Tandem Michael/Diels-Alder Addition as a New Strategy toward Tetracyclic Systems: Synthesis of 11-Deoxyanthracyclinones[1]

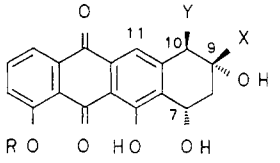
Yoshinori Naruta,* Yutaka Nishigaichi, and Kazuhiro Maruyama*

Department of Chemistry, Faculty of Science, Kyoto University, Kyoto 606, Japan

Received July 27, 1987

Tetracyclic systems of 11-deoxyanthracyclinones were synthesized very facilely by Lewis acid mediated tandem Michael/Diels-Alder reaction of 3-acryloyl quinone **12** with pentadienyltins (**13–16**, **20**). The applied Lewis acid affected the yield of the tandem adducts: among several Lewis acids, $SnCl_4$ gave the highest efficiency in the reaction of trimethyl-2,4-pentadienyltin (**13**). From NMR study, the stereoisomeric mixture of (*E*)- and (*Z*)-trimethyl-2,4-pentadienyltins was transmetalated with $SnCl_4$ under the applied conditions to form the corresponding (*E*)-trichlorotin **20** in a stereoselective manner as the reactive species in situ. 2-Substituted-2,4-pentadienyltins (**14–16**) gave the tandem adduct in a good yield in the presence of $(i\text{-PrO})_3TiCl$. These tandem adducts were converted to 11-deoxydaunomycinone (**1**), its analogue **7**, and 11-deoxyfeudomycinones **5** and **6**. The mechanism of the tandem addition was discussed.

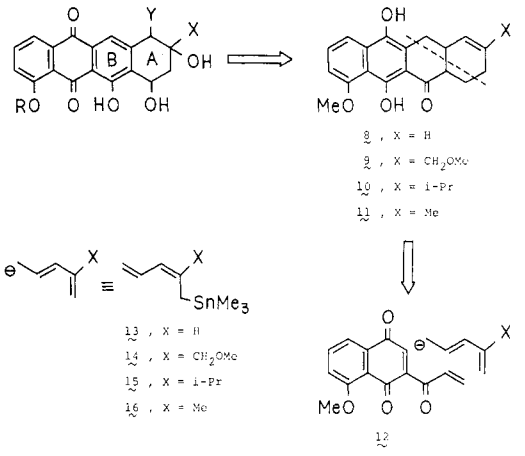
The anthracyclines[2] are the most promising and clinically efficacious agents against a wide range of neoplasms. In particular, 11-deoxyanthracyclines such as 11-deoxydaunomycin[2c] and aclacinomycin A[2d] are known for their high activity and their lower toxicity than the 11-hydroxy homologues, e.g., daunomycin and adriamycin. Numerous synthetic efforts, therefore, have been made for the preparation of their aglycons, 11-deoxyanthracyclinones, in recent years by many workers including ourselves.[3,4]



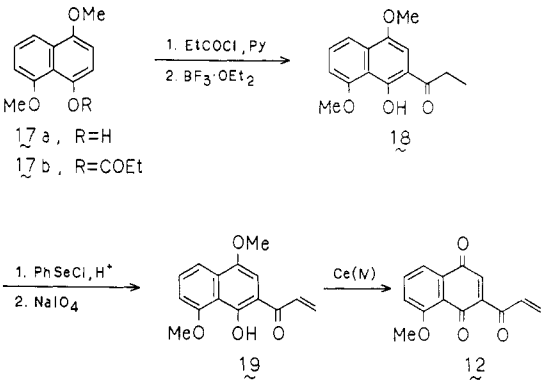
		R	X	Y
1	(11-Deoxydaunomycinone)	Me	COMe	H
2	(Aklavinone)	H	Et	CO_2Me
3	(13-Methylaklavinone)	H	i-Pr	CO_2Me
4	(Auramycinone)	H	Me	CO_2Me
5	(11-Deoxyfeudomycinone C)	Me	Me	H
6	(11-Deoxyfeudomycinone D)	Me	Me	OH
7		Me	CH_2OMe	H

The key in their synthesis is the regio- and stereoselective arrangement of the functional groups on their tetracycles, which have been constructed via a "perpendicular" connection.[3a,d] Our retrosynthetic scheme is based on "diagonal" disconnection of the A and B rings (Scheme I).[5] If one can introduce a 2,4-pentadienyl group to the 2-position of the acryloyl quinone **12**, the spontaneous intramolecular Diels-Alder cyclization is expected to lead to the tetracyclic product **8**, which possesses the suitable functionality at the proper position on the rings for the conversion to the target compound. Furthermore, if it is possible to introduce a properly substituted pentadienyl group to the quinone in a regioselective manner, the tandem adducts would be led to the target compounds

Scheme I



Scheme II



(1) Synthesis of Naturally Occurring Quinones. 20. For 19, see: Naruta, Y.; Nagai, N.; Maruyama, K. *J. Chem. Soc., Perkin Trans. 1*, in press.

(2) (a) Arcamone, F. *Doxorubicin*; Academic Press: New York, 1981. (b) *Anthracycline Antibiotics*; El Khadem, H. S., Ed.; Academic Press: New York, 1982. (c) Arcamone, F.; Cassineli, G.; DiMatteo, F.; Forenza, S.; Ripamonti, M. C.; Rivola, G.; Vigevani, A.; Clardy, J.; McCabe, T. *J. Am. Chem. Soc.* **1980**, *102*, 1462. (d) Hori, S.; Shirai, M.; Hirano, S.; Oki, T.; Inui, T.; Tsukagoshi, S.; Takeuchi, T.; Umezawa, H. *Gann* **1977**, *68*, 685.

(3) For reviews of anthracyclinone synthesis, see: (a) Remers, W. A. *The Chemistry of Antitumor Antibiotics*; Wiley: New York, 1979; pp 221–276. (b) Arcamone, F. *Anticancer Agents Based on Natural Product Models*; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; pp 1–41. (c) Remers, W. A., ref 3b, pp 131–146. (d) Terashima, S. *J. Synth. Org. Chem. Jpn.* (*Yuki Gosei Kagaku Kyokaishi*) **1982**, *40*, 20. (e) Broadhurst, M. J.; Hassall, C. H.; Thomas, G. J. *Chem. Ind.* (*London*) **1985**, 106. (f) Krohn, K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 790. (g) Kelly, T. R., Ed. *Tetrahedron* (*Symposia-in-Print No. 17*) **1984**, *40*, 4537–4793. (h) Tornare, J.-M.; Vogel, P. *Helv. Chim. Acta* **1985**, *68*, 1069 and references cited therein. (i) Thomson, R. H. *Naturally Occurring Quinones, III*; Chapman and Hall: London, 1987; pp 527–563.

(4) (a) Naruta, Y.; Kashiwagi, M.; Nishigaichi, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1983**, 1687. (b) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Chem. Lett.* **1986**, 1703. (c) Uno, H.; Naruta, Y.; Maruyama, K. *Tetrahedron* **1984**, *40*, 4725.

(5) See ref 4a and 4b. A similar strategy appeared recently: Kraus, G. A.; Fulton, B. S. *J. Org. Chem.* **1985**, *50*, 1782; *Tetrahedron* **1984**, *40*, 4777.

0022-3263/88/1953-1192$01.50/0

in a few steps. Thus, this tandem reaction is expected to be one of the most effective routes to anthracyclinones.

The major problem in our strategy is to design a suitable pentadienyl nucleophile: the requirements for the accomplishment of the tandem reaction are (1) regioselective introduction of the pentadienyl group and (2) prevention of *intermolecular* Diels–Alder reaction to acryloyl quinone, which is not only a good Michael acceptor but also a very good dienophile. Our previous study[6] revealed that 2,4-pentadienyltin (PDT) satisfies the above requirements, and we already made its preliminary application to the anthracyclinone synthesis.[4a,b]

In the present paper, we describe the facile synthesis of several 11-deoxyanthracyclinone derivatives using the tandem Michael/Diels–Alder reaction between acryloyl quinone and unsubstituted or substituted PDTs in the presence of Lewis acid. It was made possible to prevent the undesirable intermolecular Diels–Alder reaction and to introduce the pentadienyl chain in a regio- and stereoselective manner by applying an appropriate combination of PDT and Lewis acid.

Results and Discussion

As a key electrophile of the tandem reaction, 3-acryloyl-5-methoxy-1,4-naphthoquinone (**12**) is required. The quinone **12** was synthesized in quantity according to Scheme II. Fries rearrangement of propionyl ester **17b** with BF_3·OEt_2 gave propionylnaphthol **18**,[7] of which selenylation–oxidative elimination (PhSeCl, cat. HCl; $NaIO_4$)[8] gave vinyl ketone **19** in 56% overall yield from naphthol **17a**.

The vinyl ketone **19** was readily oxidized by Ce(IV) to the corresponding 3-acryloyl-5-methoxy-1,4-naphthoquinone (**12**) in an almost quantitative yield with sufficient purity. Due to the instability of the quinone, it was prepared just before use and employed without purification.

Next, we mention the synthesis of 2-substituted-PDTs. Regioselective preparation of 2-substituted-PDTs (**14**: X = CH_2OCH_3, **15**: X = $CHMe_2$, **16**: X = Me) is essential, because it is known that allyltins and PDTs normally undergo regioselective reaction at their terminal positions with aldehydes[6] and acyl quinones.[9] The preparation was realized by the coupling of the 2-substituted-pentadienyllithium (potassium) with Me_3SnBr.[10]

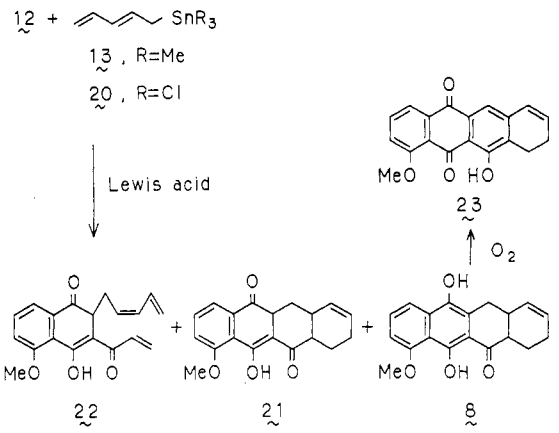
2-Substituted-pentadienyllithium (X = CH_2OCH_3) or potassium (X = $CHMe_2$, Me) was quenched with Me_3SnBr to give the corresponding 2-substituted-PDT as the major product. The ratios of 2-substituted-PDT:4-substituted-PDT were 93:7 for **14** and **15** and 71:29 for **16**. For realizing higher regioisomeric purity[11] of 2-substituted-PDT, we treated the each crude substituted PDT with maleic anhydride.[12] 4-Substituted-PDT was preferentially removed[13] by Diels–Alder reaction and successive treatment with an alkaline solution. The purity of each 2-substituted-PDT was increased to more than 95%.

Table I. Tandem Michael/Diels–Alder Reaction of PDT 13[a] with 12

entry	Lewis acid (equiv)	reactn temp, °C	product ratio[b] (21 + 8):22	overall yield[c] of 23, %
1	BF_3·OEt_2 (1.2)	−78	30:(70)[d]	30
2	$TiCl_4$ (1.2)	−78	79:21	13
3	$(i\text{-PrO})_3TiCl$ (1.2)	−78	40:(60)[d]	30
4[e]	$SnCl_4$ (1.2)	0/−78	trace:100	
5	$SnCl_4$ (1.2)	−78	45:55	35
6[f]	$SnCl_4$ (1.2)	−78 to 40	80:20	31
7	$SnCl_4$ (1.2)	−100	80:20	48
8[g]	$SnCl_4$ (1.2)	−78	76:24	45
9[g]	$SnCl_4$ (3.2)	−78	89:11	46
10[g]	$SnCl_4$ (4.0)	−78	90:10	52
11[g]	$SnCl_4$ (6.0)	−78	94:6	54

[a] An isomeric mixture (E/Z = ca. 7/3) was used. [b] Determined by ^1H NMR. [c] Isolated yield of **23** based on **19**. [d] Containing some other unidentified products. [e] The solution of the quinone **12** and the PDT **13** was stirred at 0 °C for 1 h prior to the addition of $SnCl_4$ at −78 °C. [f] The reaction mixture was refluxed for 1 h after the addition of $SnCl_4$ at −78 °C. [g] The quinone **12** was added to the premixed solution of the PDT **13** and $SnCl_4$ at −78 °C; see Experimental Section.

Scheme III



Tandem Michael/Diels–Alder Reaction. We examined the tandem reaction of the unsubstituted PDT **13**[14] with the quinone **12** in the presence of various Lewis acids (Table I). The reaction procedure was almost the same in every case; 1.2 equiv of a Lewis acid was added to the mixture of the quinone **12** and the PDT **13** (E/Z = ca. 7/3) at the indicated temperature and the mixture was quenched after 10–30 min of stirring (Scheme III). The yields were determined as the quinone **23** after oxidation with molecular oxygen.[15] Under these conditions (O_2, DMF, 100 °C), the tetracyclic adducts **21** and **8** were oxidized to the quinone **23**, and the uncyclized adduct **22** decomposed to unassignable compounds. Even the crude mixture of the tandem reaction gave the quinone **23** without loss of efficiency.

(6) Naruta, Y.; Nagai, N.; Arita, Y.; Maruyama, K. *Chem. Lett.* **1983**, 1685.

(7) **18** was synthesized according to a similar method of the literature: Naruta, Y.; Uno, H.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1981**, 1277.

(8) (a) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (b) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(9) Uno, H. *J. Org. Chem.* **1986**, *51*, 350.

(10) 2-(Methoxymethyl)-1,4-pentadiene was converted to the corresponding lithium derivative with *n*-BuLi in THF. The addition of Me_3SnBr to this solution at −78 °C afforded [2-(methoxymethyl)-2,4-pentadienyl]trimethyltin (**14**) (containing the 4-methoxymethyl derivative in 7%) in 70% overall yield. The other PDTs were prepared in a similar manner: Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Chem. Lett.* **1988**, 135.

(11) In particular, both regioisomers of **14** were able to be isolated by chromatography on silica gel.

(12) Bachman, G. B.; Goebel, C. G. *J. Am. Chem. Soc.* **1942**, *64*, 787. See also ref 14a.

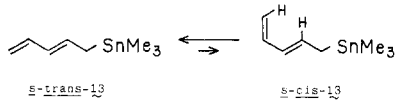
(13) From steric requirements, 1,3-disubstituted butadienes (such as 4-substituted-PDT) are prone to be the *s*-cis conformer compared with 1,1-disubstituted butadienes (such as 2-substituted PDT) which favors the *s*-trans conformation. Only the former preferentially undergoes Diels–Alder reaction. See: Martin, J. G.; Hill, R. K. *Chem. Rev.* **1961**, *61*, 537.

(14) Trimethyl-2,4-pentadienyltin (**13**) was prepared according to the following references: (a) Seyferth, D.; Goldman, E. W.; Porney, J. *J. Organomet. Chem.* **1981**, *208*, 189. (b) Jones, M.; Kitching, W. *J. Organomet. Chem.* **1983**, *247*, C5. (c) Reference 5.

(15) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688.

The applied Lewis acid has intensive effects both on the product ratio and on the yield of the bicyclized product. BF_3·OEt_2, which satisfactorily catalyzed the reaction between acyl quinones and allyltins,[9] gave the tetracyclic quinone **23** in a moderate yield. Although the ratio of the tetracyclic product to the uncyclized one was improved in the mediation of $TiCl_4$, the yield of **23** was low owing to the formation of many unidentified products. On the other hand, $SnCl_4$ gave good results in the selectivity of the tetracyclic products (entries 5–7). However, when the mixture of **12** and **13** was stirred for 1 h at 0 °C prior to the addition of $SnCl_4$ at −78 °C (entry 4), exclusive formation of the uncyclized product **22** was observed. From ^1H NMR inspection, the obtained **22** was revealed to have a cis configuration in its dienyl chain. Also in other entries, the configuration of the dienyl chain of **22** was determined to be cis without exceptions after isolation as its diacetate. This result suggests one of the major pathways to the undesirable acyclic product **22**, of which suppression is the key for the improvement of the product selectivity.

When the mixture of the quinone **12** and the PDT **13** was quenched at 0 °C before the addition of $SnCl_4$, the corresponding Diels–Alder adduct **27′** was obtained in an almost quantitative yield.[16] The structure of this adduct **27′** was well characterized by means of NMR as a regioisomerically pure tricyclic compound as shown in Scheme V. Treatment of the isolated **27′** with $SnCl_4$ at −78 °C afforded *cis*-**22** through destannylative ring-opening with retention of the double-bond geometry between C-2 and C-3 (path A). Thus, the formation of the undesirable *cis*-**22**[17] (or its aromatized form) was attributed to the direct Diels–Alder reaction to the quinoid 2,3-positions to a considerable extent in competition with the formation of the direct Michael adduct A. As another possibility, the direct Michael addition of *s*-*cis*-**13**, to which equilibrium is sterically unfavorable especially at low temperature, would contribute to the formation of the adduct *cis*-**22** to a minor extent.

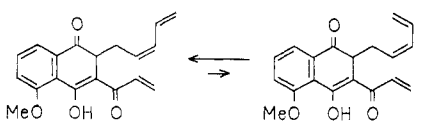


s-trans-13 s-cis-13 (1)

This conclusion lead to the following strategy for improvement of the tandem cyclization: (i) lowering the reaction temperature and (ii) decreasing the electron density of the PDT to become a less reactive diene. These modifications will serve to prevent the preferential formation of the direct Diels–Alder adduct **27′** (entries 8–11 for trichloropentadienyltin).

(16) It is noteworthy that the residual PDT **13** after the intermolecular Diels–Alder reaction was mainly the cis isomer while the starting **13** was mainly the trans isomer (cis:trans ca. 3:7) before the reaction. This implied that *cis*-**13** is less reactive in the Diels–Alder reaction.

(17) (a) *cis*-2,4-Pentadienyl adduct **22** did not give the intramolecularly cyclized product **8** even under high pressure or elevated temperature. This low reactivity of **22** is explainable by means of steric effects: (1) *cis*-pentadienyl side chain favors *s*-trans conformation, which is unsuitable for the completion of the required intramolecular Diels–Alder reaction[13] and (2) even if the dienyl side chain takes *s*-cis conformation, it is sterically difficult to attain the sufficient overlapping between the dienyl moiety and the enone residue. Furthermore, attempted isomerization of *cis*-**22** with iodine or triplet sensitizer provided inefficiently the desired tetracyclic product (10–25% conversion).



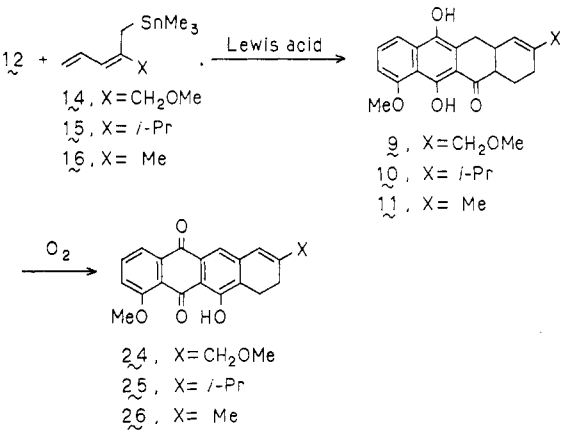
s-trans-22 s-cis-22 (i)

Table II. Tandem Michael/Diels-Alder Reaction of Substituted PDTs[a] with 12

entry	X (tin reagent)	Lewis acid[b]	product[c]	overall yield,[d] %
1	CH_2OMe (**14**)	BF_3·OEt_2	**24**	18
2	CH_2OMe (**14**)	$SnCl_4$	**24**	trace
3	CH_2OMe (**14**)	$(i\text{-PrO})_2TiCl_2$	**24**	62
4	CH_2OMe (**14**)	$(i\text{-PrO})_3TiCl$	**24**	69
5	*i*-Pr (**15**)	$(i\text{-PrO})_3TiCl$	**25**	59
6	Me (**16**)	$(i\text{-PrO})_3TiCl$	**26**	67

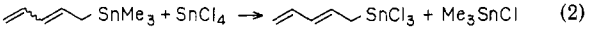
[a] 2-Substituted PDTs were used after purification to regioisomerically pure form (>95%). [b] 3 equiv of Lewis acid to **12** was used. [c] Tetracyclic quinone after oxidation. [d] Isolated yield of the corresponding tetracyclic quinone based on **19**.

Scheme IV



As shown in entry 7 of Table I, the reaction at lower temperature (−100 °C) improved both the selectivity and the yield as expected. However, a considerable amount of uncyclized *cis*-**22** still remained and its complete elimination was difficult.

We found that some allyltins readily react with $SnCl_4$ to yield trichloroallyltins through transmetalation very smoothly even at −78 °C.[18] In such allyltins, the electron-donating trialkyltin group was replaced by the electron-withdrawing trichlorotin group, so that decreased electron density on the allyl moiety could be expected.[19] Similarly, trimethyl-2,4-pentadienyltin afforded the corresponding trichlorotin derivative **20** quantitatively.[18] Its geometry was established to be exclusively *E* at the low temperature (−50 °C) by ^1H NMR.[4b]



13 20 (2)

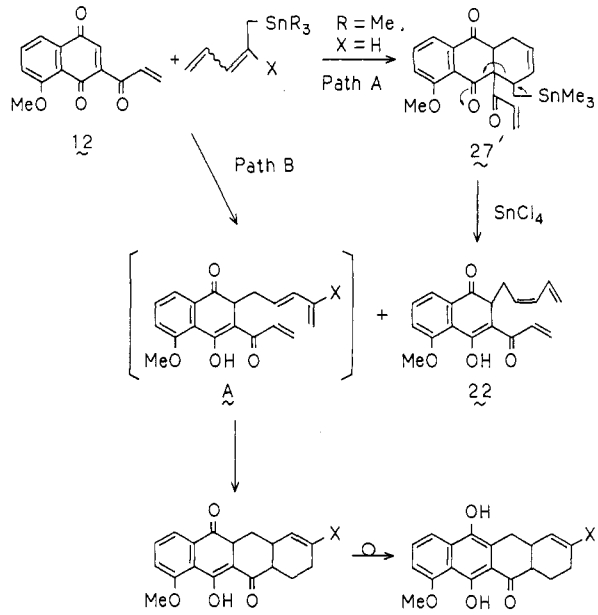
The tandem reaction with (*E*)-trichloropentadienyltin (**20**) proceeded satisfactorily as expected (Table I, entries 8–11). The higher ratio of $SnCl_4$ to the quinone afforded the higher yield of the tetracyclic compounds presumably because of the exclusive formation of **20** in the reaction mixture. The reaction with 6 equiv of $SnCl_4$ exhibited 94% selectivity of the tetracyclic products (54% yield, entry 11).

Introduction of functionalities X to the 9-position of the tetracyclic system is important for the synthesis of the natural anthracyclines. We applied the tandem reaction

(18) The transmetalation of trialkyltin to the corresponding trichlorotin in allyl- and 2,4-pentadienyltin[4b] systems was proved by ^1H, ^{13}C, and ^{119}Sn NMR at −50 °C in $CDCl_3$; Naruta, Y.; Nishigaichi, Y.; Maruyama, K., in preparation.

(19) This feature was also observed in PDT.[18] ^{13}C NMR spectra depicted the lower electron density on the pentadienyl moiety of the trichlorotin derivative **20** than that of trimethyl-2,4-pentadienyltin (**13**).

Scheme V



to three 2-substituted PDTs (**14–16**) prepared regio- and stereoselectively.[10] These tin reagents possess either a coordinative methoxymethyl group to Lewis acids or a noncoordinative alkyl group, methyl or isopropyl, as a substituent. The results are summarized in Table II. The yields were again determined as the corresponding tetracyclic quinones (**24–26**) after molecular oxygen oxidation (Scheme IV).

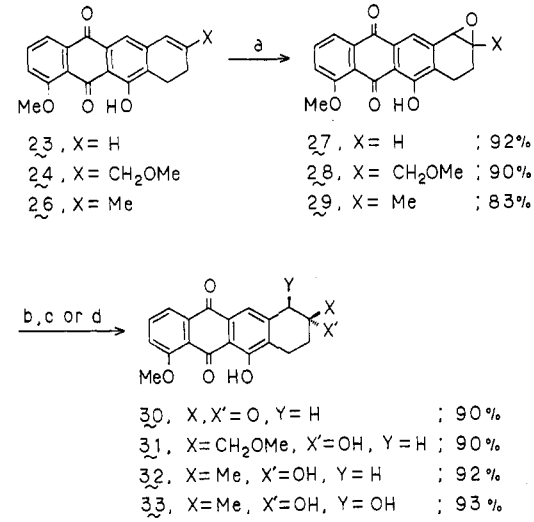
Choice of Lewis acid was essential for the realization of the regio- and stereoselective reaction.[20] In the case of **14** (X = CH_2OCH_3), Lewis acid (i-PrO)$_3$TiCl or (i-PrO)$_2$TiCl$_2$ gave a better yield than BF_3·OEt_2 or $SnCl_4$. The alkyl-substituted-PDTs, **15** and **16**, exhibited also good yields with (i-PrO)$_3$TiCl.

The amount of Lewis acid, in addition, affected the yield: at least 3 equiv was necessary for realization of a good yield.

As already mentioned, the applied PDTs with their substituent at the 2-position were found in more than 95% purity and were considered to have an analogous structure to 1,1-disubstituted butadienes,[13] which do not stay in the required *s*-cis conformation in the Diels–Alder reaction. This is the reason why the intermolecular Diels–Alder reaction did not take place in these instances. Indeed, [(*E*)-4-(methoxymethyl)pentadienyl]tin[11] underwent the Diels–Alder reaction as well as unsubstituted (*E*)-PDT (*E*-**13**).

The profile of the tandem reaction is summarized in Scheme V. When electron-rich **13** (R = Me) was employed in the reaction, the intermolecular Diels–Alder reaction

Scheme VI[a]

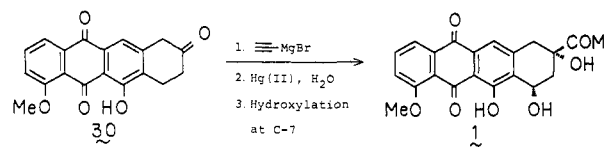


[a] (a) MCPBA; (b) $TMSOSO_2CF_3$ and 2,6-lutidine for **30**; (c) H_2 and Pd/C for **31** and **32**; (d) H_2SO_4 for **33**.

preferentially proceeded especially at the higher temperature (path A). The adduct **27′** underwent destannylative ring-opening to form *cis*-**22** by $SnCl_4$. The thermal intermolecular Diels–Alder reaction was depressed at the lower temperature. Some of **13** (R = Me) might be transmetalated to **20** (R = Cl) at the lower temperature and followed path B. When the transmetalation was thoroughly carried out at the first stage or 2-substituted-PDTs were used, exclusive Michael addition occurred through path B which realized the introduction of the (*E*)-pentadienyl chain. The regio- and stereoselective Michael addition was followed by spontaneous intramolecular Diels–Alder reaction to give the tetracyclic products.

The tetracyclic quinones **23** (X = H), **24** (X = CH_2OCH_3), **25** (X = i-Pr), and **26** (X = Me) are considered to be precursors of various anthracyclinones. As reported by Hauser et al.,[21] **23** is a precursor of 11-deoxydaunomycinone (**1**). However, since the reported method[21] did not provide a satisfactory yield of **30** from **27**, we developed a more efficient method to it. In the isomerization of epoxide **27** to the corresponding ketone **30**, use of trimethylsilyl triflate in the presence of lutidine[22] showed high yield and good reproducibility; the yield was as high as 90%, while free sulfonic acids were less effective on this conversion.

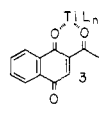
The triketone **30** was converted to 11-deoxydaunomycinone (**1**)[23] via the addition of ethynyl Grignard reagent to **30** as the first step, where the yield of the adduct was



(3)

as high as 30%: the major part of **30** was recovered (60%). The improvement of this step is rather difficult especially for the 11-deoxy-type triketone,[24] because of its easily

(20) (a) Some model experiments between 2-acetyl-1,4-naphthoquinone and substituted PDTs have revealed the following facts: (i) BF_3·OEt_2 showed poor selectivity as in the case of unsubstituted PDT; (ii) transmetalation by $SnCl_4$ changed **14** (X = CH_2OCH_3) into an unreactive species and **15** (X = $CHMe_2$) into a species which introduced the undesirable regioisomeric dienyl chain; (iii) (i-PrO)$_3$TiCl gave the most satisfactory results in both yield and selectivity. This Lewis acid was designed to be bidentative and not to undergo transmetalation owing to the deactivating isopropoxy ligand, but was active enough for Michael addition. (b) It is expected that such Lewis acid is chelated by an acyl quinone like B as to activate the C-3 position selectively.



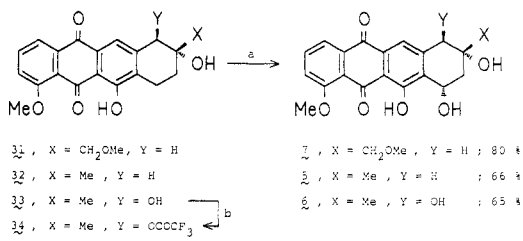
B

(21) Hauser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328.

(22) Murata, S.; Suzuki, M.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 247.

(23) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. Gesson, J.-P.; Mondon, M. *J. Chem. Soc., Chem. Commun.* **1982**, 421.

Scheme VII[a]



[a] (a) Br_2, $h\nu$ then OH^-; (b) $(CF_3CO)_2O$.

enolizable character. Hence, it becomes very important to introduce the substituent required at C-9 such as **24–26** at the stage of the tin reagents **14–16** rather than the later steps.

11-Deoxydaunomycinone analogues **5–7** were effectively derived from the tetracyclic adducts **24** and **26** in a few steps as shown in Schemes VI and VII. The methoxymethyl analogue **24** was converted to **7**[25] via epoxidation, hydrogenation, and hydroxylation at C-7[26] in 65% overall yield. Similarly, the methyl analogue **26**[27] was also transferred to 11-deoxyfeudomycinone C (**5**) in 50% overall yield. Hydration of the epoxide **29** gave the corresponding 9,10-diol **33**, which was turned into 11-deoxyfeudomycinone D (**6**) via hydroxylation at C-7 after protection of OH at C-10 with trifluoroacetic anhydride[28] in 50% overall yield from **26**.

Thus, we completed total synthesis of 11-deoxyanthracyclinones.

Conclusion

The tetracycles required in the synthesis of 11-deoxyanthracyclinones were constructed in one step based on "diagonal connection" strategy. Tandem Michael/Diels–Alder reaction was developed. Lewis acid mediated reaction of acryloyl quionone **12** with 2,4-pentadienyltins (PDTs) gave selectively the required tetracycles **8–11** in good yields among several possible reaction modes. Functionalized PDTs **14–16** prepared in a regio- and stereoselective manner were also essential for the accomplishment of the present cyclization.

Experimental Section

General Method. Melting points were determined on a micromelting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were observed on JEOL JNM-PS-100 and JNM-FX400 spectrometers. Chemical shifts are reported as δ values in part per million relative to tetramethylsilane (δ 0.00) as an internal standard. Infrared spectra were observed with a JASCO IRA-1 spectrometer. Mass spectra were measured with a JEOL JMS-DX 300 mass spectrometer. Elemental analyses were performed by the Microanalytical Laboratory of Kyoto University. Column chromatography was performed on Wakogel C-200 and Merk Kieselgel 60H for flash column chromatography. All solvents were freshly distilled and stored under a nitrogen atmosphere. Dichloromethane was distilled from phosphorus pentoxide. Ether and THF were distilled from benzophenone ketyl and stored over sodium wire. Toluene and xylene were stored over molecular sieves 4A after distillation. Other solvents were used after simple distillation. The following Lewis acids were used as CH_2Cl_2 solutions except $(i\text{-PrO})_3TiCl$: $SnCl_4$, $TiCl_4$, $BF_3{\cdot}OEt_2$, $(i\text{-PrO})_3TiCl$ (in hexane), and $(i\text{-PrO})_2TiCl_2$. As a standard workup procedure, a solution of a reaction mixture was washed with water and then brine, dried over $MgSO_4$, and evaporated in vacuo.

1,5-Dimethoxy-3-propionyl-4-naphthol (18) was prepared according to the reported method[7,9] from 1,5-dimethoxy-4-naphthol (**17a**; 5.00 g, 24.5 mmol) and propionyl chloride (4.3 mL).

1,5-Dimethoxy-4-(propionyloxy)naphthalene (17b; 5.85 g, 22.5 mmol, 92%) was obtained after purification by short column chromatography (CH_2Cl_2); white flakes (from ether–hexane): mp 109–110 °C; NMR ($CDCl_3$) δ 1.29 (t, 3 H, J = 7.5 Hz), 2.65 (q, 2 H, J = 7.5 Hz), 3.86 (s, 3 H), 3.94 (s, 3 H), 6.71 (d, 1 H, J = 8 Hz), 6.83 (d, 1 H, J = 8 Hz), 6.92 (d, 1 H, J = 8 Hz), 7.32 (t, 1 H, J = 8 Hz), 7.83 (d, 1 H, J = 8 Hz); IR (KBr) 1750, 1590; MS, m/e (relative intensity) 260 (M^+, 26), 204 (100), 189 (82).

1,5-Dimethoxy-3-propionyl-4-naphthol (18; 4.80 g, 18.5 mmol, 92% from 5.20 g (20 mmol) of **17b**) was obtained after chromatographic purification (CH_2Cl_2); yellow needles (from methanol): mp 129–130 °C; NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7.5 Hz), 3.03 (q, 2 H, J = 7.5 Hz), 3.88 (s, 3 H), 3.97 (s, 3 H), 6.83 (d, 1 H, J = 8 Hz), 6.87 (s, 1 H), 7.39 (t, 1 H, J = 8 Hz), 7.68 (d, 1 H, J = 8 Hz), 13.43 (s, 1 H); IR (KBr) 3400, 1615, 1595, 1570; MS, m/s (relative intensity) 260 (M^+, 67), 245 (14), 231 (100). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.22; H, 6.20. Found: C, 69.25; H, 6.14.

3-Acryloyl-1,5-dimethoxy-4-naphthol (19). To a solution of **18** (1.70 g, 6.53 mmol) in ethyl acetate (60 mL) were added phenylselenyl chloride (1.50 g) and three drops of 36% HCl. After being stirred for 5 h at room temperature, the mixture was poured into water–CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined CH_2Cl_2 solution was worked up as usual. The residue was purified by chromatography (benzene) to give 2.28 g (5.49 mmol, 84%) of 1,5-dimethoxy-3-(2-phenylselenopropionyl)-4-naphthol, brownish yellow crystals (from methanol): mp 140.5–141.5 °C; NMR ($CDCl_3$) δ 1.66 (d, 3 H, J = 7.5 Hz), 3.89 (s, 3 H), 4.06 (s, 3 H), 5.02 (q, 1 H, J = 7.5 Hz), 6.96 (d, 1 H, J = 8 Hz), 7.04 (s, 1 H), 7.30 (m, 2 H), 7.52 (m, 4 H), 7.84 (d, 1 H, J = 8 Hz), 12.54 (s, 1 H); IR (KBr) 3380, 1615, 1590, 1560; MS, m/e (relative intensity) 418 (M^+, 6), 416 (M^+, 27), 414 (M^+, 14), 413 (M^+, 6), 412 (M^+, 5), 259 (73), 231 (100). The selenide (2.08 g, 5.0 mmol) was dissolved in a mixture of THF (60 mL) and methanol (40 mL). To the solution were added water (15 mL), $NaHCO_3$ (0.51 g), and $NaIO_4$ (2.49 g) with vigorous stirring at room temperature. After 2 h, the mixture was poured into a saturated aqueous $NaHCO_3$ and filtered, and then the residue was washed with benzene. The combined filtrate was washed 5% aqueous HCl and then worked up as usual. The residue was purified by flash column chromatography (benzene) to give 1.03 g (3.99 mmol, 80%) of 3-acryloyl-1,5-dimethoxy-4-naphthol (**19**), red prisms (from ether): mp 86–87.5 °C; NMR ($CDCl_3$) δ 3.93 (s, 3 H), 4.03 (s, 3 H), 5.86 (dd, 1 H, J = 11, 2 Hz), 6.51 (dd, 1 H, J = 17, 2 Hz), 6.92 (d, 1 H, J = 8 Hz), 6.98 (s, 1 H), 7.37 (dd, 1 H, J = 11, 17 Hz), 7.50 (t, 1 H, J = 8 Hz), 7.79 (d, 1 H, J = 8 Hz), 13.57 (s, 1 H); IR (KBr) 3380, 1620, 1595, 1570; MS, m/e (relative intensity) 258 (M^+, 100), 243 (18), 215 (49), 187 (15). Anal. Calcd for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 69.64; H, 5.43.

3-Acryloyl-5-methoxy-1,4-naphthoquinone (12). A cold (0 °C) aqueous solution (5 mL) of cerium(IV) ammonium nitrate (1.3 g) was added to an acetonitrile solution (15 mL) of **19** (258 mg, 1.0 mmol) at 0 °C. After being stirred for 5 min at 0 °C, the mixture was poured into water–CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. After the combined organic phase was worked up as usual, 3-acryloyl-5-methoxy-1,4-naphthoquinone (**12**) was obtained almost quantitatively, orange needles (from ether–hexane): mp 157–161 °C dec; NMR ($CDCl_3$) δ 4.00 (s, 3 H), 6.00 (dd, 1 H, J = 10, 1 Hz), 6.27 (dd, 1 H, J = 17, 1 Hz), 6.76 (dd, 1 H, J = 10, 17 Hz), 6.92 (s, 1 H), 7.32 (m, 1 H), 7.70 (m, 2 H); IR (KBr) 1650, 1640, 1575; MS, m/e (relative intensity) 242 (M^+, 100), 225 (63), 214 (46), 187 (39). The quinone **12** was used without further purification because of its instability and sufficient purity.

Tandem Michael/Diels–Alder Reaction of Acryloyl Quinone 12 with PDT (13). Method A (Table I, Entries 1–7).

(24) For the 11-hydroxyl derivatives, organocerium and manganese reagents have been reported to be effective: Suzuki, M.; Kimura, Y.; Terashima, S. *Chem. Pharm. Bull.* **1986**, *34*, 1531. Hiyama, T.; Sawahata, M.; Kusano, Y. *Chem. Lett.* **1985**, 611. Recently, it was reported that organocerium reagent is also effective for 11-deoxydaunomycin synthesis: Tamura, Y.; Akai, S.; Kishimoto, H.; Kirihara, M.; Sasho, M.; Kita, Y. *Tetrahedron Lett.* **1987**, *28*, 4583.

(25) For a similar compound: Broadhurst, M. J.; Hassal, C. H.; Thomas, G. J. Eur. Pat. 44954.

(26) Krohn, K. *Liebigs Ann. Chem.* **1981**, 2285.

(27) An ethyl analogue of **26** has been reported by Hauser and Prasanna. Hauser, F. M.; Prasanna, S. *Tetrahedron* **1984**, *40*, 4711.

(28) Krohn, K.; Priyono, W. *Tetrahedron* **1984**, *40*, 4609.

To a solution of acryloyl quinone **12** (0.5 mmol) in CH_2Cl_2 (10 mL) were added PDT **13** (130 mg, 0.56 mmol) in CH_2Cl_2 (1 mL) and Lewis acid (0.6 mmol) at the indicated temperature in Table I under nitrogen. After being stirred for 15 min (except entry 6; see footnote in Table I) at the indicated temperature, the reaction mixture was poured into 5% aqueous HCl. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase was washed with 5% aqueous HCl three times and worked up as usual.

Method B (Table I, Entries 8–11). To a solution of PDT **13** (130 mg, 0.56 mmol) in CH_2Cl_2 (5 mL) was added the indicated amount of $SnCl_4$ at −78 °C under nitrogen, and the mixture was stirred for 10 min. A cold (−78 °C) solution of **12** (0.5 mmol) in CH_2Cl_2 (5 mL) was added to the tin compound solution at −78 °C. After stirring the reaction mixture for 15 min at −78 °C, it was worked up as stated in method A.

7,8,10a,11-Tetrahydro-5,12-dihydroxy-4-methoxy-6-(6a*H*)-naphthacenone[29] **(8)** was isolated by chromatography (10% ethyl acetate in CH_2Cl_2), yellow crystals (from CH_2Cl_2): mp 183–185 °C (lit.[21] mp 239–242 °C); NMR ($CDCl_3$) δ 1.85 (m, 1 H), 2.15 (m, 3 H), 2.82 (dd, 1 H, *J* = 15, 8 Hz), 2.85–2.88 (m, 2 H), 3.07 (dd, 1 H, *J* = 15, 4 Hz), 4.01 (s, 3 H), 4.62 (s, 1 H), 5.62 (dm, 1 H, *J* = 10 Hz), 5.73 (dm, 1 H, *J* = 10 Hz), 6.86 (d, 1 H, *J* = 7 Hz), 7.53 (t, 1 H, *J* = 7 Hz), 7.61 (d, 1 H, *J* = 7 Hz), 15.22 (s, 1 H); IR (KBr) 3400, 1610, 1590, 1560; MS, *m/e* (relative intensity) 310 (M^+, 100).

The keto form (**21**) of the tetracyclic product could not be isolated because of its easy isomerization to the hydroquinone **8** during chromatographic purification and its presence in the reaction mixture was observed by ^1H NMR. **21**: NMR ($CDCl_3$) δ ca. 1.6, 3.55 (dd, *J* = 11, 4 Hz), 16.81 (s, OH).

3-Acryloyl-4-hydroxy-5-methoxy-2-((*Z*)-2,4-pentadienyl)-1(2*H*)-naphthalenone (22), unstable oil: NMR ($CDCl_3$) δ 2.55 (dd, 1 H, *J* = 7.9, 7.2 Hz), 3.73 (t, 1 H, *J* = 7.2 Hz), 4.02 (s, 3 H), 5.02 (d, 1 H, *J* = 10.1 Hz), 5.14 (d, 1 H, *J* = 16.8 Hz), 5.22 (dt, 1 H, *J* = 10.7, 7.9 Hz), 5.76 (dd, 1 H, *J* = 10.4, 1.8 Hz), 5.97 (dd, 1 H, *J* = 10.7, 11.3 Hz), 6.25 (ddd, 1 H, *J* = 16.8, 11.3, 10.1 Hz), 6.46 (dd, 1 H, *J* = 16.8, 1.8 Hz), 6.66 (dd, 1 H, *J* = 10.4, 16.8 Hz), 7.31 (d, 1 H, *J* = 7.6 Hz), 7.50 (d, 1 H, *J* = 7.6 Hz), 7.62 (t, 1 H, *J* = 7.6 Hz), 16.93 (s, 1 H).

The yield of the tetracyclic product shown in Table I was determined after oxidation to the corresponding tetracyclic quinone **23** according to the following procedure.

7,8-Dihydro-6-hydroxy-4-methoxy-5,12-naphthacenedione (23). The crude tetracyclic product **8** obtained above was dissolved in DMF (5 mL) in a round-bottomed flask equipped with a gas inlet and a balloon as an oxygen reservoir. The solution was heated at 100 °C with vigorous stirring under an oxygen atmosphere for 3 h. After DMF was removed under reduced pressure, the residue was purified by chromatography (CH_2Cl_2) to give **23** in the indicated overall yield from acryloyl quinone **12** in Table I. **23**, orange needles (from benzene–methanol): mp 211–213 °C (lit.[21] mp 217–220 °C); NMR ($CDCl_3$) δ 2.40 (dt, 2 H, *J* = 4, 9 Hz), 2.93 (t, 2 H, *J* = 9 Hz), 4.04 (s, 3 H), 6.24 (dt, 1 H, *J* = 10, 4 Hz), 6.50 (d, 1 H, *J* = 10 Hz), 7.29 (d, 1 H, *J* = 8 Hz), 7.39 (s, 1 H), 7.66 (t, 1 H, *J* = 8 Hz), 7.90 (d, 1 H, *J* = 8 Hz), 13.19 (s, 1 H); IR (KBr) 3400, 1660, 1625, 1610, 1575; MS, *m/e* (relative intensity) 306 (M^+, 100), 291 (35), 288 (32). Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.48; H, 4.61.

Intermolecular Diels–Alder Reaction between 12 and 13. 4a-Acryloyl-1,4,4a,10a-tetrahydro-5-methoxy-4-[(trimethylstannyl)methyl]-9,10-anthracenedione (27′). To a solution of **12** (0.5 mmol) in CH_2Cl_2 (10 mL) was added PDT **13** (130 mg, 0.56 mmol) at 0 °C. After stirring the mixture for 1 h at 0 °C, the solvent was evaporated. The crude product was applied to NMR measurement without purification owing to its instability. **27′**: NMR ($CDCl_3$) δ 0.04 (s, 9 H, J_{Sn-H} = 53.7, 51.3 Hz), 0.70 (dd, 1 H, *J* = 11.5, 3.5 Hz), 0.83 (dd, 1 H, *J* = 13.3, 11.5 Hz), 2.12 (dm, 1 H, *J* = 16.6 Hz), 2.81 (br d, 1 H, *J* = 18.6 Hz), 3.15 (br d, 1 H, *J* = 13.3 Hz), 3.88 (dd, 1 H, *J* = 7.5, 4.2 Hz), 3.96 (s, 3 H), 5.60 (dm, 1 H, *J* = 10.0 Hz), 5.67 (dd, 1 H, *J* = 10.7, 2.0 Hz), 5.69 (dm, 1 H, *J* = 10.0 Hz), 6.31 (dd, 1 H, *J* = 16.9, 2.0 Hz), 6.85 (dd, 1 H, *J* = 16.9, 10.7 Hz), 7.28 (d, 1 H, *J* = 8.1 Hz), 7.61 (d, 1 H, *J* = 8.1 Hz), 7.67 (t, 1 H, *J* = 8.1 Hz); IR (neat) 1690, 1600, 1580.

Tandem Michael/Diels–Alder Reaction of 12 and 2-Substituted-PDTs 14–16. General Method (Table II). To a solution of acryloyl quinone **12** (0.5 mmol) in CH_2Cl_2 (10 mL) were added a substituted PDT (0.6 mmol)[10] in CH_2Cl_2 (1 mL) and Lewis acid (1.5 mmol) at −78 °C under nitrogen. After being stirred for 1.5 h at −78 °C, the reaction mixture was poured into 5% aqueous H_2SO_4. The aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with 5% aqueous H_2SO_4 five times and worked up as usual. After filtration through silica gel (10% ethyl acetate in CH_2Cl_2), the product mixture was subjected to oxidation in a manner analogous to that mentioned above for **23**. The tetracyclic quinone was isolated by column chromatography (CH_2Cl_2).

7,8-Dihydro-6-hydroxy-4-methoxy-9-(methoxymethyl)-5,12-naphthacenedione (24), orange needles (from benzene–methanol): mp 225–227 °C; NMR ($CDCl_3$) δ 2.35 (t, 2 H, *J* = 8.6 Hz), 2.97 (t, 2 H, *J* = 8.6 Hz), 3.40 (s, 3 H), 4.05 (s, 2 H), 4.06 (s, 3 H), 6.51 (br, 1 H), 7.33 (d, 1 H, *J* = 8 Hz), 7.48 (s, 1 H), 7.70 (t, 1 H, *J* = 8 Hz), 7.94 (d, 1 H, *J* = 8 Hz), 13.26 (s, 1 H); IR (KBr) 3400, 1650, 1620, 1580; MS, *m/e* (relative intensity) 350 (M^+, 100), 335 (24), 318 (48), 305 (57). Anal. Calcd for $C_{21}H_{18}O_5$: C, 71.99; H, 5.18. Found: C, 71.67; H, 5.06.

7,8-Dihydro-6-hydroxy-9-isopropyl-4-methoxy-5,12-naphthacenedione (25), orange needles (from CH_2Cl_2–ether): mp 163–165 °C; NMR ($CDCl_3$) δ 1.15 (d, 6 H, *J* = 6.8 Hz), 2.33 (t, 2 H, *J* = 8.3 Hz), 2.48 (heptet, 1 H, *J* = 6.8 Hz), 2.93 (t, 2 H, *J* = 8.3 Hz), 4.07 (s, 3 H), 6.30 (d, 1 H, *J* = 1.5 Hz), 7.33 (d, 1 H, *J* = 8 Hz), 7.45 (s, 1 H), 7.70 (t, 1 H, *J* = 8 Hz), 7.94 (d, 1 H, *J* = 8 Hz), 13.27 (s, 1 H); IR (KBr) 3430, 1660, 1635, 1615, 1580; MS, *m/e* (relative intensity) 348 (M^+, 99), 333 (37), 305 (100), 290 (26), 287 (37). Anal. Calcd for $C_{22}H_{20}O_4$: C, 75.84; H, 5.79. Found: C, 75.74; H, 5.84.

7,8-Dihydro-6-hydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (26), orange needles (from CH_2Cl_2–hexane): mp 232–234 °C; NMR ($CDCl_3$) δ 1.97 (br s, 3 H), 2.32 (t, 2 H, *J* = 8 Hz), 2.96 (t, 2 H, *J* = 8 Hz), 4.05 (s, 3 H), 6.28 (br s, 1 H), 7.31 (d, 1 H, *J* = 8 Hz), 7.38 (s, 1 H), 7.68 (t, 1 H, *J* = 8 Hz), 7.93 (d, 1 H, *J* = 8 Hz), 13.25 (s, 1 H); IR (KBr) 3420, 1665, 1620, 1615, 1580; MS, *m/e* (relative intensity) 320 (M^+, 100), 305 (79), 302 (30), 290 (24), 287 (28). Anal. Calcd for $C_{20}H_{16}O_4$: C, 74.99; H, 5.03. Found: C, 74.90; H, 4.93.

Epoxidation of Tetracyclic Quinones. General Method. To a solution of a tetracyclic quinone (1 mmol) in CH_2Cl_2 (40 mL) was added *m*-chloroperbenzoic acid (80%, 324 mg, 1.5 mmol) at 0 °C. Stirring was continued for 8 h at 0 °C to room temperature. An aqueous solution of $NaHSO_3$ (2%) was added to the reaction mixture. The organic phase was washed with a saturated $NaHCO_3$ solution twice and worked up as usual. The residue was chromatographed (5% ethyl acetate in CH_2Cl_2) to give the corresponding epoxide.

9,10-Epoxy-7,8,9,10-tetrahydro-6-hydroxy-4-methoxy-5,12-naphthacenedione (27; 367 mg, 1.14 mmol, 92% from 380 mg (1.24 mmol) of **23**), orange yellow needles (from CH_2Cl_2–hexane): mp 198–200 °C dec (lit.[21] mp 217–219 °C); NMR ($CDCl_3$) δ 1.75 (ddd, 1 H, *J* = 13.6, 6.4, 5.6 Hz), 2.40 (ddd, 1 H, *J* = 16.7, 6.4, 5.6 Hz), 2.51 (dd, 1 H, *J* = 13.6, 5.6 Hz), 3.17 (dd, 1 H, *J* = 16.7, 5.6 Hz), 3.78 (br, 1 H), 3.91 (d, 1 H, *J* = 4.0 Hz), 4.07 (s, 3 H), 7.35 (d, 1 H, *J* = 8 Hz), 7.74 (t, 1 H, *J* = 8 Hz), 7.83 (s, 1 H), 7.96 (d, 1 H, *J* = 8 Hz), 13.28 (s, 1 H); IR (KBr) 3440, 1665, 1625, 1580; MS, *m/e* (relative intensity) 322 (M^+, 100), 307 (26), 305 (28), 294 (31). Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.53; H, 4.22.

9,10-Epoxy-7,8,9,10-tetrahydro-6-hydroxy-4-methoxy-9-(methoxymethyl)-5,12-naphthacenedione (28; 104 mg, 0.283 mmol, 87% from 114 mg (0.326 mmol) of **24**), orange yellow needles (from CH_2Cl_2–hexane): mp 219–221 °C dec; NMR ($CDCl_3$) δ 1.79 (m, 1 H), 2.47 (m, 2 H), 3.23 (m, 1 H), 3.45 (s, 3 H), 3.65 (d, 1 H, *J* = 11.2 Hz), 3.78 (d, 1 H, *J* = 11.2 Hz), 3.90 (s, 1 H), 4.08 (s, 3 H), 7.37 (dd, 1 H, *J* = 8, 1.0 Hz), 7.75 (t, 1 H, *J* = 8 Hz), 7.84 (s, 1 H), 7.97 (dd, 1 H, *J* = 8, 1.0 Hz), 13.28 (s, 1 H); IR (KBr) 3430, 1670, 1620, 1585; MS, *m/e* (relative intensity) 366 (M^+, 55), 338 (37), 323 (31), 321 (100), 306 (25). Anal. Calcd for $C_{21}H_{18}O_6$: C, 68.85; H, 4.95. Found: C, 68.83; H, 4.75.

9,10-Epoxy-7,8,9,10-tetrahydro-6-hydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (29; 184 mg, 0.547 mmol, 83%

(29) The numbering of the tetracyclic compounds (naphthacene derivatives) will obey the anthracycline numbering here.

from 211 mg (0.659 mmol) of **26**), orange yellow needles (from CH_2Cl_2–hexane): mp 235–239 °C dec; NMR ($CDCl_3$) δ 1.57 (s, 3 H), 1.75 (ddd, 1 H, J = 14.7, 13.1, 5.9 Hz), 2.29 (dd, 1 H, J = 14.7, 6.4 Hz), 2.43 (ddd, 1 H, J = 16.7, 13.1, 6.4 Hz), 3.12 (dd, 1 H, J = 16.7, 5.9 Hz), 3.68 (s, 1 H), 4.04 (s, 3 H), 7.32 (dd, 1 H, J = 8.1, 1.0 Hz), 7.70 (t, 1 H, J = 8.1 Hz), 7.75 (s, 1 H), 7.91 (dd, 1 H, J = 8.1, 1.0 Hz), 13.22 (s, 1 H); IR (KBr) 3430, 1665, 1620, 1580; MS, m/e (relative intensity) 366 (M^+, 59), 321 (39), 308 (100), 293 (34). Anal. Calcd for $C_{20}H_{16}O_5$: C, 71.42; H, 4.79. Found: C, 71.39; H, 4.74.

7,8-Dihydro-6-hydroxy-4-methoxy-5,9(10*H*),12-naphthacenetrione (30). To a solution of epoxide **27** (229 mg, 0.711 mmol) in CH_2Cl_2–toluene (30 mL, 1:1) were added 2,6-lutidine (0.18 mL) and trimethylsilyl trifluoromethanesulfonate (0.30 mL) successively at room temperature under nitrogen. The solution was heated at 80 °C for 5 h with stirring. The reaction mixture was quenched with water after cooling and extracted with CH_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ and 5% aqueous HCl and worked up as usual. The residual toluene solution was poured onto silica gel and eluted with CH_2Cl_2 and then 5% ethyl acetate in CH_2Cl_2 to give 206 mg (0.64 mmol, 90%) of trione **30**, orange needles (from benzene–methanol–CH_2Cl_2): mp >250 °C dec (lit. 258–259 °C,[30] 241–243 °C dec,[31] 256–258 °C,[21] 256–257 °C dec[32]); NMR ($CDCl_3$) δ 2.61 (t, 2 H, J = 6.8 Hz), 3.24 (t, 2 H, J = 6.8 Hz), 3.68 (s, 2 H), 4.09 (s, 3 H), 7.37 (d, 1 H, J = 8 Hz), 7.54 (s, 1 H), 7.76 (t, 1 H, J = 8 Hz), 7.97 (dd, 1 H, J = 8, 1 Hz), 13.45 (s, 1 H); IR (KBr) 3420, 1710, 1670, 1625; MS, m/e (relative intensity) 322 (M^+, 100), 294 (86), 279 (86). Anal. Calcd for $C_{19}H_{14}O_5$: C, 70.80; H, 4.38. Found: C, 70.65; H, 4.29.

7,8,9,10-Tetrahydro-6,9-dihydroxy-4-methoxy-9-(methoxymethyl)-5,12-naphthacenedione (9-Deacetyl-7,11-dideoxy-9-(methoxymethyl)daunomycinone) (31). To a suspension of Pd/C (10%, 5 mg) in ethanol (5 mL) were added epoxide **28** (81.7 mg, 0.223 mmol) in THF (10 mL), triethanolamine (3 mL), and ethanol (3 mL) under hydrogen at room temperature with vigorous stirring. After 5 h, the reaction mixture was filtered to remove Pd/C, and the filtrate was partitioned with water and CH_2Cl_2. The organic phase was dried and evaporated. The residue was purified by chromatography (10% ethyl acetate in CH_2Cl_2) to give alcohol **31** (77.5 mg, 0.205 mmol, 92%), orange needles (from CH_2Cl_2–hexane): mp 208–210 °C; NMR ($CDCl_3$) δ 1.80 (ddd, 1 H, J = 13.2, 8.8, 7.3 Hz), 2.00 (dt, 1 H, J = 13.2, 6.4 Hz), 2.52 (br s, 1 H), 2.91 (m, 4 H), 3.38 (s, 2 H), 3.44 (s, 3 H), 4.06 (s, 3 H), 7.33 (dd, 1 H, J = 8.3, 1.0 Hz), 7.47 (s, 1 H), 7.71 (dd, 1 H, J = 8.3, 7.8 Hz), 7.93 (dd, 1 H, J = 7.8, 1.0 Hz), 13.36 (s, 1 H); IR (KBr) 3470, 1665, 1620, 1580; MS, m/e (relative intensity) 368 (M^+, 34), 350 (14), 323 (96), 305 (100). Anal. Calcd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47. Found: C, 68.60; H, 5.35.

7,8,9,10-Tetrahydro-6,9-dihydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (7,11-dideoxyfeudomycinone C) (32) was synthesized by a similar method to that for **31**. From 55 mg (0.164 mmol) of **29**, 51 mg (0.151 mmol, 92%) of **32** was obtained after chromatographic purification. **32**, orange needles (from CH_2Cl_2–hexane): mp 220–222 °C (lit.[33] mp 202 °C); NMR ($CDCl_3$) δ 1.39 (s, 3 H), ca. 1.8 (br, 1 H), 1.80 (ddd, 1 H, J = 13.7, 8.3, 7.3 Hz), 1.97 (dt, 1 H, J = 13.7, 5.9 Hz), 2.89 (m, 4 H), 4.06 (s, 3 H), 7.33 (dd, 1 H, J = 7.8, 1.0 Hz), 7.41 (s, 1 H), 7.70 (t, 1 H, J = 7.8 Hz), 7.90 (dd, 1 H, J = 7.8, 1.0 Hz), 13.32 (s, 1 H); IR (KBr) 3430, 1660, 1620, 1580; MS, m/e (relative intensity) 338 (M^+, 94), 320 (80), 305 (100), 295 (99). Anal. Calcd for $C_{20}H_{18}O_5$: C, 71.00; H, 5.36. Found: C, 70.71; H, 5.31.

7,8,9,10-Tetrahydro-6,9,10-trihydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (7,11-Dideoxyfeudomycinone D) (33). A solution of epoxide **29** (49 mg, 0.145 mmol) in acetone (25 mL) and 6 N H_2SO_4 (0.3 mL) was heated at 60 °C for 30 min with stirring. The reaction mixture was poured into aqueous $NaHCO_3$–ice and extracted with CH_2Cl_2. The organic phase was washed with water and brine. The aqueous phase reextracted with CH_2Cl_2. The combined organic phase was dried over $MgSO_4$ and evaporated. The residue was chromatographed (CH_2Cl_2–ethyl acetate (20% to 50%)) to give **33** in 93% yield (47 mg, 0.133 mmol), yellow crystals (from CH_2Cl_2): mp 252–256 °C dec; NMR ($CDCl_3$) δ 1.26 (s, 3 H), 1.86 (br, 1 H), 1.94 (ddd, 1 H, J = 13.5, 9.1, 6.7 Hz), 2.07 (ddd, 1 H, J = 13.5, 6.7, 4.4 Hz), 2.44 (d, 1 H, J = 5.6 Hz), 2.81 (ddd, 1 H, J = 19.4, 9.1, 6.7 Hz), 3.01 (ddd, 1 H, J = 19.4, 6.7, 4.4 Hz), 4.07 (s, 3 H), 4.59 (d, 1 H, J = 4.4 Hz), 7.35 (dd, 1 H, J = 8, 1.2 Hz), 7.74 (t, 1 H, J = 8 Hz), 7.96 (s, 1 H), 7.97 (dd, 1 H, J = 8, 1.2 Hz), 13.33 (s, 1 H); IR (KBr) 3520, 3440, 1650, 1620, 1580; MS, m/e (relative intensity) 354 (M^+, 49), 307 (29), 296 (43), 293 (100), 268 (61). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.58; H, 5.15.

7,8,9,10-Tetrahydro-6,7,9-trihydroxy-4-methoxy-9-(methoxymethyl)-5,12-naphthacenedione (9-Deacetyl-9-(methoxymethyl)-11-deoxydaunomycinone) (7). A solution of **31** (67 mg, 0.182 mmol) and Br_2 (58 mg) in CCl_4 (200 mL) was stirred for 1 h at room temperature with light irradiation. After evaporation of the solvent in vacuo, 50 mL of aqueous NaOH solution (0.5 N) was added and stirred for 30 min at 0 °C. The dark purple mixture was neutralized with cold 5% H_2SO_4, and the resulting orange suspension was extracted with CH_2Cl_2 three times. The combined extract was worked up as usual. After chromatographic purification (2% methanol in CH_2Cl_2), 56 mg (0.146 mmol, 80%) of **7** was obtained, orange yellow flakes (from ethanol–CH_2Cl_2–ether): mp 223–227 °C dec; NMR ($CDCl_3$) δ 1.99 (dd, 1 H, J = 14.4, 5.1 Hz), 2.33 (dt, 1 H, J = 14.4, 2.3 Hz), 2.93 (d, 1 H, J = 7.7 Hz), 3.03 (dd, 1 H, J = 7.7, 1.9 Hz), 3.41 (s, 2 H), 3.45 (s, 3 H), 3.64 (s, 1 H), 3.69 (d, 1 H, J = 5.1 Hz), 4.06 (s, 3 H), 5.29 (br s, 1 H), 7.35 (dd, 1 H, J = 8.4, 0.9 Hz), 7.53 (s, 1 H), 7.73 (t, 1 H, J = 8.4, 7.9 Hz), 7.93 (dd, 1 H, J = 7.9, 0.9 Hz), 13.60 (s, 1 H); IR (KBr) 3520, 3480, 1665, 1620, 1580; MS, m/e (relative intensity) 384 (M^+, 45), 366 (13), 348 (28), 321 (100), 293 (30), 268 (18). Anal. Calcd for $C_{21}H_{20}O_7$: C, 65.62; H, 5.24. Found: C, 65.32; H, 5.13.

7,8,9,10-Tetrahydro-6,7,9-trihydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (11-Deoxyfeudomycinone C) (5). In a similar method to that applied for the synthesis of **7**, 55 mg (0.155 mmol, 66%) of **5** was obtained after chromatographic purification (2% methanol in CH_2Cl_2) from 79 mg (0.233 mmol) of **32** and 56 mg of Br_2. **5**, orange yellow needles (from ethanol–CH_2Cl_2–ether): mp 233–238 °C dec; NMR ($CDCl_3$) δ 1.44 (s, 3 H), 1.96 (dd, 1 H, J = 15.0, 5.1 Hz), 2.36 (dt, 1 H, J = 15.0, 2.1 Hz), 2.84 (d, 1 H, J = 17.5 Hz), 3.08 (dd, 1 H, J = 17.5, 2.1 Hz), 3.48 (br, 1 H), 3.58 (br, 1 H), 4.08 (s, 3 H), 5.31 (m, 1 H), 7.37 (dd, 1 H, J = 8.5, 0.9 Hz), 7.57 (s, 1 H), 7.75 (t, 1 H, J = 8.5, 7.7 Hz), 7.97 (dd, 1 H, J = 7.7, 0.9 Hz), 13.66 (s, 1 H); IR (KBr) 3480, 1660, 1620, 1580; MS, m/e (relative intensity) 354 (M^+, 29), 336 (26), 318 (100), 300 (90), 272 (28), 268 (29). Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 67.56; H, 4.94.

7,8,9,10-Tetrahydro-6,7,9,10-tetrahydroxy-4-methoxy-9-methyl-5,12-naphthacenedione (11-Deoxyfeudomycinone D) (6). Protection of 45 mg (0.127 mmol) of **33** was carried out with trifluoroacetic anhydride (0.35 mL) in 3 mL of CH_2Cl_2 at room temperature under nitrogen for 4.5 h. Ice–water was added to the reaction mixture and the product was extracted with CH_2Cl_2. The organic phase was washed with cold water and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the residue was applied to hydroxylation at C-7 in a similar manner as mentioned above with Br_2 (41 mg). Chromatographic purification (3% methanol in CH_2Cl_2) gave **6** (30.6 mg, 0.083 mmol, 65%), orange crystals (from ethanol–benzene): mp 230–235 °C dec; NMR ($CDCl_3$) δ 1.38 (s, 3 H), 2.13 (dd, 1 H, J = 14.8, 3.8 Hz), 2.26 (d, 1 H, J = 4.8 Hz), 2.38 (dd, 1 H, J = 14.8, 4.8 Hz), 3.22 (s, 1 H), 3.58 (d, 1 H, J = 2.4 Hz), 4.09 (s, 3 H), 4.56 (d, 1 H, J = 4.8 Hz), 5.28 (dt, 1 H, J = 5.2, 2.5 Hz), 7.39 (dd, 1 H, J = 8.6, 1.0 Hz), 7.78 (t, 1 H, J = 8.6, 7.6 Hz), 7.91 (s, 1 H), 7.99 (dd, 1 H, J = 7.6, 1.0 Hz), 13.70 (s, 1 H); IR (KBr) 3550, 3430, 1660, 1615, 1580; MS, m/e (relative intensity) 370 (M^+, 2), 352 (100), 334 (56), 310 (88), 309 (89), 294 (47). Anal. Calcd for $C_{20}H_{18}O_7$: C, 64.86; H, 4.90. Found: C, 65.00; H, 4.75.

Registry No. **5**, 112740-45-1; **6**, 112740-47-3; **7**, 112740-44-0; **8**, 88792-66-9; **12**, 88792-65-8; (*E*)-**13**, 78823-83-3; (*Z*)-**13**, 78823-84-4; **14**, 112740-33-7; **15**, 112740-35-9; **16**, 112740-36-0; **17a**,

(30) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, W. *Tetrahedron Lett.* **1980**, 3351.

(31) Alexander, J.; Flynn, D. L.; Mitscher, L. A.; Veysogln, T. *Tetrahedron Lett.* **1981**, *22*, 3711.

(32) Tamura, Y.; Sasho, M.; Akai, S.; Wada, A.; Kita, Y. *Tetrahedron* **1984**, *40*, 4539.

(33) Krohn, K.; Broser, E. *Liebigs Ann. Chem.* **1982**, 1907.

3843-55-8; **17b**, 112740-31-5; **18**, 88792-61-4; **19**, 88792-64-7; **21**, 112740-32-6; **22**, 109273-93-0; **23**, 84810-71-9; **24**, 112740-37-1; **25**, 112740-38-2; **26**, 112740-39-3; **27**, 84810-72-0; **27'**, 109273-94-1; **28**, 112740-40-6; **29**, 112763-18-5; **30**, 77219-86-4; **31**, 112740-41-7; **32**, 112740-42-8; **33**, 112740-43-9; **34**, 112740-46-2; 1,5-dimethoxy-3-[2-(phenylseleno)propionyl]-4-naphthol, 88792-63-6; 2-(methoxymethyl)-1,4-pentadiene, 57217-20-6; [(*Z*)-4-(methoxymethyl)-2,4-pentadienyl]trimethyltin, 112740-34-8.

Furan-2-carbaldehyde Dimethylhydrazones in Diels–Alder Cycloadditions[1]

Kevin T. Potts* and Eileen B. Walsh

Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12181

Received March 5, 1987

Furan-2-carbaldehyde dimethylhydrazone and maleic anhydride and N-substituted maleimides and fumaronitrile in chloroform at room temperature readily formed nonisolable 1:1 cycloadducts which spontaneously lost water, giving 1,2,3-trisubstituted benzenes in good yield. With alkynic dienophiles no cycloaddition occurred, and with quinones Michael addition of the furan nucleus to the quinone was the preferred reaction.

1,4-Cycloadditions of furans with alkenic and alkynic dienophiles provide convenient entry to a variety of 7-oxabicyclo[2.2.1]heptanes and -heptenes,[2] which, by opening of the oxygen bridge, offer a convenient route to unusually substituted benzenes. Cycloadditions of substituted thiophenes[3] and *N*-aminopyrrole derivatives[4] are also useful methods for obtaining substituted benzenes as well as for the annulation of benzene rings. Vinyl derivatives of these five-membered heterocycles, however, also undergo cycloaddition under a variety of reaction conditions except that in these instances the diene is comprised of the exocyclic vinyl group and the endocyclic double bond of the heterocyclic ring. Such cycloadditions result in benzo[*b*]furans,[5a] benzo[*b*]thiophenes,[5b] and benzo[*b*]-pyrroles[5c] when electron-deficient dienophiles are used.

Furfural and related furans substituted with electron-withdrawing groups are poor dienes in these types of cycloadditions, restricting entry to arenes containing 1,2,3 arrangements of electron-withdrawing groups. As these initial furan substituents are meta-directing groups in benzene substitution, more circuitous routes are needed for the synthesis of these arenes. Recent work in which methacrolein dimethylhydrazone functioned[6] as a 1-azadiene leading to pyridine derivatives suggested that incorporation of the dimethylhydrazono group into furan and related five-membered heterocycles would have the potential for enhancing the dienic character of the ring system. MO calculations[7] show that by introducing the dimethylhydrazono group into the furan nucleus an increase in its HOMO energy, relative to that of furan and 2-vinylfuran, results. A significant increase in the HOMO coefficient at the C-5 position compared to that at the C-2 position also occurs, consistent with an increase in electron density at that position due to resonance interaction with the hydrazono substituent (Figure 1).

Furfural dimethylhydrazone (**1a**), readily prepared[8] from furfural and *unsym*-dimethylhydrazine in refluxing benzene/catalytic amount of *p*-toluenesulfonic acid, reacted with maleic anhydride in $CHCl_3$ (room temperature, 16 h), giving 3-dimethylhydrazonophthalic anhydride (**3a**) in almost quantitative yield as bright yellow needles. Similarly, **1a** and *N*-ethylmaleimide resulted in **3b** (90%).

The reactions proceed by formation of an initial 1:1-cycloadduct **2** derived from the dienic system of the furan ring and the dienophile. This initial cycloadduct cannot be isolated and undergoes aromatization by the spontaneous elimination of H_2O. We were not able to follow the development of the intermediate **2** using NMR techniques. This is analogous to the reported[9] aromatization of the adduct from maleic anhydride and the bis-anil formed from substituted furfural and *p*-phenylenediamines. In addition, the dehydration to the benzenoid system is aided by electron donation from the hydrazono substituent assisting in the rupture of the oxygen bridge. Cycloaddition occurring across the furan ring rather than across the vinyl system may also be due to the conformational preference of the furan aldehyde group,[10] which does not favor the cisoid azadiene form of the hydrazone.

These cycloadditions provide a convenient route to substituted benzenes such as 3-hydroxyphthalide-7-carboxylic acid (**4**). This was obtained by acid hydrolysis (15% aqueous HCl) of **3a** to give the formyl dicarboxylic acid which rearranged to **4**. Spectral data were consistent with the assigned structure **4**, especially ν_{OH} 3500–3160 cm^{-1}, ν_{CO} 1800–1610 cm^{-1}, and the presence of a benzylic hydrogen at δ 8.26. The phthalide **4** is of special interest

(1) Abstracted from the Ph.D. Thesis of E.B.W., 1985.
(2) For recent reviews, see: Dean, F. M. *Adv. Heterocycl. Chem.* **1981**, *30*, 168.
(3) Helder, R.; Wynberg, H. *Tetrahedron Lett.* **1972**, 605.
(4) Schultz, A. G.; Shen, M. *Tetrahedron Lett.* **1979**, 2969.
(5) (a) Paul, R. *Bull. Soc. Chim. Fr.* **1943**, 163. Davidson, W. J.; Elix, J. A. *Aust. J. Chem.* **1973**, *26*, 1059. (b) Szmuszkovicz, J.; Modest, E. J. *J. Am. Chem. Soc.* **1950**, *72*, 571. Pryor, W. A.; Cocco, J. H.; Daly, W. H.; Houk, K. N. *J. Am. Chem. Soc.* **1974**, *96*, 6112. (c) Lee, C. K.; Bae, S. K.; Cheng, B. Y.; Hahn, C. S. *J. Org. Chem.* **1983**, *48*, 2488.
(6) Serckx-Poncin, B.; Hesbain-Frisque, A.; Ghosez, L. *Tetrahedron Lett.* **1982**, *23*, 3261. Potts, K. T.; Walsh, E. B.; Bhattacharjee, D. *J. Org. Chem.* **1987**, *52*, 2285.
(7) Determined by simple Hückel calculations in which the ω technique was used to obtain self-consistency [Streitwieser, A. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961, p 115].
(8) The dimethylhydrazones could be prepared in a pure state and kept without decomposition at low temperatures. They were thoroughly characterized by spectral data as satisfactory analytical data were not obtained due to slight decomposition during transit.
(9) Barlin, A. A.; Liogon'skii, B. I.; Zapadinskii, B. I.; Kozantsevc, E. A.; Stankevich, A. O. *Izv. Akad. Nauk. SSSR, Ser. Khim.* **1977**, 867.
(10) Larsen, B. R.; Nicolaisen, F.; Nielsen, J. T. *Acta Chem. Scand.* **1972**, *26*, 1736. Chadmick, D. J.; Meakins, G. D.; Richards, E. E. *Tetrahedron Lett.* **1974**, 3183.

0022-3263/88/1953-1199$01.50/0