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A SYNTHESIS OF THE NAPHTHALENE CORE OF STREPTOVARICIN D VIA A SYNTHON OF NH_2^+

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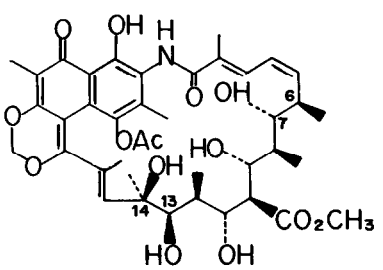
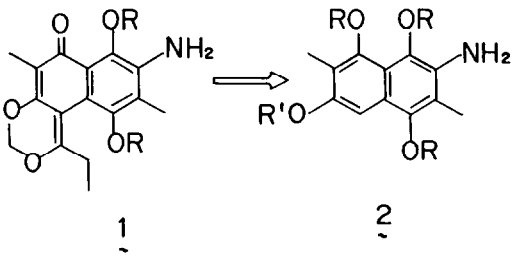
SUMMARY: A Five step synthesis of the naphthalene nucleus of streptovaricin D in 33% overall yield uses phenylthiomethyl azide for introduction of the amino group.

The ansamycins are a large class of complex natural products characterized by a highly functionalized aliphatic bridge linking non-adjacent positions of a normally highly substituted aromatic nucleus.[1] Synthetic approaches envision the construction of these two units separately and their subsequent linking.[2,3] For the synthesis of **1**, a naphthalene derivative with differentiated



Streptovaricin D



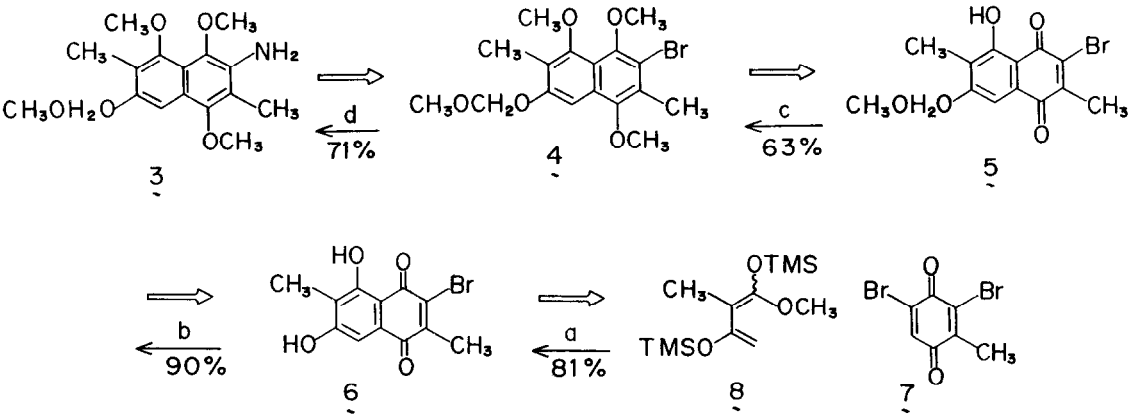
1 **2**

hydroxyl groups such as **2** is required. We wish to report the synthesis of **2** based upon the concept of $^+NH_2$.[4,5]

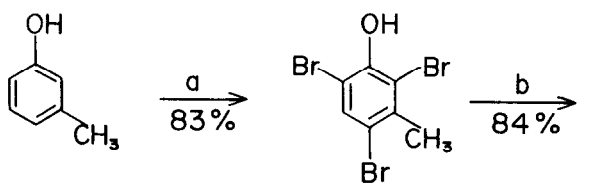
As summarized in the retrosynthetic analysis outlined in the Scheme, in utilizing azidomethylphenyl sulfide as a synthon for $^+NH_2$,[4] a precursor of an organometallic, e.g., a bromide as in **4**, replaces the amino group of the differentiated naphthalene derivative **3**. For a polyhydroxylated naphthalene, a quinone such as **6** becomes a logical precursor to permit differentiation of the hydroxyl groups. The Diels-Alder reaction offers the ready annulation of a substituted benzene ring onto a simple benzoquinone **7**. Introduction of a second bromine into the quinone controls the orientation of the two Diels-Alder partners, i.e., the second bromine serves as a regiochemical control element.[6]

It also provides a symmetry that permits a facile synthesis of the known quinone **7**[7] from m-cresol as outlined in eq 1.

SCHEME. Retrosynthetic Analysis and Synthesis of Naphthalene Nucleus of Streptovaricin D

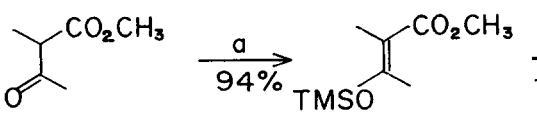


(a) C_5H_5N; $PhCH_3$, -78° to rt; then add H_2O, HCl, rt. (b) $(CH_3O)_2CH_2$, P_2O_5, $CHCl_3$ (c) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, dioxane, H_2O then $(CH_3O)_2SO_2$, NaOH, H_2O followed by $(CH_3O)_2SO_2$, NaOH, H_2O, CH_2Cl_2, $PhCH_2N(C_2H_5)_3Cl$. (d) n-C_4H_9Li, THF; $MgBr_2$; $PhSCH_2N_3$; KOH, H_2O, CH_3OH, THF



7 (1)

(a) Br_2, HOAc, rt. (b) CrO_3, HOAc, rt.



8 (2)

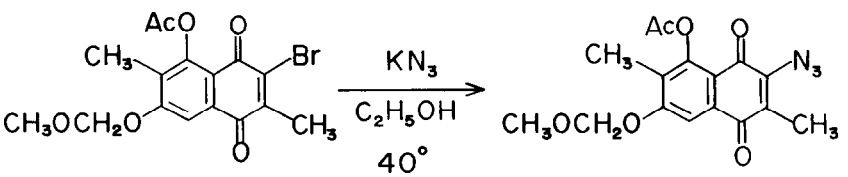
(a) $(TMS)_2NH$, imidazole, THF. (b) LDA, THF, TMEDA, TMS-Cl.

The requisite diene **8** derives by straightforward methodology from methyl methylacetoacetate as outlined in eq 2.[8,9] The tendency of the diene to undergo a silylotropic rearrangement requires its distillation to be performed

at temperatures lower than 60°.

Addition of the purified diene **8** to a toluene solution of quinone **7** and 2 eq of pyridine at -78° followed by aqueous acid workup gave the dihydroxynaphthoquinone **6**[10,11] directly. Use of crude diene gave a mixture of **6** and its monomethyl ether. Differential protection of the hydroxyl groups was provided by selective protection[12] of the more accessible C(7) hydroxyl group to give **5**.[10,11] Basic reaction conditions normally caused severe decomposition of **6**. Derivatization of the remaining oxygen atoms required reduction of the quinone and methylation. With typical reducing agents, quinone reduction proved troublesome due to competing reductive debromination. Sodium borohydride modified by lanthanide salts[13] nicely resolves this problem. In situ methylation gave a mixture of **4** and partially methylated intermediates. The partially methylated crude product was directly subjected to phase transfer methylation to give pure **4**.[10,11]

Gratifyingly, the Grignard reagent derived from **4** smoothly condensed with azidomethylphenyl sulfide and the resultant triazene efficiently hydrolyzed to give the sought-after amine **3** in good yield. As this example illustrates. steric hindrance does not retard this approach for introduction of the nitrogen. Thus, **3**[10,11] is available in 33% overall yield from the known quinone **7** in only five steps. For comparison, the bromoquinone **9**,[10] readily derived from **5** by acetylation [C_5H_5N, DMAP, 80°], reacted sluggishly with azide ion to give **10** in only 24% yield. Further, the ability to delay introduction



9 **10**

of the nitrogen until a late stage of synthesis as in this approach using a $^{+}NH_2$ synthon diminishes the use of protecting groups and offers practical experimental advantages in terms of handling intermediates.

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9. After we completed our synthesis of diene **8**, a report describing it appeared: Anderson, G.; Cameron, D.W.; Feutrill, G.I.; Read, R.W. Tetrahedron Lett. **1981**, 22, 4347.
10. All new compounds have been fully charcterized including combustion analysis and/or analysis by high resolution mass spectroscopy.
11. **6** (Red needles, mp 226-8°) IR ($CHCl_3$): 3620, 3200, 1667, 1628, 1595, 1565 $cm.^{-1}$ NMR (DMSO-d_6): δ12.18 (s, 1H), 11.22 (s, 1H), 7.08 (s, 1H), 2.21 (s, 3H), 2.02 (s, 3H). Anal. ($C_{12}H_9BrO_4$): C, H, MW.
5 (Orange needles, mp 127.5-128.5°) IR ($CHCl_3$): 3200-2800, 1668, 1630, 1595, 1580, 1563, 1500 $cm.^{-1}$ NMR ($CDCl_3$): δ12.1 (s, 1H), 7.41 (s, 1H), 5.35 (s, 2H), 3.50 (s, 3H), 2.35 (s, 3H), 2.10 (s, 3H). Anal. ($C_{14}H_{13}BrO_5$): C, H, MW.
4 (Colorless, mp 60-1°) IR ($CHCl_3$): 1625, 1590, 1492 $cm.^{-1}$ NMR ($CDCl_3$): δ7.41 (s, 1H), 5.35 (s, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.53 (s, 3H), 2.50 (s, 3H), 2.35 (s, 3H). Anal. ($C_{17}H_{21}BrO_5$): MW.
3 (Mp of benzamide derivative mp 214.5-215.0°) IR ($CHCl_3$): 3445, 3400, 1612, 1572, 1494 $cm.^{-1}$ NMR ($CDCl_3$): δ7.36 (s, 1H), 5.30 (s, 3H), 3.95 (6s, 2H), 3.82 (s, 3H), 3.81 (s, 3H), 3.79 (s, 3H), 3.53 (s, 3H), 2.35 (s, 3H), 2.28 (s, 3H). Anal. ($C_{17}H_{23}NO_5$): MW. Anal. of benzamide ($C_{24}H_{27}NO_6$): C, H, N, MW.
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