bridgehead protons are clearly observable at 5.78 and 3.15 ppm respectively. The equilibrium constant was determined at each temperature by integration of the unobscured bicyclic form doublet at 3.15 ppm (S:N > 10:1) relative to both the ^{13}C satellites of COT[7] and COT itself. As the equilibrium constants measured by integration are on the order of 10^{-3}, we are well within the dynamic range limit of the spectrometer. Integration of ^{13}C satellites served as an internal check on the accuracy of the COT integration and we found all COT–^{13}C satellite ratios to be within 5% of the naturally occurring isotope ratio, so no saturation of the COT resonance occurred. Given the 16-ms residence time for our system, the maximum free energy of activation required for equilibrium is calculated to be 45 and 31 kcal/mol at 700 and 400 °C, respectively. Both of these values are substantially higer than the reported activation energy for the COT equilibration process,[2,3,8] so complete equilibration occurs in the oven. The trapping process involves an intermolecular vibrational energy transfer at the cold surface which is known to occur with a rate of 10^{12} sec^{-1}.[9] Because this rate is considerably faster than the reequilibration rate, the trapping efficiency should be essentially unity. In fact, we have previously shown that complete trapping occurs at 20 K with a conformational mixture which reequilibrates at 45 K.[5b]

A van't Hoff plot of K_{eq} over the temperature range 400–700 °C yielded values of 5.5 ± 0.6 kcal/mol for $\Delta H°$ and −4.3 ± 0.7 eu for $\Delta S°$. Extrapolation of our data to 100 °C yields a $\Delta G°$ value of 7.1 kcal/mol, which is in good agreement with Huisgen's indirect estimate. The relatively large entropy difference between I and II can be attributed to the different flexibilities of the two species.[10] Semibullvalene has been found to be 3.02 eu less entropically favorable than COT.[11] However, because semibullvalene can undergo a very facile Cope rearrangement[12] it would be expected to be entropically more favorable than the rigid II. Our value for $\Delta S°$ bears this out.

Also observed from our pyrolysis of COT were resonances due to both dihydropentalene and semibullvalene in amounts which varied with temperature. Semibullvalene had not been detected in previous COT flash pyrolytic studies;[13,14] however, the detection methods used in those studies (GC and IR) would not adequately resolve the expected small amounts of semibullvalene from COT. It has recently been suggested that semibullvalene is not produced directly from COT but rather through the bicyclo[3.3.0]octa-2,6-diene-4,8-diyl biradical which can also produce dihydropentalene.[12] Our results agree with these authors in that dihydropentalene must be produced via a much higher energy transition state than semibullvalene since we trap approximately 5-fold less dihydropentalene than semibullvalene. Direct production of semibullvalene from COT[15,16] is, however, not ruled out by either set of experiments. The COT ⇄ semibullvalene equilibrium may not be completely established with our system, but we see 5.0% semibullvalene, which substantially agrees with the results of Martin et al.[11] Our results establish the usefulness of this trapping technique and, due to the strong entropic contribution to $\Delta G°$, show that temperature effects will be quite important in the synthetic chemistry of the COT system.

Registry No. I, 629-20-9; II, 4011-16-9; dihydropentalene, 91981-09-8; semibullvalene, 6909-37-1.

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(10) The rotational contribution to the entropy for species I and II favors II by R ln 4 due to symmetry; however, the flexibility of I compared to the extremely constrained nature of II will create a large and predominant vibrational contribution to the entropy favoring I. This contribution must also predominate for the COT–semibullvalene equilibrium.
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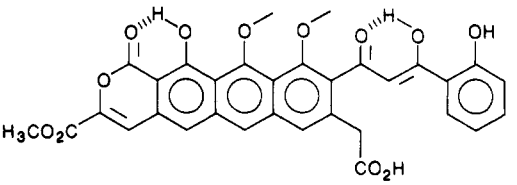
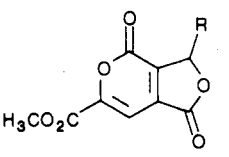
Thermorubin. 3. Synthesis of Novel Tetralone and Isocoumarin Synthons as C–D Ring Precursors to Thermorubin: An Unmasking Procedure for a Latent α-Pyrone Ring

Summary: Novel tetralone and isocoumarin synthons have been developed as C–D ring precursors to thermorubin.

Sir: Thermorubin,[1] a potent antibiotic substance of unique structure[2] (1) produced by the thermophilic fungus Thermoactinomyces antibioticus, shows selective toxicity toward procaryotic cells. Its mechanism of action involves the inhibition of protein synthesis at the level of translation, whereas DNA and RNA synthesis are unaffected.[3,4] Unlike the related tetracyclines and anthracyclines virtually all of the oxygen atoms of this achiral compound are contiguous along one edge of the molecule. This combination of unique pharmacological behavior and unusual structure has led us to investigate synthetic routes to 1.



1



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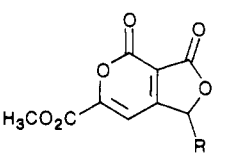

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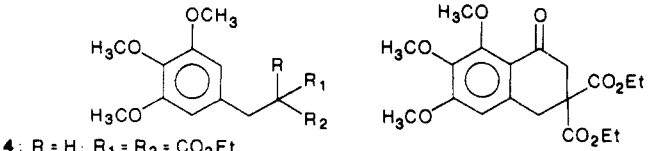
Our initial efforts to produce a synthon for the CD ring system of 1 on which to construct the remainder of the tetracyclic moiety, focussed on the synthesis of the bromophthalides **2** (R = H or Br) and **3** (R = H or Br)[5]. However none of these materials survived the coupling procedures that had been used by ourselves[6] or others[7] in successful synthetic work on the tetracyclic framework of the anthracyclines. This led us to consider masking the α-pyrone in the form of a cleavable (Woodward fission) polyoxygenated benzene ring. With the synthesis of **17** and its conversion to **20**, we now report success in this endeavor. The synthetic methodology introduces new procedures for the aromatization of 3-carboxymethyl-1-tetralones and for the oxidative cleavage of *o*-naphthoquinones.

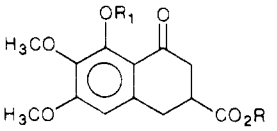
Alkylation of the known[8] benzyl malonate **4** with methyl bromacetate provided **5**[9] (68%), mp 68.5–70.5 °C, contaminated with a small amount (<10%) of the alcohol exchange product **6**, which was easily removed by recrystallization. Selective hydrolysis of the methyl ester of **5** using 1 equiv of KOH afforded the crystalline monoacid **7** (69%), mp 122.5–124.5 °C, which on cyclization [$CF_3CO_2H/(CF_3CO)_2O$] gave a quantitative yield of the 1-tetralone **8** (mp 57–59 °C). This was hydrolyzed and decarboxylated to give monoacid **9**, mp 142–144 °C, as a pale brown solid in 84% overall yield from **7**. The corresponding methyl ester **10** (CH_2N_2/CH_3OH; 85% yield), mp 61–62 °C, when subjected to selective demethylation at the 8-methoxy group using BCl_3, gave the pivotally important, functionally differentiated hydroxytetralone **11**, mp 163–164 °C, whose structure was supported by the presence in the ^1H NMR spectrum of a hydroxyl absorption at δ 12.49. Such a large downfield shift for a phenolic OH is characteristic when strong hydrogen-bonding is present. Protection of this 8-hydroxyl group as the MOM ether was accomplished easily and **12**, the first of the desired synthons was isolated in 83% yield, after chromatographic purification.

The search for a high yield aromatization of tetralone **12** was unexpectedly vexing. Catalytic dehydrogenation of the model compound **10** with Pd–C in mesitylene, naphthalene, or diphenyl ether at reflux failed completely and although DDQ in benzene was successful, the desired product was formed in only[10] 50% yield; we anticipated that the more delicate **12** would likely afford poorer results in view of the highly acidic nature of the dichlorodicyanohydroquinone byproduct. The bromination–dehydrobromination[11a,b] (28%) of **11** was less encouraging and

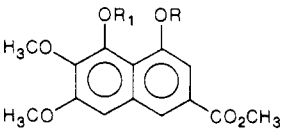


4: R = H; $R_1 = R_2 = CO_2Et$
5: R = $CH_2CO_2CH_3$; $R_1 = R_2 = CO_2Et$
6: R = $CH_2CO_2CH_3$; $R_1 = CO_2CH_3$; $R_2 = CO_2Et$
7: R = CH_2CO_2H; $R_1 = R_2 = CO_2Et$

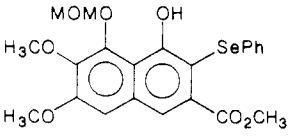
8



9: R = H; $R_1 = CH_3$
10: $R = R_1 = CH_3$
11: R = CH_3; R_1 = H
12: R = CH_3; R_1 = MOM
13: R = CH_3; $R_1 = COCH_3$



14: R = H; R_1 = MOM
16: R = CH_3; R_1 = MOM
17: R = CH_3; R_1 = H



15

the MOM ether **12** afforded products of aromatic ring bromination with concomitant loss of the protecting group.[11c]

A new solution had to be devised. This involved the treatment of **12** with 3 equiv of LDA followed by 2 equiv of phenyl selenium bromide.[11d] This afforded the 1-hydroxynaphthalene **14** in 75% yield, mp 81–82.5 °C, after chromatographic purification to separate traces (~5–10%) of the seleniated compound **15** (mp 108–110 °C). Brandstrom extractive alkylation[12] of **14** using excess dimethyl sulfate proceeded without event to provide 71% of **16**, mp 86–87 °C, after chromatography. Removal of the MOM protecting group by acetal exchange gave the critical highly functionalized naphthol **17**, mp 129–131 °C, in quantitative yield. It was then gratifying to find that oxidation of the latter with sodium metaperiodate under carefully controlled conditions led to the *o*-naphthoquinone **18** in 95% yield, mp 217.5–219 °C, as a brilliant red-orange solid.[13] Examination of the literature revealed that few methods are available for the cleavage of *o*-benzoquinones and *o*-naphthoquinones and that those which are known use harsh conditions and the yields are variable.[14] Wiessler,[15]

(5) The synthesis of lactones **2** and **3** will be the subject of a forthcoming publication.

(6) (a) Kim, K. S.; Spatz, M. W.; Johnson, F. *Tetrahedron Lett.* **1979**, 331. (b) Kim, K. S.; Vanotti, A. S.; Johnson, F. *J. Am. Chem. Soc.* **1979**, *101*, 2483. (c) Kimball, S. D.; Walt, D. R.; Johnson, F. *J. Am. Chem. Soc.* **1981**, *103*, 1561. (d) Kimball, S. D.; Kim, K. S.; Mohanty, D.; Vanotti, E.; Johnson, F. *Tetrahedron Lett.* **1982**, 3871.

(7) For recent examples of the use of phthalide anions in anthracycline syntheses, see: (a) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1862. (b) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1984**, *106*, 1098. (c) Hanser, F. M.; Prasanna, S.; Combs, D. W. *J. Org. Chem.* **1983**, *48*, 1328. (d) Russell, R. A.; Krauss, A. S.; Warrener, R. N.; Irvine, R. W. *Tetrahedron Lett.* **1984**, *25*, 1517. (e) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 101. (f) Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*, 3439 and references therein.

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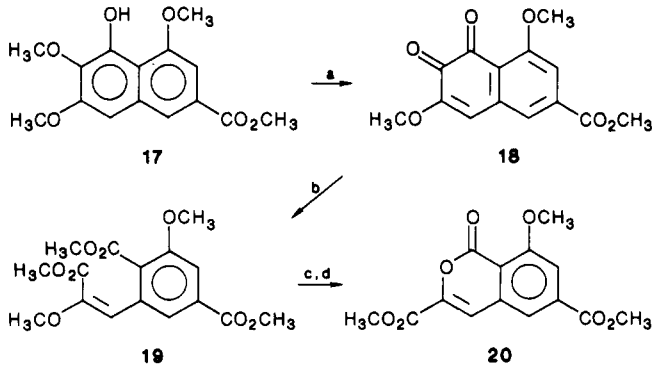
(9) All new compounds showed spectral and analytical data consistent with the assigned structures.

(10) Interestingly, the 8-acetoxy-1-tetralone **13** failed to undergo reaction with DDQ in benzene even at reflux for 50 h and 95% of the starting material was reisolated.

(11) (a) For position-specific monobromination of ketone enolates, see: Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2578. (b) For bromination dehydrobromination of a related tetralone, see: Haworth, R. D.; Jones, B.; Way, Y. M. *J. Chem. Soc.* **1943**, 10. Kasturi, T. R.; Arunachalam, T. *Can. J. Chem.* **1968**, *46*, 3625. (c) A reviewer has suggested the use of a dehydrogenation method employing $PdCl_2$ in hydroxylic solvents at elevated temperature: Bierling, V. B.; Kirschke, K.; Oberender, H. *J. Prakt, Chem.* **1972**, *314*, 170–180. We rejected this method in our initial survey of methods, because HCl is generated and this would be expected to cause loss of the MOM protecting function, inasmuch as this occurred during the attempted bromination–dehydrobromination mentioned in the text. (d) The method involves the generation of the *dianion* of **12**, the monophenylselenylation of the dianion at either position 2 or 3, followed by the immediate elimination of phenylselenoate anion which reacts with the second equivalent of added phenyl selenium bromide to form diphenyl diselenide. Two equivalents of phenylselenium bromide must be used because we have found that the rate of elimination of phenylselenoate anion is comparable to the rate of phenylselenation of unreacted dianion. This reaction constitutes the use of phenylselenium bromide as a halogen surrogate and does not involve any oxidative eliminated of the phenylseleno residue.

(12) Brandstrom, A. *Preparative Ion Pair Extraction, An Introduction to Theory and Practice* Apotekarsocieteten/Hassle Lakemedel: Stockholm, 1974.

(13) For the related oxidation of guaiacol to *o*-benzoquinone and the oxidation of 2,6-dimethoxyphenol, see: (a) Adler, E.; Magnusson, R. *Acta Chem. Scand.* **1959**, *13*, 505. (b) Adler, E.; Magnusson, R.; Berggren, B.; Thomelius, H. *Acta Chem. Scand.* **1960**, *14*, 515.



Reagents (a) $NaIO_4$, HOAc-H_2O (2/1 v/v); 0 °C, 6 min; 0-20 °C, 5 min; 22 °C, 18 min; (b) $Pb(OAc)_4$ (1.15 equiv), CH_3OH-benzene (1/1 v/v); 0 °C, 1.2 h; room temperature, 0.5 h; (c) HOAc/concentrated HCl (1/3 v/v), 4 h reflux; (d) CH_2N_2, CH_3OH.

however, was able to cleave simple benzoquinones to *cis*-muconic acid dimethyl esters using lead tetraacetate, and an earlier Italian paper[16] describes the use of the same reagent for the cleavage of phenanthraquinones and simple 1,2-diones. Thus we felt that this reaction might be applied to *o*-naphthoquinones despite the fact that $Pb(OAc)_4$ will oxidize[17] guaiacols (2-methoxyphenols) to the *p*-quinones. In any event our expectations were rewarded in that treatment of **18** in benzene–methanol with this reagent caused cleavage and afforded the triester **19** in 98% yield (mp 121–123 °C). Finally when the latter was heated under reflux with HCl/HOAc/H_2O the diacid corresponding to **20** was obtained (96%) (mp 307–310 °C), and this on brief treatment with diazomethane afforded the desired benzo-α-pyrone diester **20** in 75% yield (mp 248–249 °C). Further investigations of **12**, **16**, and **20** as synthons for the elaboration of the complete tetracyclic portion of the thermorubin molecule will be reported in subsequent papers.

Acknowledgment. We thank Dr. C. R. Iden for mass spectral data and R. Krant for secretarial assistance. We are grateful to the National Institutes of Health for a grant (AI 19709) which made this work possible.

(14) (a) For an excellent summary, see: Grundmann, C. *Houben-Weyl Methoden Der Organishen Chemie*; Grundmann, C., Ed.; Georg Thieme Verlag: Stuttgart, 1979; Band 7, 3b, pp 141–143. (b) Kojima, H.; Takahashi, S.; Hagihara, N. *Tetrahedron Lett.* **1973**, *14*, 1991.

(15) Wiessler, M. *Tetrahedron Lett.* **1977**, *18*, 233.

(16) Canonica, L.; Danieli, B.; Manitto, P.; Russo, G. *Gazz. Chim. Ital.* **1970**, *100*, 1026.

(17) (a) Teuber, H. J.; Rau, W. *Chem. Ber.* **1953**, *86*, 1036. (b) Wessely, F.; Kotlan, J. *Monatsh. Chem.* **1953**, *84*, 291.

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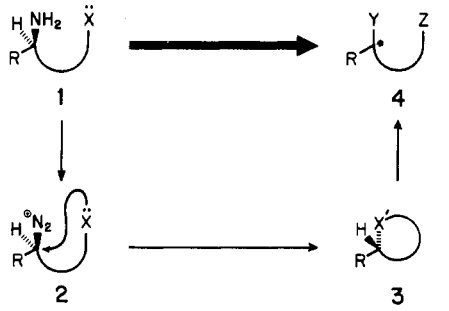
Sodium Nitroprusside Mediated Substitution of Oxygen for Nitrogen at Saturated Carbon Centers

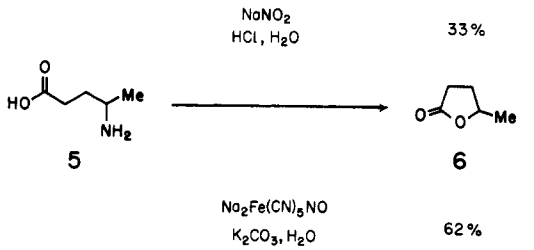
Summary: Sodium nitroprusside under mildly basic conditions has been found to effect the conversion of nitrogen to oxygen at saturated carbon centers.

Sir: Methodology for the stereocontrolled displacement of amines at saturated carbon centers is surprisingly limited, given the potential utility of such synthetic transformations.[1] The examples where these substitutions have been successful generally share several common features, including an amine activation step (i.e., **1** → **2**) followed by intramolecular displacement to give a cyclic species (**2** → **3**), which may be cleaved (**3** → **4**) to afford the product with either overall retention or inversion of configuration (Scheme I).[2] In connection with studies targeting the total synthesis of polyketide-derived natural products, we were interested in developing a method by which asymmetric amines, derived from readily available amino acids, could be utilized as synthetic precursors to asymmetric alcohols. We report herein that using sodium nitroprusside for the amine activation step of the scheme in Scheme I (**1** → **2**) offers a promising method for realizing the desired nitrogen → oxygen conversion.

Scheme I



When standard conditions for diazotization ($NaNO_2$, HCl, H_2O) were applied to model substrate **5**, the desired lactone **6** was afforded in 33% yield together with 24% of the pentenecarboxylic acids resulting from elimination of the diazonium ion intermediate.[3,4] We anticipated that



undesirable side reactions could be suppressed if participation by the carboxyl functionality was enhanced through deprotonation. With this in mind, our attention was drawn to sodium nitroprusside [$Na_2Fe(CN)_5NO$] as a result of its apparently unique ability to effect diazotization under basic conditions.[5,6] Our expectations were fulfilled when basic $Na_2Fe(CN)_5NO$ treatment led to a 62% yield of the

(1) For reviews, see: (a) Kirmse, W. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 251. (b) Baumgarten, R. J.; Curtis, V. A. In *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; Supplement F, Part 2, Chapter 22.

(2) For some recent examples, see: (a) Duhamel, P.; Duhamel, L.; Gralak, J. *Tetrahedron Lett.* **1972**, 2329. (b) Eguchi, C.; Kakuta, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1704. (c) Taniguchi, M.; Kaga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547. (d) Mori, K. *Tetrahedron* **1976**, *32*, 1101. (e) Tersahima, S.; Tseng, C. C.; Koga, K. *Chem. Pharm. Bull.* **1979**, *27*, 747. See also ref 1.

(3) The acids were obtained as a 2:1 mixture of 3-pentenoic acid/4-pentenoic acid.

(4) All yields are reported subsequent to distillation or chromatographic purification.

(5) (a) Maltz, H.; Grant, M. A.; Navaroli, M. C. *J. Org. Chem.* **1971**, *36*, 363. (b) Kirmse, W.; Gruber, W. *Chem. Ber.* **1973**, *106*, 1365. (c) Beck, M. T.; Katho, A.; Dozsa, L. *Inorg. Chim. Acta* **1981**, *55*, L55. (d) Butler, A. R.; Glidewell, C.; Reglinski, J.; Waddon, A. *J. Chem. Res. Miniprint* **1984**, 2768.

(6) $Na_2Fe(CN)_5NO$ mediates diazotization reactions up to pH 12.5. See ref 5a and references cited therein.

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