ORGANIC LETTERS

2001
Vol. 3, No. 17
2661−2663

Synthesis of the Naphthalene Portion of the Rubromycins

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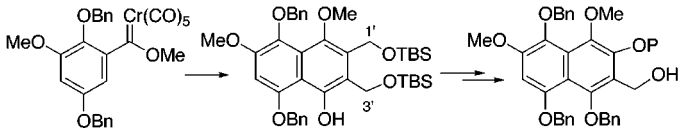
Received June 1, 2001

ABSTRACT



A synthesis of a reduced version of the naphthazarin found in the rubromycin class of natural products is reported. The naphthalene ring system is formed via a Dötz reaction with a symmetrical alkyne. Differentiation between the C1′ and C3′ groups of the Dötz adduct is achieved by selective oxidation since the two methylene groups possess different oxidation potentials.

γ-Rubromycin (**1**),[1] purpuromycin (**2**),[2] heliquinomycin,[3] and the griseorhodins[4] are a set of structurally related pigments consisting of naphthazarin and isocoumarin ring structures linked through a 5,6-spiroketal. The synthesis of this unique class of antitumor antibiotic compounds has not yet been achieved, although they display a range of biological activity. γ-Rubromycin (**1**) exhibits activity against the reverse transcriptase of human immunodeficiency virus-1[5] and against human telomerase, which is overproduced in cancer cells.[6] Purpuromycin (**2**) is a potential topical agent for vaginal infections,[7] and heliquinomycin is an inhibitor of DNA helicase.[3]

As part of an effort toward the synthesis of this group of natural products,[8] a highly convergent assembly of the hexaoxonaphthyl system was desired. Even though a linear elaboration from 1,5-naphthalene diol has been attempted, difficulties in installing the correct oxygenation were encountered.[9] In our approach we have elected to employ a Dötz reaction to provide a rapid and convergent synthesis of the naphthalene core.[10] Utilization of a Dötz reaction would allow for the ready assembly of analogues by simple variation of the chromium carbene component.[11]

For a direct synthesis of the naphthazarin precursor, an oxygen-substituted alkyne **6a** would be ideal in a Dötz cyclization with chromium carbene **5**. Although such alkynes

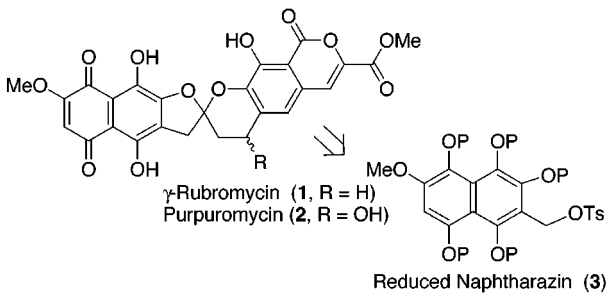


Figure 1.

(1) Brockmann, H.; Zeeck, A. *Chem. Ber.* **1970**, *103*, 1709−1726.

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(4) The griseorhodins possess a methyl group in place of the methyl ester group on the isocoumarin and also differ from γ -rubromycin with respect to the oxygenation of the spiroketal cores. (a) Eckardt, K.; Tresselt, D.; Ihn, W. *J. Antibiot.* **1978**, *31*, 970−973. (b) Stroshane, R. M.; Chan, J. A.; Rubalcaba, E. A.; Garretson, A. L.; Aszalos, A. A.; Roller, P. P. *J. Antibiot.* **1979**, *32*, 197−204. (c) Suetsuna, K.; Osajima, Y. *Agric. Biol. Chem.* **1989**, *53*, 241−242. (d) Panzone, G.; Trani, A.; Ferrari, P.; Gastaldo, L.; Colombo, L. *J. Antibiot.* **1997**, *50*, 665−670.

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10.1021/ol016220e CCC: $20.00
Published on Web 07/24/2001

can undergo Dötz cyclization reactions, steric differentiation between a suitably protected alcohol and the methylene group would likely not be sufficient to provide a selective process.[12] As such, a symmetric alkyne diol **6b**, for which the issue of regioselection is not a concern, was selected instead (Figure 2). Differentiation of the two termini from the alkyne can

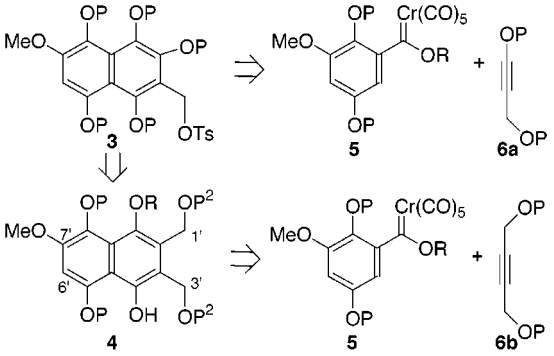
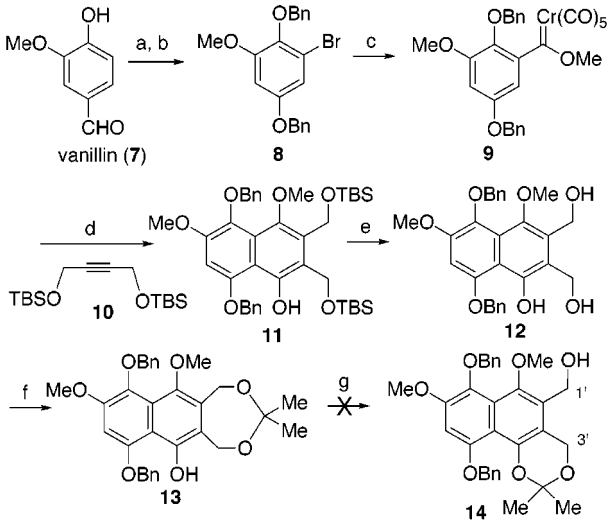


Figure 2.

be accomplished *after* the Dötz cyclization (C1′ vs C3′) on naphthol **4**.

The initial implementation of this strategy is shown in Scheme 1. Fischer chromium carbene intermediate **9** with benzyl ether protecting groups was selected as the precursor for the Dötz reaction with the aim of effecting a late stage global deprotection via hydrogenation. Starting with commercially available vanillin (**7**), Fischer chromium carbene intermediate **9** was produced using a modified protocol.[13] Subjection of **9** to alkyne **10**[14] in the presence of heat and Ac_2O[15] produced the Dötz adduct **11** in 40−50% yield. Removal of the silyl ethers using TBAF, which was not

Scheme 1[a]

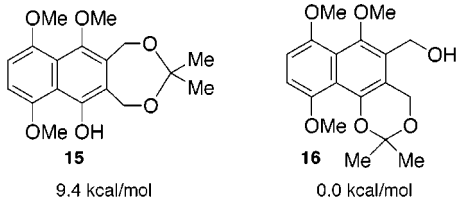


[a] (a) (i) Br_2, AcOH, (ii) NaH, BnBr; 86%; (b) (i) *m*CPBA, (ii) KOH, (iii) NaH, BnBr; 61%; (c) (i) *n*BuLi, (ii) $Cr(CO)_6$, (iii) Me_3OBF_4; 60−90%; (d) THF, Ac_2O, 53%; (e) TBAF, THF, 31%; (f) PPTS, $(MeO)_2CMe_2$; (g) PPTS, acetone.

optimized, provided the unstable naphthol derivative **12**. Further treatment with dimethoxypropane and PPTS provided the seven-membered ketal **13**. At this point, isomerization to the thermodynamically more stable six-membered ketal **14**, in which C1′ and C3′ are differentiated, was expected to occur.

Unfortunately, equilibration of seven-membered ketal **13** to six-membered ketal **14** did not proceed, even though molecular mechanics calculations[16] of **15** and **16** (Scheme 2) indicated a significant stabilization (9.4 kcal/mol) of the

Scheme 2. Calculated Relative Energies for **15** and **16** (MM2*)



six-membered derivative. From studies in a model system lacking functionalization on the left-hand aromatic ring of the naphthalene, where isomerization of the respective six-

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(8) Syntheses of these compounds have not yet been reported. For efforts towards construction of the spiroketal core, see: (a) Capecchi, T.; de Koning, C. B.; Michael, J. P. *Tetrahedron Lett.* **1998**, *39*, 5429−5432. (b) Capecchi, T.; de Koning, C. B.; Michael, J. P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2681−2688. For syntheses of the isocoumarin portion, see: (c) Thrash, T. P.; Welton, T. D.; Behar, V. *Tetrahedron Lett.* **2000**, *41*, 29−31. (d) Waters, S. P.; Kozlowski, M. C. *Tetrahedron Lett.* **2001**, *42*, 3567−3570.

(9) (a) Terada, A.; Tanoue, Y.; Hatada, A.; Sakamoto, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 205−213. (b) Tanoue, Y.; Terada, A.; Tsuboi, T.; Hayashida, T.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 2927−2930. (c) Tanoue, Y.; Terada, A.; Seto, I.; Umeza, Y.; Tsuge, O. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1221−1224. (d) Tanoue, Y.; Terada, A. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2295−2297.

(10) In the synthesis of fredericamycin, which possesses a similar naphthazarin, such a construction has been shown to be successful: (a) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1991**, *56*, 2115−2122. (b) Boger, D. L.; Hueter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839−11849.

(11) For reviews see: (a) Harrington, P. J. *Transition Metals in Total Synthesis*; Wiley: New York, 1990; p 364. (b) *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. A. G., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; p 155. (c) Dötz, K. H.; Tomuschat, P. *Chem. Soc. Rev.* **1999**, *28*, 187.

(12) For a discussion of mechanism and regioselectivity factors, see: Hegedus, L. S. *Transition Metals in The Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books, Sausalito, CA, 1999.

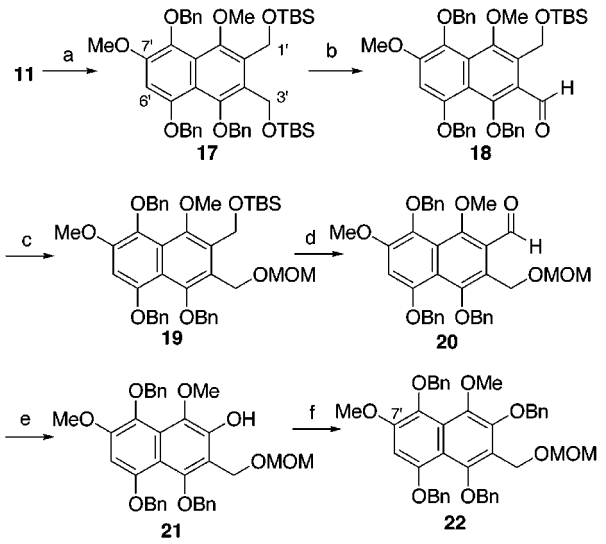
(13) Boger, D. L.; Jacobson, I. C. *J. Org. Chem.* **1990**, *55*, 1919−1928. Deprotonation of the benzylic ethers of **9** by the aryllithium intermediate could be attenuated by using 1.05 equiv of high-purity freshly titrated *n*BuLi, performing the lithiation rapidly at low temperature (<15 min at −78 °C) and adding the $Cr(CO)_6$ in one portion at low temperature. The use of freshly prepared Meerwein's reagent was also found to be absolutely necessary to obtain **9** efficiently (>90% yield over several trials).

(14) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190−6191.

membered ketal did occur, it appears that steric hindrance from the *peri*-benzyl ether groups prevents ready isomerization of the ketal to the required hydroxyl in **13**.

Since the steric bias against formation of the desired six-membered ketal **14** (Scheme 1) prevented selective functionalization of the two methyleneoxy groups, an alternate approach based on the differences in chemical reactivity of these two groups was utilized (Scheme 3). It has been shown

Scheme 3[a]

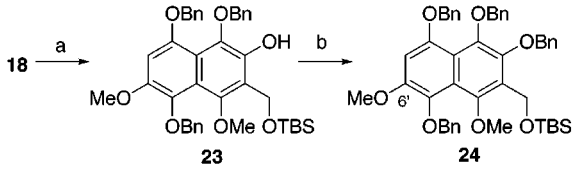


[a] (a) BnBr, K_2CO_3, 81%; (b) DDQ, $CH_2Cl_2-H_2O$, 80%; (c) (i) $NaBH_4$, (ii) MOMCl, 85%; (d) (i) TBAF, (ii) Dess−Martin, 90%; (e) (i) *m*CPBA, $NaHCO_3$, CH_2Cl_2, (ii) NH_3, EtOH; (f) BnBr, K_2CO_3, 55% from **20**.

that oxidation of benzene derivatives possessing two benzylic methylenes can be halted after oxidation to the monoaldehyde.[17] In addition, methoxy groups on benzene derivatives show a powerful effect in directing the regiochemistry of oxidation to *para*-methyleneoxy substituents over *meta*-methyleneoxy substituents, presumably by attenuating the oxidation potential via resonance effects.[17]

Protection of the remaining phenol in the Dötz adduct **11** with benzyl bromide yielded **17** in which the two $TBSOCH_2$ groups now possess different oxidation potentials (Scheme 3). As a result of the electron-donating nature of the C7′ methoxy group, the C3′ group is more electron-rich and hence more readily oxidized. Treatment of **17** with DDQ effects clean formation of aldehyde **18** in which *only one of the five* oxidizable benzyloxy groups is modified. From aldehyde **18** it is possible to generate two isomeric naphthazarin fragments in which the naphthazarin methoxy group of the natural products is present at C7′ (**22**, as in the natural products) or at C6′ (**24**, see Scheme 4).

Scheme 4[a]



[a] (a) (i) 10 mol % $(2\text{-}NO_2\text{-}C_6H_4Se)_2$, H_2O_2, (ii) KOH; (b) BnBr, K_2CO_3, 48% from **18**.

For the synthesis of the natural product precursor **22**, aldehyde **18** was reduced and the alkoxide trapped as the MOM ether to provide **19**. The silyl group was removed and the resultant benzylic alcohol was oxidized to the aldehyde with the Dess−Martin periodinane. Baeyer−Villiger oxidation was initially troublesome, but buffered *m*CPBA was found to cleanly form the respective formate ester. Hydrolysis of this formate ester intermediate with NH_3 in EtOH generated unstable phenol **21**, which was directly benzylated to provide naphthazarin derivative **22**.

Synthesis of an isomeric C6′ methoxy derivative will allow the importance and exact placement of the C7′ methoxy functional group to be assessed with respect to biological activity. With intermediate **18** available, such a derivative can be readily generated. As such, aldehyde **18** was subjected to Baeyer−Villiger oxidation. In this case, the optimal oxidant proved to be H_2O_2 with bis(2-nitrophenyl)diselenide as a catalyst. After hydrolysis of the formate ester intermediate with KOH, the resultant unstable phenol **23** was protected to provide the isomeric reduced naphthazarin **24**.

In conclusion, a general synthesis of highly oxygenated naphthalene derivatives is presented, culminating in the preparation of reduced naphthazarin precursors suitable for the synthesis of the rubromycin group of natural products including the rubromycins, purpuromycin, heliquinomycin, and the griseorhodins. In addition, a strategy to differentiate benzylic groups on highly substituted aromatic substrates by taking advantage of differences in oxidation potentials is demonstrated.

Acknowledgment. Financial support was provided by the University of Pennsylvania Research Foundation, Pharmacia Upjohn, Merck Research Laboratories, and DuPont.

Supporting Information Available: Experimental details and characterization of all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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