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Total Synthesis of Phenazinomycin and Its Enantiomer *via* High-Pressure Reaction

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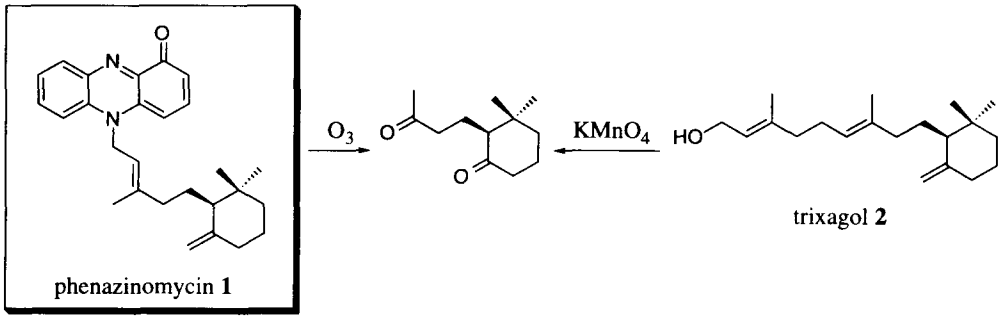
Abstract: *Total synthesis of phenazinomycin, a rare type of phenazine antibiotic, was achieved by using high pressure reaction. Chiral sesquiterpene moiety in the side chain was synthesized employing (S)-3-hydroxy-2,2-dimethylcyclohexanone as a chiral source.* © 1997 Elsevier Science Ltd.

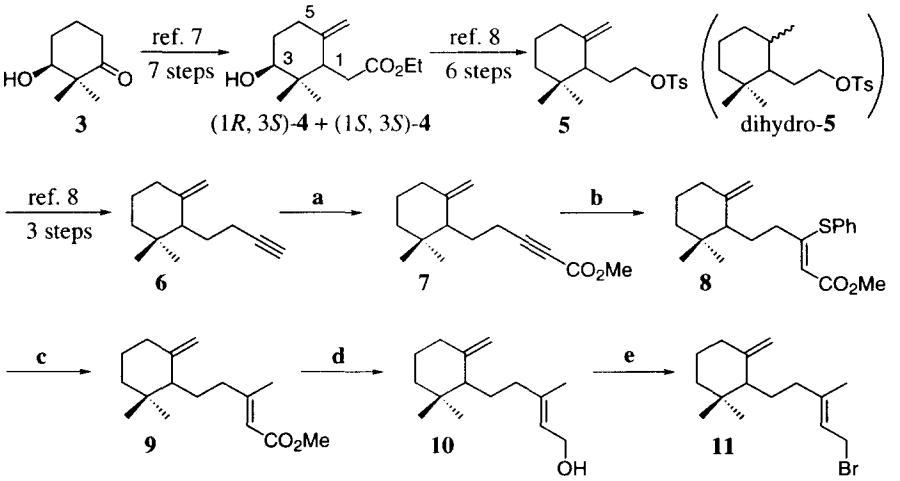
Phenazinomycin **1** was isolated from the cultural mycelium of *Streptomyces* sp. WK-2057 by Omura and co-workers, and its absolute configuration was also determined by comparing the degradation product of **1** with that of trixagol **2**, a naturally occurring diterpenoid.[1, 2] This substance possesses antitumor activity against experimental murine tumors *in vivo*, cytotoxic activity against adriamycin-resistant P388 leukemia cells and so on.[1] So far, various types of phenazine antibiotics were isolated as biologically active compounds, but most of them were *C*-substituted ones except a few examples such as **1** and lavanducyanin[3] (WS-9659[4]).



We were interested in their unique structures which comprise a 5-*N*-alkylated phenazin-1-one moiety and accomplished construction of the skeleton *via* a high-pressure reaction as shown in our earlier paper.[5] Herein we report enantioselective synthesis of **1** and its enantiomer *via* a similar strategy.

At first, to obtain optically active allylic alcohol **10**, we prepared hydroxy esters (1*R*,3*S*)-**4** and (1*S*,3*S*)-**4** from hydroxy ketone **3** (97.3% ee)[6] as reported by Suzuki and Mori.[7] We then executed experiments with (1*S*,3*S*)-**4** to establish the synthetic route to **10**. The hydroxy ester (1*S*,3*S*)-**4** was converted to enyne (*S*)-**6** through tosylate (*S*)-**5** by the Tamura and Mori method.[8] Next, it was necessary to elongate the carbon chain. We initially attempted the C3 extension and treated (*S*)-**5** with LiC≡CCH$_2$OTHP, followed by *p*-TsOH in methanol. But we could not separate the desired product from a by-product originated from dihydro-**5**.[8] So we

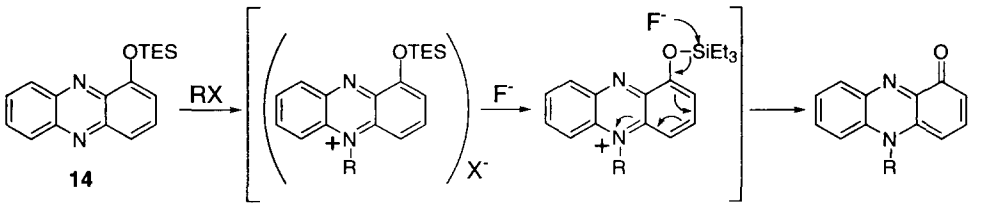
employed a stepwise C2+C1 process and, thus, reaction of lithium acetylide of (*S*)-**6** with methyl chloroformate gave (*S*)-**7** in good yield. Addition of thiophenoxide to (*S*)-**7**, followed by treating with MeMgI in the presence of CuI in THF afforded the desired (*Z*)-olefin (*S*)-**8**.[9] Finally, the desired allylic alcohol (*S*)-**10** was obtained by DIBAL reduction. Similarly, (1*R*,3*S*)-**4** was converted to allylic alcohol (*R*)-**10**.



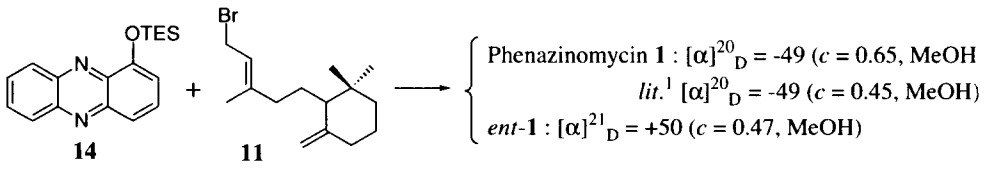
Reagents and Conditions

a) *n*-BuLi / THF ; $ClCO_2Me$, -70°C (*R*: 80%, *S*: 96%), b) PhSH, NaOH / MeOH, ice-cooled
c) MeMgI-CuI / THF, -70°C (*R*: 53%, *S*: 66% from **7**), d) DIBAL / toluene, ice-cooled (*R*: 90% *S*: 82%), e) *n*-BuLi, Ph_3CH / THF-HMPA ; TsCl ; LiBr, ice-cooled.

In our efforts to construct this rare type of compound, we attempted the reaction (see the scheme shown below) under various condition, and geranylated adduct **12** and farnesylated adduct **13** were obtained only under high-pressure condition in 20% and 11% yield, respectively.[10]



It was thus ascertained that a high-pressure reaction was applicable to higher homologues of alkyl halide. Indeed, high-pressure reaction of allylic bromide **11**, obtained from **10** by the method of Stork *et al.*,[11] with 1-triethylsilyloxyphenazine **14**[5] in freshly distilled CH_2Cl_2 (12 kbar for **1**, 14 kbar for *ent*-**1**, 23h, rt) gave ammonium salt which, without isolation, was treated with tris(dimethylaminosulfur) (trimethylsilyl)difluoride (TASF)[5] to afford phenazinomycin **1** [20% from (*R*)-**10**] or *ent*-**1** [20% from (*S*)-**10**]. Synthetic phenazinomycin **1** was identical to the natural product in all respects.[12, 13]



Reagent and Conditions
high pressure (*R*: 12 kbar, *S*: 14 kbar) / CH_2Cl_2, rt ; TASF / CH_2Cl_2, rt (*R*: 20%, *S*: 20% from **10**)

In conclusion, we accomplished the synthesis of both enantiomers of phenazinomycin, an antitumor 5-*N*-alkylphenazinone antibiotic, *via* simple *N*-alkylation under a high-pressure condition. Synthesis of various types of *N*-alkylphenazinones *via* this efficient process is in progress and the details, including the synthesis of lavanducyanin and phenazinomycin, will be soon reported in a full account. Biological activities of all these analogues are now under investigation and will be reported elsewhere.

Acknowledgments

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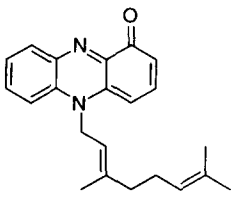
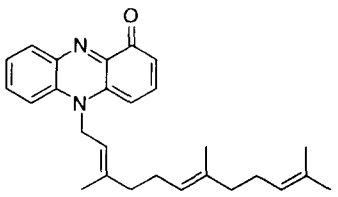
10. The structures of geranyl derivative **1 2** and *trans, trans*-farnesyl derivative **1 3** are shown below.



12



13

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12. Siganls of ^1H on phenazine skeletal carbons are broadened in CD_3OD.

    ^1H NMR data of **1**

    $\underline{CD_3OD, 500\ MHz}$ δ = 0.78 (3H, s), 0.84 (3H, s), 1.15 (2H, m), 1.44-1.55 (4H, m), 1.65 (1H, m), 1.78-2.12 (4H, m), 2.00 (3H, s), 4.38 (1H,s), 4.65 (1H, s), 5.15 (1H, s), 5.36 (2H, s), 6.44 (1H, d-like), 6.63 (1H, d-like), 7.73 (1H, t-like), 7.94 (2H, d-like), 8.04 (1H, br), 8.38 (1H, br)

    $\underline{CDCl_3, 500\ MHz}$ δ = 0.81 (3H, s), 0.88 (3H, s), 1.18 (1H, m), 1.42-1.67 (5H, m), 1.82-2.10 (5H, m), 1.94 (3H, s), 4.46 (1H, d, *J* = 2.4 Hz), 4.71 (1H, t-like), 4.90 (2H, d, *J* = 5.5 Hz), 5.11 (1H, td-like), 5.85 (1H, d, *J* = 7.6 Hz), 6.56 (1H, dd, *J* = 9.5, 0.9 Hz), 7.42 (1H, d, *J* = 8.5 Hz), 7.47 (1H, ddd, *J* = 8.2, 7.0, 1.2 Hz), 7.60 (1H, dd, *J* = 9.5, 7.5 Hz), 7.76 (1H, ddd, *J* = 8.5, 7.0, 1.5 Hz), 8.36 (1H, dd, *J* = 8.2, 1.5 Hz)

    lit.[1] $\underline{CD_3OD, 300\ MHz}$ δ = 0.78 (3H, s), 0.84 (3H, s), 1.28 (2H, m), 1.48 (2H, m), 1.57 (2H, m), 1.65 (1H, m), 1.90 (2H, m), 1.98 (2H, m), 2.00 (3H, s), 4.39 (1H,s), 4.66 (1H, s), 5.14 (1H, t, *J* = 5.2 Hz), 5.32 (2H, d, *J* = 5.2 Hz), 6.39 (1H, d, *J* = 8.4 Hz), 6.59 (1H, d, *J* = 8.4 Hz), 7.70 (1H, dd, *J* = 7.8, 7.8 Hz), 7.88 (1H, d, *J* = 7.8 Hz), 7.90 (1H, dd, *J* = 8.4, 8.4 Hz), 8.02 (1H, dd, *J* = 7.8, 7.8 Hz), 8.33 (1H, d, *J* = 7.8 Hz)
13. IR data of **1**

    $\underline{\nu_{max}\ (KBr)}$ = 2929, 1633, 1502, 1464, 1444, 1244, 1161, 887, 756, 723 cm^{-1}

    lit.[1] $\underline{\nu_{max}\ (KBr)}$ = 2938, 1633, 1501, 1467, 1446, 1243, 1159, 887, 755, 723 cm^{-1}

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