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SYNTHESIS OF ANTHRACYCLINES VIA A CLAISEN–DIELS–ALDER SEQUENCE

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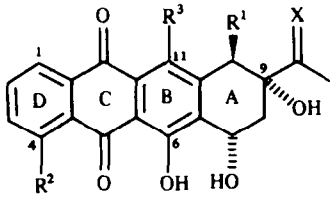
Abstract—Naphthalene **16**, a key intermediate for the synthesis of nogalamycin, was prepared in a six step sequence in 25% overall yield. The key step was a tandem Claisen–Diels–Alder sequence wherein the B- and C-rings were introduced in a single step. The naphthalene subunit was introduced by selenenylation of a β-diketone.

Both the anthracyclines and tetracyclines have been the target of numerous synthetic efforts.[1] The intense activity is a consequence of the significant biological activity exhibited by these compounds. The anthracyclines comprise a class of molecules with useful anticancer activity. Both daunomycin and aclacinomycin are used to treat cancer patients. Several variants of these compounds are being tested as future

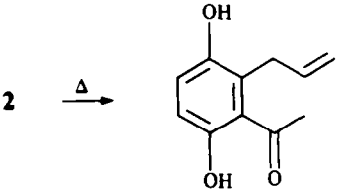


daunomycinone $R^1 = H$; $R^2 = OCH_3$; $R^3 = OH$; X = O
aklavinone $R^1 = CO_2CH_3$, $R^2 = OH$; $R^3 = H$; X = H_2

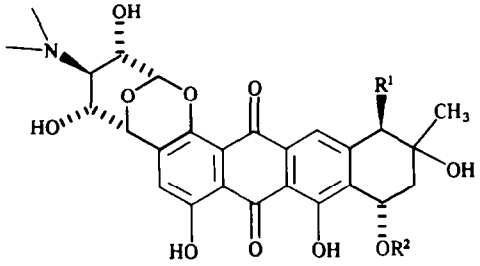
agents for chemotherapy. Another promising compound has the novel structure shown below. Nogalamycin, **1**, has many attractive features in its biological profile.[2] It is less toxic than daunomycin and is biologically active even without the carbohydrate attached at C-7. This feature should simplify the quest for active analogs of nogalamycin.

Strategies for the construction of anthracyclines generally involve the sequential appendage of aromatic rings by way of either anionic or concerted pathways. Most anionic pathways have featured Michael addition-Claisen type annulations[3] or Michael addition followed by subsequent Friedel–Crafts cyclizations.[4] Most routes involving concerted cyloadditions employ the Diels–Alder reaction. Both thermal[5] and Lewis-acid[6] mediated pathways have led to several expedient syntheses. As the search for new and more physiologically selective analogs continues, new approaches will continue to be useful. Our approach is based on the dissection shown below and originates with ketone **2**. The key step involves a tandem Claisen–Diels–Alder reaction to introduce rings B and C in a single step.

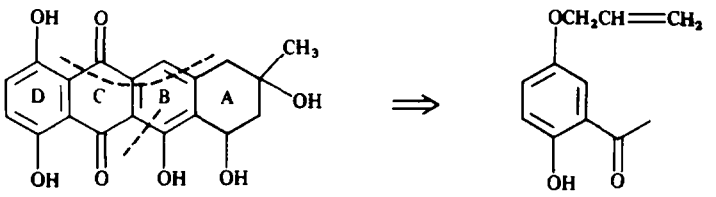
Our study of the tandem Claisen–Diels–Alder sequence was prompted by the regioselective Claisen rearrangement of **2** which produced only **3** and none of



3



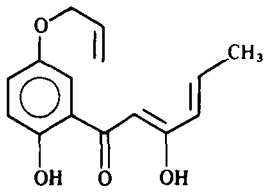
1 $R^1 = CO_2CH_3$
R^2 = carbohydrate portion



2

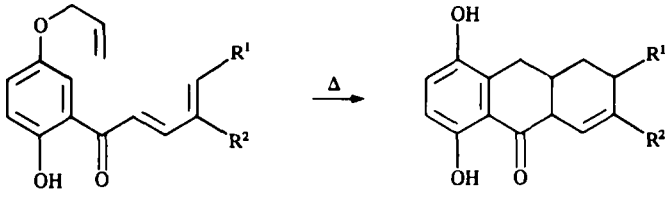
the regioisomeric hydroquinone. In the ^{13}C-NMR spectrum of both the hydroquinone and the quinone only one compound was evident. A search of the literature revealed that 3-propenyloxyacetophenone also afforded a regioselective Claisen rearrangement[7] and that methyl 3-propenyloxybenzoate gave mostly the isomer in which the allyl group was ortho to both the phenol and the carbomethoxy group.[8] In contrast, the Claisen rearrangement of the analogous *m*-methyl, *m*-methoxy and *m*-trifluoromethylphenyl allyl ethers showed no selectivity. Additionally, the acetate and methyl ether derivatives of **2**, when subjected to the Claisen rearrangement conditions, produced approximately a 55:45 ratio of isomers. Presumably, the protection of the phenol in **2** forces the acetyl group out of the plane of the aromatic ring, thus diminishing its directing effect. The surprising selectivity produced by a meta acyl group may be explained by an argument recently put forth by Kruse and Cha.[9] They contend that Claisen regioselectivity can be predicted by comparing the relative stability of the valence bond resonance forms before aromatization. Carpenter's[10] analysis of the Claisen rearrangement by way of isoconjugate transition states also provides a useful theory by which this selectivity can be explained.

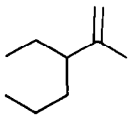
Our initial efforts at coupling the Claisen and Diels–Alder reactions began with dienones **4** and **5** which could be readily prepared by the reaction of **2** with crotonaldehyde and perillaldehyde, respectively, using the lithium salt of 2,6-dit-butyl-4-methylphenol.[11] The initially formed aldol product underwent dehydration *in situ* to afford a 40–50% yield of dienone. Thermolysis of **4** provided tricyclic hydroquinone **6** in 61% yield. The 300 MHz NMR spectrum of **6** indicated that it was a mixture of diastereomers in a ratio of 4.3 : 1, with the *cis*-ring juncture isomer predominating. The thermolysis of **5** afforded a 70% isolated yield of tetracyclic hydroquinone **7**. While **7** contains functionality which seem suitable for its elaboration into a nogalamycin precursor, all attempts to oxidize the central rings failed. Oxidation of the triacetate of **7** with DDQ, trityl fluoroborate or palladium acetate yielded complex product mixtures. Attempted benzylic bromination with NBS resulted in isomerization of the isopropenyl group. In view of these unexpected difficulties, we elected to increase the likelihood of selective oxidation by synthesizing a compound containing a β-diketone subunit in place of the β,γ-unsaturated ketone unit. The synthesis of ketone **8** then became necessary. The condensation of **2** with ethyl crotonate failed to afford **8**.



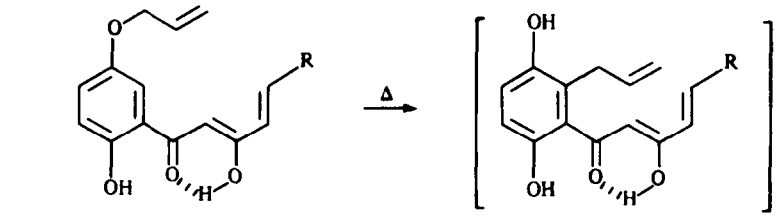
8

The reaction of the dianion of **2** (2.1 eq. iPr_2NLi, 0° or −78°) with crotonoyl chloride furnished variable yields of **8**. However, the ketoester reacted with the potassium tertbutoxide-t-butanol complex to afford a 45% yield of **8**. Eventually, a one pot procedure was developed wherein the anion of **2** was acylated and the resultant ketoester was treated with base to afford **8**. Analogously, ketones **10** and **11** were synthesized in 57% and 68% yields, respectively. Thermolysis of **8** at 210° for 12 hr followed by chromatographic purification gave tricyclic β-diketone **12** in 84% yield. Assuming the transition state shown below, cyclization followed by β-diketone formation should give a *cis* relationship between the methine hydrogen and the alkyl group. While 300 MHz decoupling experiments supported this idea, we chose to confirm it chemically by degradation of **13**. The β-diketone **13** was available from the acid chloride of sorbic acid in two steps. Silylation of the hydroquinone and β-diketone subunits followed by ozonolysis at low temperature in the presence of sudan red as an indicator[12] yielded an aldehyde which could be isomerized to a different aldehyde with diazabicyclononane (DBN) in benzene. These experiments define the original relationship of the methine hydrogen and the propenyl group as *cis*.

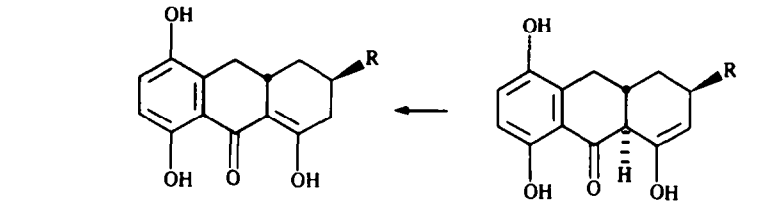


	R^1	R^2	% Yield	Compound
5			70	**7**
4	CH_3	H	61	**6**

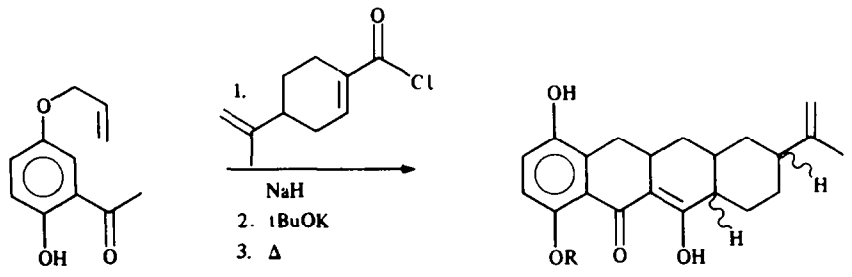
The acid chloride of perillic acid[13] was treated with **2** under the reaction conditions previously described to produce a ketone in 68% yield which could be transformed into tetracyclic β-diketone **14**. The ^{13}C-NMR indicated that a mixture of isomers was present. This was expected in that the remote isopropenyl group should exert little directing effect on the cycloaddition reaction. However, the central two rings will be aromatic rings in the final product and the mixture of isomers could be used without separation in subsequent experiments.



8 R = CH_3
10 R = $CH{=}CHCH_3$
11 R = $C(CH_3){=}CH_2$

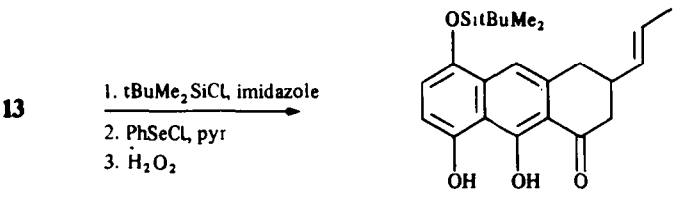


12 R = CH_3
13 R = $CH{=}CHCH_3$



14

Initially, the diketone **13** was used to define aromatization conditions. Since the hydroquinone subunit would be expected to oxidize most easily, the monosilylated derivative was studied. Silylation of the non H-bonded phenol with t-butyldimethylchlorosilane and imidazole[14] (84% yield) followed by selenenylation of the β-diketone with phenylselenenylchloride–pyridine complex and subsequent oxidation with hydrogen peroxide[14] afforded naphthalene **15**. The structure assignment was supported by a broad singlet at δ7.4 in the proton NMR. The same reaction sequence was conducted on **14** and resulted in the synthesis of **16**. Naphthalene **16** was produced by a 6 step route from perillic acid in 25% overall yield. It



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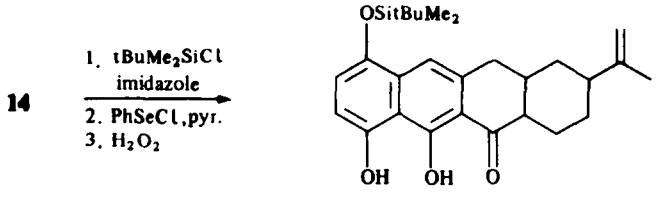

16

contains a selectively protected hydroquinone subunit which will be necessary for the regioselective appendage of the C-glycoside unit in nogalamycin.

EXPERIMENTAL

Unless otherwise noted, materials were obtained from commercial suppliers and were used without purification. Diethyl ether and THF were distilled from $LiAlH_4$ prior to usage. Dichlormethane was distilled from P_2O_5. M.ps were determined on a Fisher–Johns m.p. apparatus and are uncorrected. IR spectra were determined on a Beckman IR-4250 spectrometer. NMR spectra were determined on a Varian EM-360 60 MHz instrument. ^{13}C-NMR spectra were determined on a JOEL FX-900 Fourier transform instrument. Both proton and carbon chemical shifts are expressed in ppm downfield from internal TMS. High-resolution mass spectra were recorded on an AEI MS-902 high-resolution mass spectrometer. Analyses were performed by Galbraith Laboratories.

General conditions for the synthesis of ketones **8**, **10** *and* **11**

To a suspension of 1 equiv of NaH (hexanes washed) in dry tetrahydrofuran (THF) (0.5 M) was added by syringe a soln of the requisite *o*-hydroxyacetophenone (1 equiv) in THF. The mixture was allowed to warm to ambient temp for 30 min and then cooled to 0°. After the addition of the acid chloride (1 equiv) at 0°, the resulting yellow soln was stirred for 1 hr at 0°. The t-KOBu/t-BuOH complex (2 equivs) was then added rapidly as a solid. The deep red soln was stirred at 0° for 1 hr. Two equivs of glacial AcOH were then added followed by water. After ether extraction, the organic layer was dried and concentrated *in vacuo*. Column chromatography on silica gel with various mixtures of hexane and CH_2Cl_2 provided pure products.

3-*Hydroxy*-1-(5-*allyloxy*-2-*hydroxyphenyl*)-*hexa*-2-4-*dien*-1-*one* (**8**). NMR ($CDCl_3$) δ 1.92 (d, J = 7 Hz, 3H), 5.2–7.7 (m, 8H), 4.57 (d, J = 4 Hz, 2H), 6.05 (s, 1H), IR(nujol) 1640, 1570, 790 cm^{-1}.

3-*Hydroxy*-1-(5-*allyloxy*-2-*hydroxyphenyl*)-*octa*-2,4,6-*trien*-1-*one* (**10**). NMR ($CDCl_3$) δ 1.88 (d, J = 5 Hz, 3H), 4.48 (d, J = 5 Hz, 2H), 5.12–6.4 (m, 6H), 6.07 (s, 1H), 6.80–7.32 (m, 3H), 11.72 (s, 1H), 14.7 (bs, 1H). IR(CCl_4) 1635, 1555, 770, 750 cm^{-1}. (Found: C, 71.52; H, 6.48. Calc for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34%).

3-(4-(2-*Propenyl*)-*cyclohexenyl*)-3-*hydroxy*-1-(5-*allyloxy*-2-*hydroxyphenyl*)*prop*-2-*en*-1-*one* (**11**). NMR ($CDCl_3$) δ 1.78 (bs, 3H), 1.92–2.60 (m, 7H), 4.50 (d, J = 5 Hz, 2H), 4.75 (bs, 2H), 5.12–6.15 (m, 3 HO, 6.21 (s, 1H), 6.80–7.35 (m, 4H), 11.80 (s, 1H), 15.40 (s, 1H). (Found: C, 74.07; H, 7.17. Calc for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11%).

General procedure for the Claisen–Diels–Alder reaction

A 0.10 M soln of the requisite ketone in benzene with a trace of hydroquinone was deoxygenated and then heated in a sealed tube at 210° for 12 hr. The crude product was chromatographed on silica gel to afford pure product.

Diketone **12**. NMR ($CDCl_3$) δ 1.02 (d, J = 7 Hz, 3H), 1.35–3.03 (m, 7H), 3.25 (d, J = 4 Hz, 1H), 6.52 (AB q, 2H), 11.05 (s, 1H), 14.20 (s, 1H). IR(film) 3450, 1625, 1585 cm^{-1}. Mass spectrum *m/e* 260.

Diketone **13**. 300 MHz NMR ($CDCl_3$) δ 1.63 (d, J = 6 Hz, 3H), 1.86–1.99 (m, 2H), 2.08–2.40 (m, 2H), 2.62–2.78 (m, 3H), 3.15–3.22 (d, d, J = 4.7, 5 Hz, 1H), 5.40–5.68 (m, 2H), 6.62 (d, J = 8.8 Hz, 2H), 7.03 (d, (d, J = 8.8 Hz, 2H), 11.36 (s, 1H), 14.67 (s, 1H). IR(film) 3440, 1625, 1580 cm^{-1}. UV(MeOH) 340,380. High resolution mass spectrum requires *m/e* 286.12051, found 286.12023. (Found: C, 71.17; H, 6.27. Calc for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34).

Diketone **14**. NMR ($CDCl_3$) δ 1.30–3.10 (m, H), 1.72 (br s, 3H), 4.72 (br s, 2H), 6.75 (q, J = 8 Hz, 2H), 11.50 (s, 1H), 14.0 (s, 1H). IR(film) 3440, 1620, 1585, 1475 cm^{-1}. Mass spectrum *m/e* 340. (Found: C, 73.97; H, 7.22. Calc for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11).

General conditions for the preparation of **15** *and* **16**

The hydroquinones (1.0 eq.) were monosilylated with t-butyldimethylchlorosilane (1.2 eq.) and imidazole (2.5 eq.) in DMF (0.5 M) at room temp for 20 hr. Partition between ether and water (pH 5.5), drying and chromatography on silica gel provided pure monosilyl compound. One equivalent of the monosilylated diketone was treated with one equiv of phenylselenenyl chloride-pyridine complex in CH_2Cl_2 (1 M) at 0°. After extraction with HCl, the organic layer was treated with excess 30% aqueous H_2O_2. After the standard workup, the crude product was isolated and was purified by silica gel chromatography.

Naphthalene **15**. NMR ($CDCl_3$) δ 1.63 (d, J = 6 Hz, 3H), 2.40–3.2 (m, 5 Hz), 5.35–5.60 (m, 2H), 6.45–7.05 (m, 2H), 7.40 (s, 1H), 9.35 (s, 1H). IR (film) 3440, 1610 cm^{-1}. (Found: C, 69.41; H, 7.38. Calc for $C_{23}H_{30}O_4Si$: C, 69.31; H, 7.59).

Naphthalene **16**. NMR ($CDCl_3$) δ 1.62 (d, J = 6 Hz, 3H), 1.2–3.0 (m, 11H), 4.75 (br s, 2H), 6.6–6.95 (m, 2H), 7.35 (s, 1H), 9.10 (s, 1H).

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