General Enantiospecific Route to Isochromanquinones. Synthesis of (−)-Nanaomycin D

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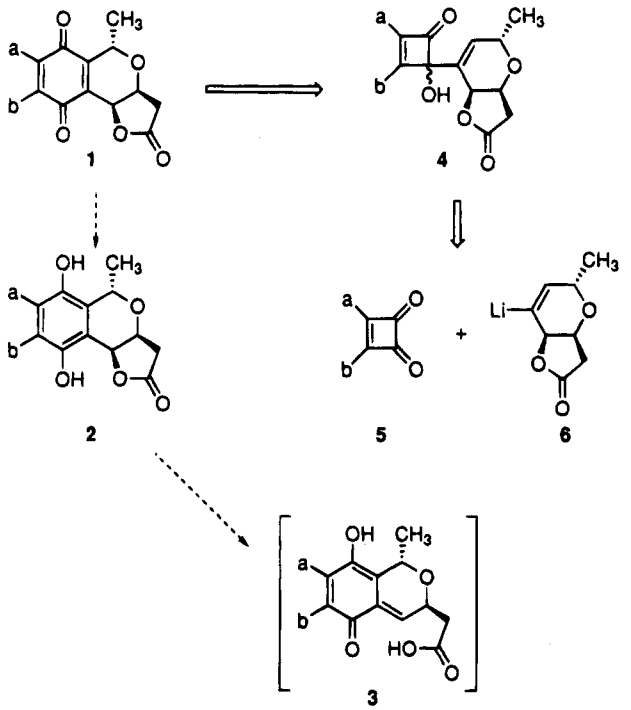
Summary: A general enantiospecific synthesis of isochromanquinones is presented. This entails an efficient synthesis of (3a*S*, 5*S*, 7a*R*)-7-bromo-3,3a,5,7a-tetrahydro-5-methyl-2*H*-furo[3,2-*b*]pyran-2-one (**12**) and ultimately the lithium agent **15** from commercially available L-rhamnose. Addition of **15** to the appropriate cyclobutenedione followed by thermolysis of the resulting cyclobutenone leads to the isochromanquinones **16a–c**. In an analogous fashion the naturally occurring product, (−)-nanaomycin D, was synthesized. In addition, new methodology involving the ring expansion of iminocyclobutenones to aminophenols was discovered.

Reported here is a general enantiospecific synthesis of isochromanquinones of general structure **1**, some members of which are biologically active natural products. Syntheses of the naturally occurring (−)-nanaomycin D (**27**), along with six unnatural analogs **19a–d**, **23**, and **24**, are described as illustrative examples of this convergent method.[2,3] The generality is particularly noteworthy since the method provides an efficient route to analogs in which the quinone nucleus and thus the reduction potential can be extensively varied. This is of potential importance since the biologically active isochromanquinone natural products (>45 examples) have been suggested to be bioreductive alkylating agents, and as such are precursors to reactive *o*-quinone methides formed subsequent to an *in vivo* reductive activation of the quinone to the corresponding hydroquinone, e.g., **1** → **2** → **3** (Scheme 1).[4]

The syntheses are based upon the previously reported thermal ring expansion of 4-alkenyl-4-hydroxycyclobutenones to hydroquinones.[5] This is retrosynthetically illustrated in Scheme 1 as it applies to the isochromanquinone syntheses. Thus, the cyclobutenones **4** undergo ring expansion upon mild thermolysis giving the corresponding hydroquinones, oxidation of which provides the isochromanquinones **1**. The cyclobutenones, in turn, stem from the cyclobutenediones **5** and the equivalent of the lithium reagent **6**.[6]

Scheme 1



An efficient enantiospecific synthesis of butenolide **12**, the precursor to the required alkenyllithium agent, was accomplished as outlined in Scheme 2. It starts with commercially available L-rhamnose which was converted to **7** as previously reported.[7] Swern oxidation of **7** followed by treatment of the resulting enone **8** with bromine and triethylamine gave **9** in 90% overall yield. Reduction ($NaBH_4$, $CeCl_3$) of the enone **9** to the alcohol **10** followed by direct mesylation gave **11** in 90% overall yield. Hydrolysis of the ester using LiOH at 0 °C to give the carboxylic acid followed by treatment with triethylamine in refluxing benzene gave the desired butenolide **12** $[\alpha]^{20}_D$ 16.40 (c = 0.25, $CHCl_3$) in 85% yield. Thus, synthesis of **12** can be conveniently accomplished in 67% overall yield to give enantiomerically pure product in gram quantities.

In order to obtain a viable lithium reagent required for the ring expansion step, **12** was converted to a 7:3 mixture of diastereomeric lactols **13** in 80% by an initial

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(1) This work is taken principally from the PhD dissertation of Michael Winters.

(2) One other enantiospecific synthesis of (−)-nanaomycin D has appeared. See: Tatsuta, K.; Akimoto, M.; Annaka, M.; Ohno, Y.; Kinoshita, M. *Bull Chem. Soc. Jpn.* **1985**, *58*, 1699. Tatsuta, K.; Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. *J. Antibiot.* **1985**, *38*(5), 680–2.

(3) For other selected synthetic efforts in the nanaomycin family see: Li, T.; Ellison, R. H. *J. Am. Chem. Soc.* **1978**, *100*(19), 6263–5. Kraus, G. A.; Roth, B. *J. Org. Chem.* **1978**, *43*(26), 4923–4. Ichihara, A.; Ubukata, M.; Oikawa, H.; Murakami, K.; Sakamura, S. *Tetrahedron Lett.* **1980**, *21*(46), 4469–72. Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*(21), 5850–2. Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. *J. Org. Chem.* **1982**, *47*(22), 4382–4. Naruta, Y.; Uno, H.; Maruyama, K. *Chem. Lett.* **1982**, (5), 609–12. Kraus, G. A.; Cho, H.; Crowley, S.; Roth, B.; Sugimoto, H.; Prugh, S. *J. Org. Chem.* **1983**, *48*(20), 3439–44. South, M. S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1984**, *106*(15), 4181–5. Yoshii, E.; Kometani, T.; Nomura, K.; Takeuchi, Y.; Odake, S.; Nagata, Y. *Chem. Pharm. Bull.* **1984**, *32*(12), 4779–85. Akimoto, K.; Annaka, M.; Ohno, Y.; Kinoshita, M. Tennen *Yuki Kagobutsu Toronkai Koen Yoshishu* **1985**, *27th*, 303–10. Kraus, G. A.; Semmelhack, M. F.; Bozell, J. J.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W.; Zask, A. *Tetrahedron* **1985**, *41*(24), 5803–12. Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*(26), 5566–74. Molina, M. T.; Walling, J. A. *J. Chem. Soc., Chem. Commun.* **1986**, (21), 1568–9. Uno, H. *J. Org. Chem.* **1986**, *51*(3), 350–8. Kraus, G. A.; Molina, M. T.; Walling, J. A. *J. Org. Chem.* **1987**, 52(7), 1273–6. Decker, O. H. W.; Moore, H. W. *J. Org. Chem.* **1987**, *52*(6), 1174–5. Foland, L. D.; Decker, O. H. W.; Moore, H. W. *J. Am. Chem. Soc.* **1989**, *111*(3), 989–95. Yamaguchi, M.; Nakamura, S.; Okuma, T.; Minami, T. *Tetrahedron Lett.* **1990**, *31*(27), 3913–16. Brimble, M. A.; Stuart, S. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, (4), 881–5.

(4) Moore, H. W. *Science* **1977**, *197*, 527.

(5) For a recent review see: Moore, H. W.; Yerxa, B. R. *Chemtracts* **1992**, *5*, 273–313.

(6) Spectral and analytical data for all new compounds reported here are in agreement with their assigned structures.

(7) Roth, W.; Pigman, W. *Methods Carbohydr. Chem.* **1963**, *2*, 405. Okazaki, K.; Nomura, K.; Yoshii, E. *J. Chem. Soc., Chem. Commun.* **1989**, 354.

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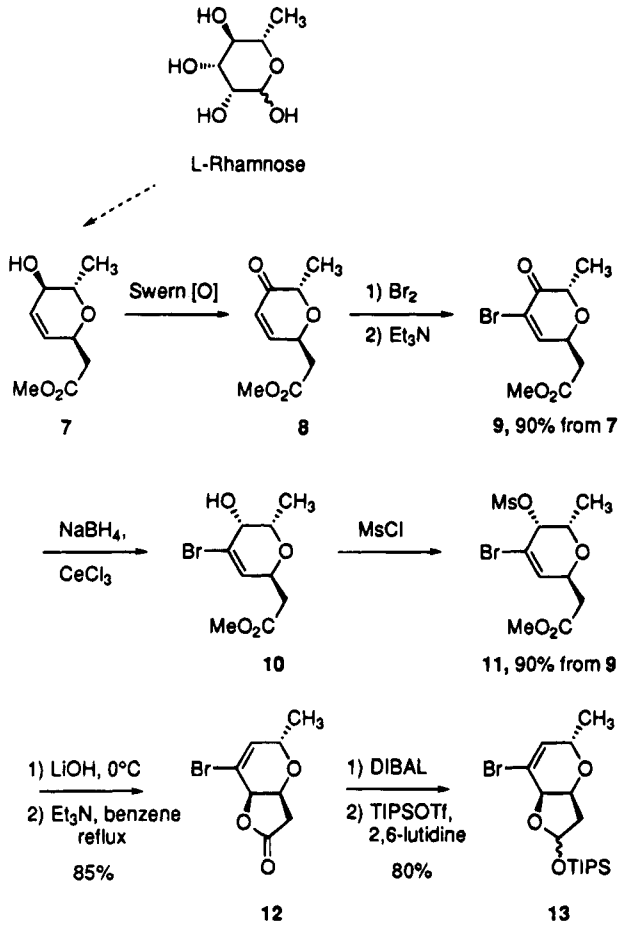
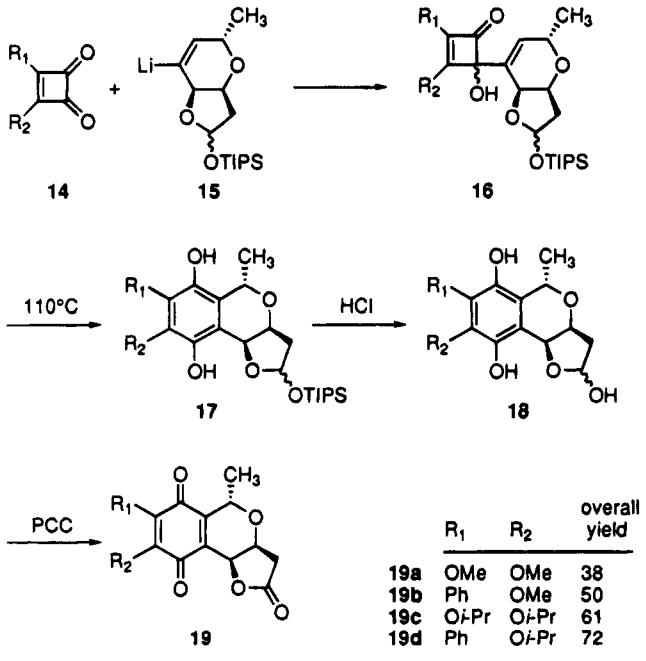
Scheme 2



Scheme 3

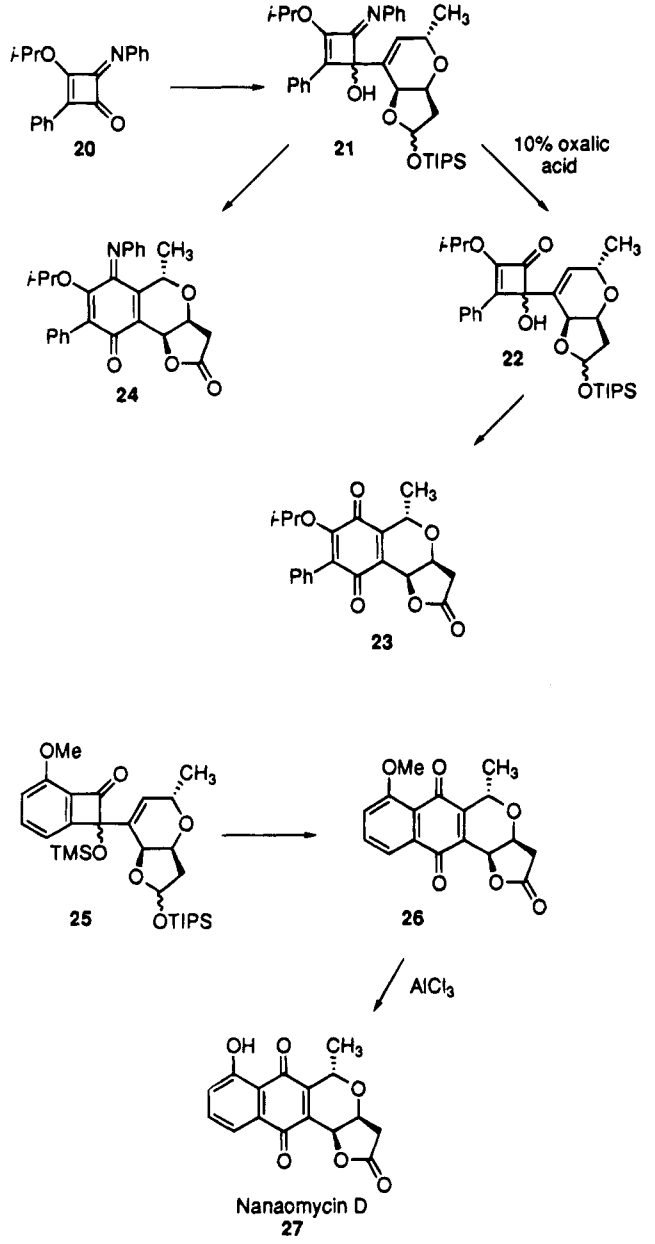


	R_1	R_2	overall yield
19a	OMe	OMe	38
19b	Ph	OMe	50
19c	O*i*-Pr	O*i*-Pr	61
19d	Ph	O*i*-Pr	72

DIBAL reduction followed by treatment of the resulting hemiketal with triisopropylsilyl triflate. This then led to the vinyllithium reagent **15** upon treatment with *tert*-butyllithium in ether at −78 °C.

Examples of the utility of the above reagent for the synthesis of isochromanquinones are outlined in Scheme 3. Specifically, treatment of dimethyl squarate (**14a**) with the lithium reagent **15** in ether at −78 °C gave **16a**

Scheme 4



as a mixture of diastereomers in 51% yield. These were readily converted to the ring expanded hydroquinone **17a** upon thermolysis in refluxing toluene for 1 h. Finally, treatment of **17a** with HCl followed by PCC oxidation resulted in the isochromanquinone **19a** as a single enantiomer in 75% yield (38% overall). In a similar manner **19b**, **19c**, and **19d** were obtained in, respectively, 50%, 61%, and 72% overall yield from 3-methoxy-4-phenylcyclobutenedione (**14b**), diisopropyl squarate (**14c**), and 4-phenyl-3-isopropoxycyclobutenedione (**14d**).[5]

New protecting group chemistry involving iminocyclobutenones was developed in order to prepare **23**, the regioisomer of **19d** (Scheme 4).[8] Specifically, the iminocyclobutenedione **20** was obtained in 65% yield upon treatment of **14c** with phenyllithium followed by trifluoroacetic anhydride and aniline. Treatment of **20** with the lithium reagent **15** gave crude iminocyclobutenone **21** which was selectively hydrolyzed with 10% oxalic acid

(8) For related methods see: Liebeskind, L. S.; Granberg, K. L.; Zhang, J. *J. Org. Chem.* **1992**, *57*, 4345. Gayo, L. M.; Winters, M. P.; Moore, H. W. *J. Org. Chem.* **1992**, *57*, 6896. Liebeskind, L. S.; Wirtz, K. R. *J. Org. Chem.* **1990**, *55*, 5350.

in THF to give **22** in 56% isolated yield. Thermolysis of **22** in refluxing *p*-xylene for 4 h gave the hydroquinone which was converted to quinone **23** (68%) upon deprotection and oxidation.

Additionally, **21** was thermolyzed in refluxing *p*-xylene to give the corresponding aminophenol which was converted to iminoquinone **24** upon deprotection and oxidation (56% from **13**). This is a noteworthy result since it demonstrates the first example of the ring expansion of iminocyclobutenones to aminophenols.

Finally, (−)-nanaomycin D (**27**) was prepared in similar fashion starting with 3-methoxybenzocyclobutenedione (Scheme 4).[5] This was converted to the adduct **25** (65%) upon treatment with the lithium reagent **15** in THF at −78 °C followed by a trimethylsilyl chloride quench. Thermolysis in refluxing *p*-xylene followed by hydrolysis and oxidation gave 9-*O*-methylnanaomycin D **26** ($[\alpha]^{20}_D$ −66.0° (*c* = 0.20, $CHCl_3$) (lit.[2] $[\alpha]^{24}_D$ −65° (*c* = 0.50, $CHCl_3$))) in 66% overall isolated yield. Demethylation ($AlCl_3$) as reported in the literature then gave the natural product **27**.[2]

The significant points reported in this paper are the following: (1) the butenolide **12** is readily available in enantiomerically pure form from commercially available L-rhamnose; (2) the ring expansion methodology allows the enantiospecific synthesis of isochromanquinones and isochromaniminoquinones in the nanaomycin family; (3) the natural product, (−)-nanaomycin D, was prepared in 6.5% overall yield from L-rhamnose; and (4) new methodology involving the ring expansion of iminocyclobutenones was discovered, and this allows further control of the regiochemistry of these quinone syntheses.

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Supplementary Material Available: Experimental procedures and characterization data (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.