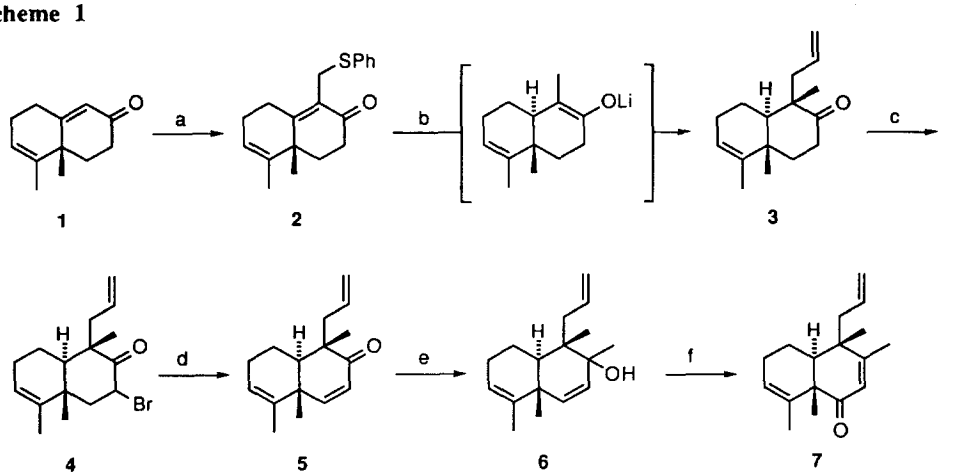
Terpentecin is a clerodane family antibiotic[1] which exhibits significant antitumor activity through topoisomerase II mediated DNA cleavage.[2] Quite different from other topo poisons,[3] these antibiotics do not contain any aromatic heterocycles. Instead, they have a highly oxidated sidechain which is thought to be responsible for their antitumor activity. Recently, we reported a stereoselective route to the sidechain moiety.[4] Subsequently, we wish to describe here a synthesis of the carbobicyclic decalin moiety toward a total synthesis.

Structural features of the decalin moiety of terpentecin are five contiguous chiral centers and *trans* configuration of dimethyls at C8 and C9. Particularly, 8,9-*trans* stereochemistry is very rare in clerodane family diterpenes.[5] In spite of extensive synthetic studies on clerodane diterpenoids, there has been only a few reports concerning the construction of 8,9-*trans*-dimethylclerodane skeleton.[6] In the present investigation we could construct the decalin moiety in a stereoselective manner featuring (1) reductive alkylation of enone derived from (+)-Wieland-Miescher ketone[7] and (2) Birch reduction of enone **A**.



Enone **1** possessing the endocyclic double bond was prepared from enantiomerically pure (+)-Wieland-Miescher ketone by the known four steps procedure.[8] Introduction of (phenylthio)methyl group to C9 gave **2**[9] in 77% yield.[10] As anticipated, reductive alkylation of **2** employing the method of Smith and co-workers[11] proceeded stereoselectively to give *trans*-decalone **3** in 78% yield along with 7% of diallylated product (not shown). In this case, allyl bromide must be added as rapidly as possible to a solution of lithium enolate prepared with lithium in liquid ammonia and THF. Slow addition was found to increase the amount of undesirable diallylated product. In order to rearrange the carbonyl group at C8 to C6, the following transformation was carried out. Decalone **3** was converted into monobromide **4** followed by dehydrobromination to afford enone **5** in 52% overall yield. Addition of methyl lithium to **5** gave 1,2-adduct **6** as a diastereomeric mixture (10:1 ratio) in 92% yield. Treatment of the tertiary allyl alcohol **6** with pyridinium chlorochromate gave transposed enone **7** in 85% yield.

Scheme 1

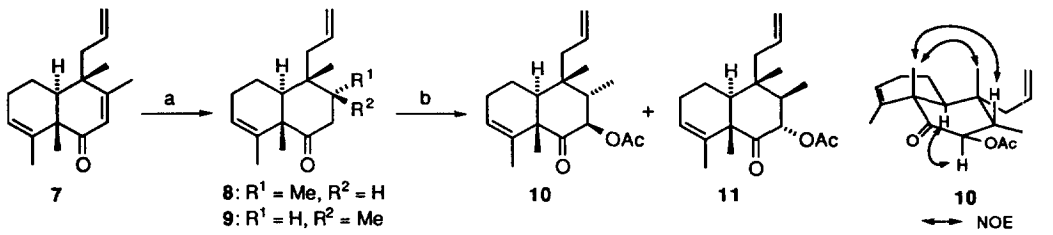


Reagents and Conditions: **a** aq. HCHO, PhSH, Et_3N, EtOH, 75 °C, 77%; **b** Li, H_2O, liq. NH_3, THF, allyl bromide, -78 °C, 78%; **c** LiHMDS, NBS, THF, -78 °C, 67%; **d** LiBr, Li_2CO_3, DMF, reflux, 78%; **e** MeLi, Et_2O, 0 °C, 92%; **f** PCC, MS-3A, CH_2Cl_2, 85%.

Construction of 8,9-*trans* stereochemistry was indeed most difficult in the present study. After a systematic survey of reducing reagents,[12] we found that Birch reduction of **7** gave predominantly the desired 8,9-*trans* **8**.[13] In our initial conditions (Li, *t*-BuOH, liq. NH_3, THF, -78 °C), 8,9-*trans* **8** and 8,9-*cis* **9** were obtained as *ca.* 1:1 inseparable mixture. However, when the reduction was carried out in the absence of proton source at -33 °C, the stereoselectivity of the reaction was improved to *ca.* 3:1 (*trans*:*cis*). Since overreduction of the resulting ketones to the corresponding alcohols was observed in some extent during Birch reduction, the mixture was subjected to Dess-Martin oxidation[14] to obtain **8** and **9** in 70% combined yield. Installation of hydroxyl group into C7 was stereoselectively achieved. Thus, potassium enolate of the mixture of **8** and **9** was oxidized with 2-(benzenesulfonyl)-3-phenyloxaziridine,[15] and the crude α-hydroxy ketones were acetylated to isolate acetates **10** and **11** in 52% and 7% yields, respectively. The structure of the major product **10** was unambiguously confirmed by the ^1H NMR analysis and NOE experiments. A large coupling constant between H7 and H8 (J = 13.9 Hz) was observed. Also, NOEs were observed between H7 and H10

(15.9%), CH_3-5 and H8 (7.6%), and CH_3-5 and CH_3-9 (1.6%). These results indicated that the cyclohexanone ring of **10** took a boat form.[1b]

Scheme 2

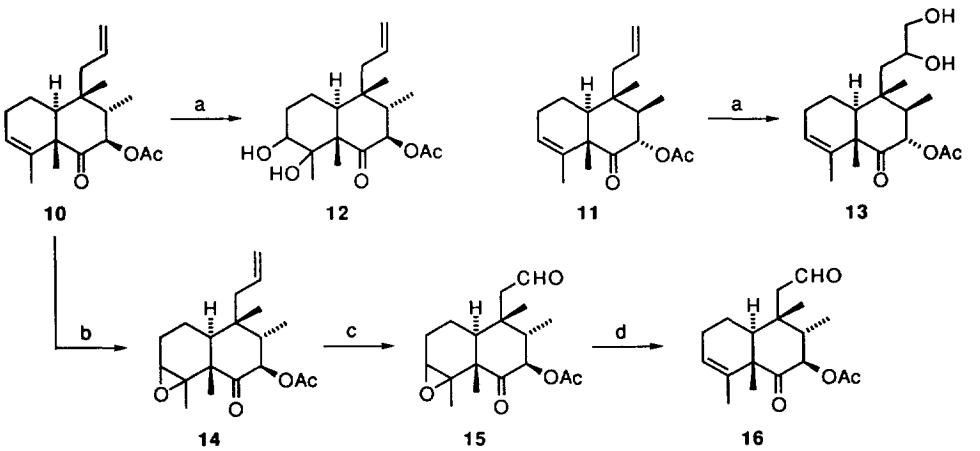


7 8: R^1 = Me, R^2 = H 9: R^1 = H, R^2 = Me 10 11 10

Reagents and Conditions: **a** i) Li, liq. NH_3, THF, -33 °C; ii) Dess-Martin periodinane, CH_2Cl_2, 70%; **b** i) KHMDS, oxaziridine deriv., THF, -78 °C; ii) Ac_2O, pyridine, **10** 52%, **11** 7%.

Having established the construction of the five contiguous asymmetric centers, we next examined the transformation of the vinyl group of **10** into formyl group. We initially expected that dihydroxylation of the double bond at side chain is faster than that of the endocyclic double bond considering the steric environment. However, careful treatment of **10** with osmium tetroxide and trimethylamine *N*-oxide resulted in the exclusive formation **12** (50%). On the other hand, similar treatment of 8,9-*cis* **11** gave diol **13** in 65% yield. A number of other co-oxidizing reagents were surveyed, but they all failed to exhibit the desired chemoselectivity in the case of **10**. Therefore, **10** was temporarily converted into epoxide **14** with *m*-chloroperbenzoic acid as a diastereomeric mixture (3:1 ratio) in 99% yield. Ozonolysis of the vinyl group in **14** followed by reductive workup gave quantitatively aldehyde **15**, which was subjected to deoxygenation with triphenylphosphine and iodine to obtain the endocyclic olefin **16** in 52% yield.[16]

Scheme 3



10 12 11 13 14 15 16

Reagents and Conditions: **a** OsO_4, TMNO, aq. acetone, 50% for **12**, 65% for **13**; **b** mCPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, 99%; **c** O_3 then PPh_3, CH_2Cl_2, -78 °C, quant.; **d** PPh_3, I_2, CH_2Cl_2, 52%.

In conclusion, we could develop a stereoselective route to the carbobicyclic decalin moiety of terpentecin starting from (+)-Wieland-Miescher ketone. Five contiguous asymmetric center was constructed by reductive alkylation of enone **2**, Birch reduction of **7**, and stereoselective hydroxylation of ketone **8**. We are currently investigating the total synthesis of terpentecin.[17]

References and Notes

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9. All new compounds were fully characterized by ^{1}H NMR (270 MHz) and IR spectra, and satisfactory high-resolution MS was obtained for them. Selected data are as follows: **3**: $[\alpha]^{22}_D$ +98.5° (*c* 0.920, $CHCl_3$); ^{1}H NMR δ 1.07 (6 H, s), 1.42-1.69 (4 H, m), 1.62 (3 H, br s), 1.92-2.12 (4 H, m), 2.38-2.61 (3 H, m), 4.96-5.05 (2 H, m), 5.29 (1 H, br), 5.56-5.72 (1 H, m); HRMS calcd for $C_{16}H_{24}O$ (M^+) *m/z* 232.1826, found 232.1827. **10**: $[\alpha]^{22}_D$ -24.9° (*c* 2.01, $CHCl_3$); ^{1}H NMR δ 1.01 (3 H, s), 1.07 (3 H, d, *J* = 7.3 Hz), 1.36 (3 H, s), 1.57-1.76 (2 H, m), 1.75 (3 H, br s), 1.96-2.09 (3 H, m), 2.19 (3 H, s), 2.20 (2 H, d, *J* = 7.3 Hz), 2.38 (1 H, dd, *J* = 12.0, 2.1 Hz), 5.06-5.17 (2 H, m), 5.34 (1 H, br), 5.36 (1 H, d, *J* = 13.9 Hz), 5.91-6.07 (1 H, m); HRMS calcd for $C_{19}H_{28}O_3$ (M^+) *m/z* 304.2039, found 304.2029. **11**: $[\alpha]^{22}_D$ +42° (*c* 0.23, $CHCl_3$); ^{1}H NMR δ 1.04 (3 H, d, *J* = 6.6 Hz), 1.06 (3 H, s), 1.50 (3 H, s), 1.55-1.75 (3 H, m), 1.79 (3 H, br s), 1.96-2.22 (5 H, m), 2.17 (3 H, s), 4.97-5.07 (2 H, m), 5.32 (1 H, d, *J* = 12.2 Hz), 5.37 (1 H, br), 5.52-5.65 (1 H, m); HRMS calcd for $C_{19}H_{28}O_3$ (M^+) *m/z* 304.2039, found 304.2040. **16**: $[\alpha]^{22}_D$ -29° (*c* 0.70, $CHCl_3$); ^{1}H NMR δ 1.04 (3 H, d, *J* = 6.9 Hz), 1.19 (3 H, s), 1.37 (3 H, s), 1.57-1.73 (2 H, m), 1.74 (3 H, br s), 2.03-2.18 (3 H, m), 2.19 (3 H, s), 2.32 (1 H, dd, *J* = 11.2, 3.3 Hz), 2.43 (1 H, dd, *J* = 15.2, 2.8 Hz), 2.56 (1 H, dd, *J* = 15.2, 2.8 Hz), 5.34 (1 H, br), 5.44 (1 H, d, *J* = 13.5 Hz), 9.96 (1 H, t, *J* = 2.8 Hz); HRMS calcd for $C_{18}H_{26}O_4$ (M^+) *m/z* 306.1831, found 306.1829.
10. The clerodane numbering system is used throughout.
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12. In our model study, we found palladium-catalyzed hydrogenation of enone, possessing ethyl group instead of allyl group in **7**, gave predominantly the undesired 8,9-*cis* derivative (*trans*:*cis* = *ca.* 1:10). In addition, several 1,4-hydride reductions such as ($LiAlH_4$, CuI, THF), (*n*-Bu_3SnH, AIBN, toluene, reflux), and (*n*-Bu_3SnH, $Pd(PPh_3)_4$, $ZnCl_2$, THF) of the enone did not proceed.
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