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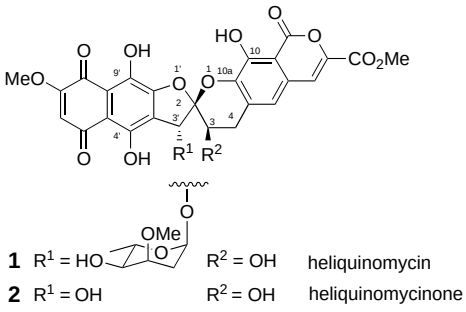
The Total Synthesis of Heliquinomycinone**

Tony Siu, Donghui Qin, and Samuel J. Danishefsky*

In the preceding communication,[1] we described the assembly of intermediate **3**, which was envisioned as a substrate for an oxidative dearomatization-spiroketalization sequence (**3** → **4**, Scheme 1), en route to heliquinomycinone (**2**), the aglycone of the naturally occurring helicase inhibitor



1 R^1 = HO R^2 = OH heliquinomycin
2 R^1 = OH R^2 = OH heliquinomycinone

heliquinomycin (**1**). A large number of reagent combinations were used in attempts to bring about the conversion of **3** into a product of the type **4** (Scheme 1). In particular, we were seeking electrophiles that could be introduced concomitantly with nucleophilic spirocyclization. Unfortunately, even after screening a large number of possibilities, this strategy was not successful. When projected electrophilic cyclizations were attempted by using halonium equivalents such as NBS, NIS, NCS, or iodine in the presence of sodium bicarbonate, oxidative demethylation and quinone formation occurred. Similar results were observed when various epoxidations of the furanoid ring were attempted.[2] An important constraining factor was the electron richness of the pentamethoxynaphthalene moiety present in **3**. This pattern lent itself to ready pairwise oxidative demethylations to produce ring A or ring B quinones, with subsequent deactivation of the furan double bond. Furthermore, no reaction occurred when metal-based reagents such as $Pd(OAc)_2$, $Ti(OAc)_3$, Re_2O_7,[3] and Hg^{II} salts were explored to activate the furan double bond for nucleophilic attack. Even after extensive experimentation, we were unable to carry out the transformation **3** → **4**. In substance, we were unable to overcome the combination of nonreactivity of the furanoid moiety to some reagent combinations, and the high vulnerability of the pentamethoxynaphthalene structure to others.

The one successful oxidation which targeted the furan ring and did not compromise the integrity of the pentamethoxynaphthalene moiety, arose from the action of osmium tetroxide on **5**,[4] which gave a diastereomeric mixture of **6** (Scheme 2, 50–60%). The product was difficult to separate and could not be satisfactorily characterized by means of ^{1}H NMR spectroscopy. Our decision to go forward with this material was based largely on a supportive mass spectrum. Deprotection of the benzyl ether exposed the C10a phenolic function, again as a poorly characterized mixture of diastereomers **7**.

With triol **7** in hand, all that remained to reach hydroquinonoid versions of **2** was acid-induced spiroketalization (Scheme 3). Remarkably, this seemingly attainable goal could not be accomplished. The hydroxy group at the pre-C3′ benzylic position was unexpectedly vulnerable.[5] An attempt at a spirocyclization under Mitsunobu-type conditions was unsuccessful and instead led to the transformation of diastereomers **7** into **9**.[6]

In retrospect, this result reflects the ease of formation of a quinone-methide-like heterolysis product, presumably mediated by the strong electron-donating nature of the five methoxy groups on the naphthalene system. Various protections of C3 and C3′ in the hope of favoring the desired spirocyclization were not productive.

A chance observation proved to be critical in solving the problem. Exposure of diastereomers **6** to air, in the presence of triethylamine/methanol led to oxidation at C3′, thus forming the α-hydroxyketone (Scheme 4).[7] Subsequent debenzylation gave **10** as a 1:1 mixture of anomers. It was hoped that the presence of the ketone would prevent bond formation between the "C10a" phenol and "C3′" (except for that arising from a presumably reversible hemicacetal link). However, the feasibility of spirocyclization in **10**, adjacent to a ketone linkage, was by no means certain.

Under Mitsunobu conditions,[6] the desired cyclization was achieved and mixture **10** afforded compounds **11** and **12** in a 1:1 ratio after removal of the silyl ethers. These products were

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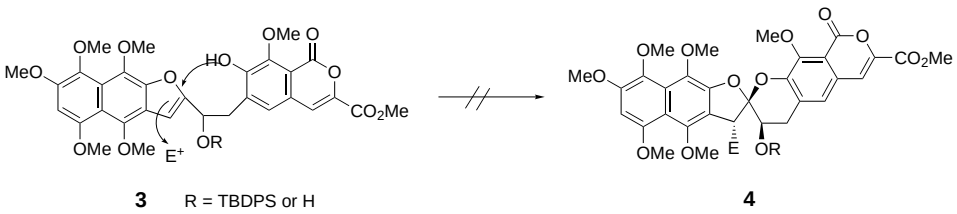
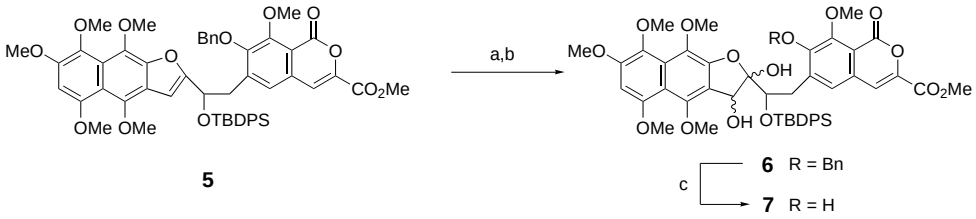
[**] This work was supported by the National Institutes of Health (Grant numbers: AI 16943 and HL25848). The authors thank Dr. Makoto Chino of Nippon Kayaku Co., Ltd. for kindly providing a sample of heliquinomycin, and Yashuiro Itagaki of Columbia University for high-resolution mass spectral analyses.



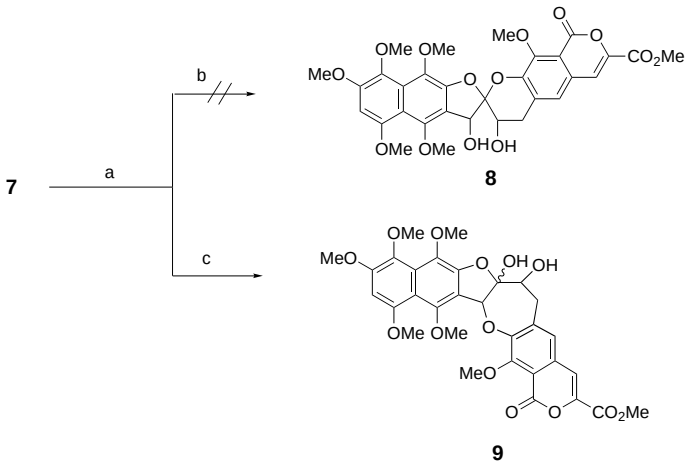
3 R = TBDPS or H **4**

Scheme 1. a) TBDPS = *tert*-butyldiphenysilyl.



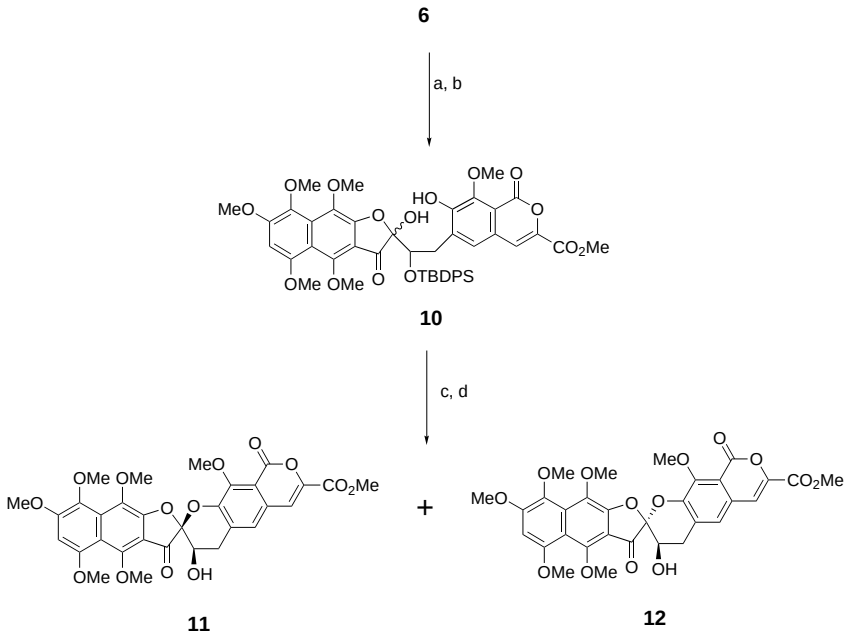
5 **6** R = Bn **7** R = H

Scheme 2. Reagents and conditions: a) OsO_4, pyridine, THF/H_2O; b) $NaHSO_3$, 3 days, 50–60 %; c) H_2, Pd/C (5 %), EtOAc, 95 %. TBDPS = *tert*-butyldiphenylsilyl. Bn = benzyl.



8 **9**

Scheme 3. Reagents and conditions: a) TBAF, THF, 95 %; b) various sources of acid; c) DIAD, PPh_3, CH_2Cl_2, 50 %. TBAF = tetrabutylammonium fluoride; DIAD = diispropylazodicarboxylate.



10 **11** **12**

Scheme 4. Reagents and conditions: a) Et_3N, MeOH, 45 %; b) H_2, Pd/C (5 %), EtOAc, 94 %; c) DEAD, PPh_3, CH_2Cl_2, −78→25 °C; d) TBAF, THF, 0 °C, 72 % (over two steps). DEAD = diethylazodicarboxylate; TBAF = tetrabutylammonium fluoride.

separated cleanly and fully characterized. It is unclear whether a given anomer in mixture **10** affords a given spiroketal (**11** or **12**) by inversion, or whether it leads to a mixture of spiroketals via the oxonium ion followed by unselective cyclization.

At this stage, we had no basis to assign the relative configurations unambiguously at C2 and C3 in **11** and **12**. We then studied in detail the reduction of ketones **11** and **12** (Scheme 5). Gratifyingly, each of these ketones underwent highly stereoselective reduction upon treatment with tetramethylammonium triacetoxyborohydride to afford **13** and **14**, respectively.[8] We could not be confident as to the relative configuration of **13** and **14**, and the ^{1}H NMR signals for the aliphatic groups of either product did not correspond with those of heliquinomycin (**1**).[9] Although comparison of **13** and **14** with compounds in the quinone series was somewhat problematic, we came to the tentative conclusion that neither of these two products had the relative configuration at C3, C2, and C3′ which we wanted in our eventual target **2**.

We now reasoned that heterolysis of the C3′ benzylic hydroxyl group, which occurred in the unwanted transformation of **7** into **9**, might allow for solvolytic inversion at C3′ in **13** or **14**. If such a reaction could be realized, and if all structures to date were correct, one of these two emerging diols would be a suitable candidate for progression to heliquinomycinone. Treatment of **13** and **14** with $BF_3 \cdot OEt_2$ in separate reactions gave **16** and **15**, respectively, in moderate yields.[10] At this stage, our prospects improved significantly. The ^{1}H NMR spectrum of **15** corresponded well with that of **1**. Moreover, from a small sample of **1**, we were able to obtain heliquinomycinone (**2**) by hydrolysis of the glycoside link. Again, there was an encouraging similarity in the upfield regions of the ^{1}H NMR spectra of **2** and **15**. In contrast, the upfield region of the ^{1}H NMR spectrum of **16** did not correspond well with that of **1** or **2**.[11] On this basis, we tentatively assigned the relative configuration of heliquinomycinone at C3′, C2, and C3 to diol **15**, and hence to its precursor **14**, as shown. As for **13** and **16** we could assign the relationship of the spiro centers and C3 to be as shown. However, we cannot rigorously assign the configurations at C3′ in

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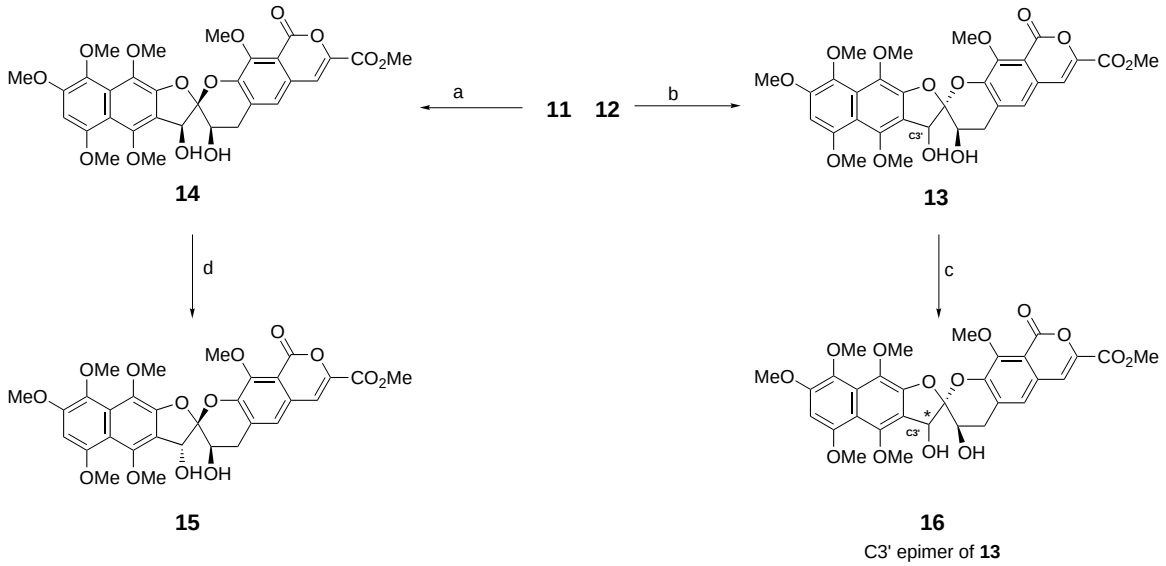
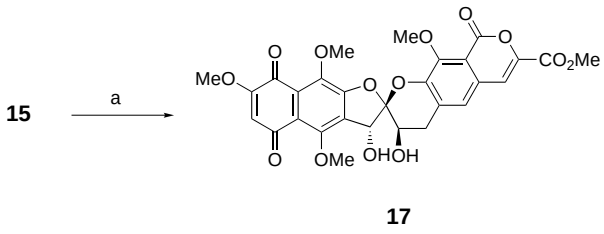


Scheme 5. Reagents and conditions: a) $Me_4NBH(OAc)_3$ MeCN/acetic acid (5:1), 72%; b) same conditions as a), 69%; c) $BF_3 \cdot OEt_2$ (0.5 equiv), CH_2Cl_2, 64%; d) same conditions as c), 71%.

these epimers, as neither corresponded to the heliquinomycin pattern.

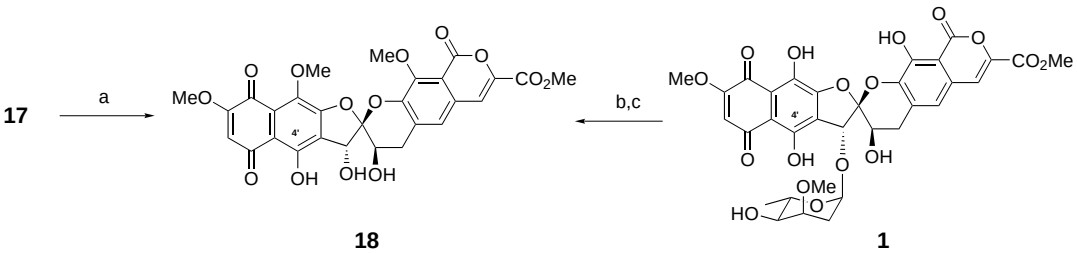
Diol **15**, which was prepared stereospecifically from ketone **11**, was treated with cerium ammonium nitrate to afford the corresponding quinone **17** (Scheme 6). There remained the daunting challenge of tridemethylation of the fully synthetic material. Treatment of **17** with $BBr_3 \cdot Me_2S$ led to initial demethylation at C4′ to form **18**. Presumably, the specificity of demethylation arises from the mediation by the proximal hydroxy group at C3′. As confirmation, compound **18** could be reached from **1** (Scheme 7). Thus, dimethylation of heliquinomycin at C9′ and C10 was carried out as shown. The selectivity must arise from the large proximal glycoside, which hinders methylation at C4′. Deglycosylation of this compound afforded naturally derived **18**. Gratifyingly, the high-field ^{1}H NMR spectra and TLC mobility of the synthetic and naturally derived bis-methyl ethers **18** were identical.



Scheme 6. Reagents and conditions: a) cerium ammonium nitrate, MeCN/H_2O (5:1), 0°C, 77%.

Compound **17** was treated with BBr_3 in dichloromethane, which resulted in the cleavage of the three appropriate methyl ethers to give fully synthetic racemic **2**. Remarkably, the aglycone is much more labile than **1**, which has the cymarose glycoside attachment. Nonetheless, synthetic **2** could be purified by sephadex LH-20 chromatography (Scheme 8). The high-field ^{1}H NMR spectrum of fully synthetic **2** is identical to that of the naturally derived aglycone. Congruity was also seen in comparison of the TLC mobility and the IR and mass spectra of the naturally derived and fully synthetic **2**; thus heliquinomycinone had been fully synthesized in a 23-step sequence, which is highlighted by a remarkable spirocyclization (see formation of **11**).

In retrospect, this total synthesis proved to be far more difficult at several points than had been anticipated. In the end, the failure to synthesize a single diol at the stage of **6** complicated matters because of our inability to rechannel the undesired anomer into the desired series. The dihydroxylation reaction is the only step without stereocontrol. It may yet be possible, when operating in an enantiomerically defined setting, to benefit from a reagent-dominated specific enantiofacial attack on a suitable precursor (cf **5**).[12] The availability of optically defined **10** would allow for clarification of the fascinating spirocyclization under Mitsunobu conditions.



Scheme 7. Reagents and conditions: a) $BBr_3 \cdot Me_2S$ (5 equiv), CH_2Cl_2, 0°C, 64%; b) Ag_2O, MeI, 65°C, $CHCl_3$; c) HCl (1N, 100 equiv), 65°C, THF, 67% (over two steps).

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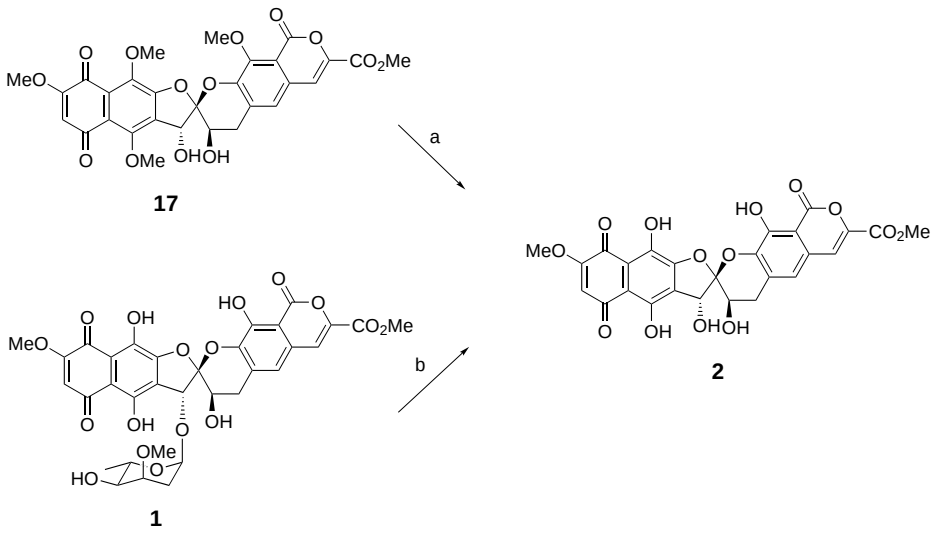

Scheme 8. Reagents and conditions: a) BBr_3 (15 equiv), CH_2Cl_2, $-78\,^{\circ}C$, 52%; b) HCl (1N, 100 equiv), 65 °C, THF, quantitative.

Our longer term goals in the project involve an enantiodefined synthesis of **2**, a synthesis of heliquinomycin itself, and an evaluation of the *anti* helicase activity of the various heliquinomycin analogues that were formed in the project. It is expected that the identification of the complexities of the problem described herein and the synthesis of the aglycone portion, will be of benefit in future synthetic projects.

Received: September 5, 2001 [Z17860]

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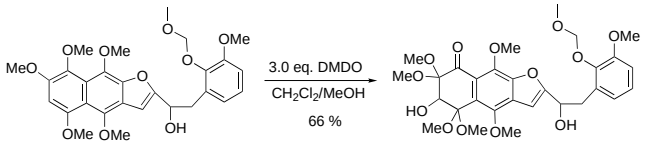
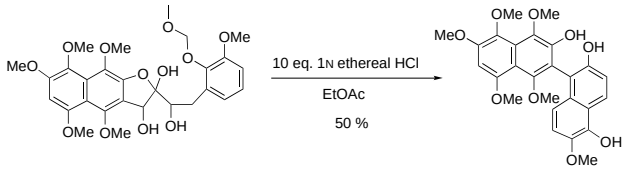
[2] An interesting example of the problems associated with the electron richness of the naphthalene ring in hindering the desired epoxidation of the furan is shown in a model substrate:



[3] a) S. Tang, R. M. Kennedy, *Tetrahedron. Lett*. **1992**, *33*, 5303; b) R. M. Kennedy, S. Tang, *Tetrahedron Lett*. **1992**, *33*, 3729.

[4] For previous examples of dihydroxylations of benzofuran and indole rings, see: a) M. P. Meisinger, F. A. Kuehl, Jr., E. L. Rickes, N. G. Brink, K. Folkers, M. Forbes, F. Zilliken, P. Gyorgy, *J. Am. Chem. Soc.* **1959**, *81*, 4979; b) G. B. Feigelson, M. Egbertson, S. J. Danishefsky, *J. Org. Chem*. **1988**, *53*, 3390.

[5] A demonstration of the vulnerability of the C3′ position even relative to C2 in a model substrate is shown below:



[6] O. Mitsunobu, *Synthesis* **1981**, 1.

[7] H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, M. Suzuki, *Chem. Pharm. Bull.* **1992**, *40*, 1148.

[8] Hydride reduction of protected variants of **11** and **12** that contained bulky protecting groups on the C3 hydroxy function also gave only products **13** and **14**.

[9] Both diastereomers show clear NOE enhancements between the C3 methine and the C3′ methine. No NOE interaction was observed between these two protons in heliquinomycin.

[10] The results of this reaction support a mechanism for epimerization at C3′ rather than the more traditional epimerization at C2 of the spiro center. Had epimerization at C2 occurred, the product of **12** would have corresponded to either one of the products derived from **11**. No such crossover was observed.

[11] The C4 protons of **16** appear as a doublet whereas the C4 protons of naturally derived heliquinomycinone appear as two doublets of doublets.

[12] H. C. Kolb, M. S. van Nieuwenhze, K. B. Sharpless, *Chem. Rev*. **1994**, *94*, 2483.

Heat Capacity of the Mixed-Valence Complex $\{[(n\text{-}C_3H_7)_4N][Fe^{II}Fe^{III}(dto)_3]\}_\infty$, Phase Transition because of Electron Transfer, and a Change in Spin-State of the Whole System**

Tadahiro Nakamoto, Yuji Miyazaki, Miho Itoi, Yuuki Ono, Norimichi Kojima,* and Michio Sorai*

Recently a novel mixed-valence complex $\{[(n\text{-}C_3H_7)_4N][Fe^{II}Fe^{III}(dto)_3]\}_\infty$ (**1**) containing asymmetric ligand dto (dithiooxalato: $C_2O_2S_2^{2-}$) was synthesized by Kojima and coworkers.[1] This complex dispalys ferromagnetic order below ~6 K and exhibits an interesting phenomenon at temperatures between 110 K and 120 K, where a change in the spin state of the whole system occurs as the result of electron transfer. This situation is schematically shown in Figure 1.

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[**] Contribution No. 48 from the Research Center for Molecular Thermodynamics. This work was partially supported by a Grant-in-Aid for Scientific Research on the Priority Areas of "Metal-Assembled Complexes" (Area No. 401/12023229) from the Ministry of Education, Science, Sports and Culture, Japan; dto = dithiooxalato.

  1433-7851/01/4024-4716 $ 17.50+.50/0