Substitution of a methyl group for the *N*-hydrogen atom turns a conformationally floppy adsorbate into a sterically constrained one. This alters the process of intramolecular vibrational energy redistribution (IVR). For pyrrolidine, the CH_2 stretch excitation can dissipate by coupling to the large-scale conformational change. This dissipation path is quenched for *N*-methylpyrrolidine. For both molecules, the CH_2 stretch can transfer its energy to other lower energy vibrations, substrate phonons, and electron–hole pairs.

Like the pyrrolidines, pyridine binds to copper predominantly through the lone pair electrons on nitrogen.[20] Only the CH (CD) stretch mode of pyridine on Cu(001) at 377 (281) mV has been observed with STM-IETS,[21] and the lineshape of this mode matches the lineshape of the *N*-methylpyrrolidine CH_2 stretch. The aromaticity of the pyridine ring constrains the molecule to a planar geometry. The rigid electronic backbone of pyridine acts like the bulky methyl group on *N*-methylpyrrolidine, keeping the molecule in just one conformation.

It is evident that molecular structure can have a significant impact on the dissipation of vibrational energy. Simple substitution of a methyl group for a hydrogen atom removes the NDR from the $I-V$ curve. Thus, as we move to ever smaller devices, consideration must be given to the effect of molecular structure and conformation on the conductivity. By changing the functional groups in a molecule, different electronic functions can be realized at the molecular level. At a more fundamental level, understanding how molecular structure and dynamics alter electron transport through single molecules has important ramifications in chemical and biological systems.

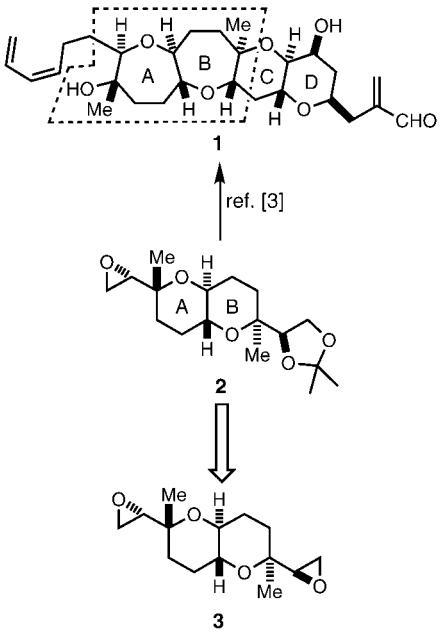
Received: May 16, 2001 [Z17121]

[1] M. Räsänen, H. Kunttu, J. Murto, *Laser Chem.* **1988**, *9*, 123.
[2] B. C. Stipe, M. A. Rezaei, W. Ho, *Science* **1998**, *279*, 1907.
[3] B. C. Stipe, M. A. Rezaei, W. Ho, *Phys. Rev. Lett.* **1998**, *81*, 1263.
[4] J. Gaudioso, L. J. Lauhon, W. Ho, *Phys. Rev. Lett.* **2000**, *85*, 1918.
[5] L. Esaki, *Phys. Rev.* **1958**, *109*, 603.
[6] *Physics and Technology of Submicron Structures* (Eds.: H. Heinrich, G. Bauer, F. Kuchar), Springer, Berlin, **1988**.
[7] I. W. Lyo, P. Avouris, *Science* **1989**, *245*, 1369.
[8] P. Bedrossian, D. M. Chen, K. Mortensen, J. A. Golovchenko, *Nature* **1989**, *342*, 258.
[9] J. Chen, M. A. Reed, A. M. Rawlett, J. M. Tour, *Science* **1999**, *286*, 1550.
[10] Y. Xue, S. Datta, S. Hong, R. Reifenberger, J. I. Henderson, C. P. Kubiak, *Phys. Rev. B* **1999**, *59*, R7852.
[11] S. M. Sze, *Physics of Semiconductor Devices*, Wiley, New York, **1981**.
[12] L. L. Chang, E. E. Mendez, C. Tejedor, *Resonant Tunneling in Semiconductors*, Plenum, New York, **1991**.
[13] *Molecular Electronics: Science and Technology* (Eds.: A. Aviram, M. Ratner), New York Academy of Sciences, New York, **1998**.
[14] B. C. Stipe, M. A. Rezaei, W. Ho, *Rev. Sci. Instrum.* **1999**, *70*, 137.
[15] B. C. Stipe, M. A. Rezaei, W. Ho, *Science* **1998**, *280*, 1732.
[16] J. C. Evans, J. C. Wahr, *J. Chem. Phys.* **1959**, *31*, 655.
[17] P. K. Hansma, *Tunneling Spectroscopy*, Plenum, New York, **1982**.
[18] G. Pfafferott, H. Oberhammer, J. E. Boggs, *J. Am. Chem. Soc.* **1985**, *107*, 2309.
[19] I. F. Shishkov, L. V. Vilkov, N. F. Pyatakov, *J. Struct. Chem.* **1992**, *33*, 38.
[20] B. J. Bandy, D. R. Lloyd, N. V. Richardson, *Surf. Sci.* **1979**, *89*, 344.
[21] L. J. Lauhon, W. Ho, *J. Phys. Chem. A* **2000**, *104*, 2463.

First Desymmetrization of a Centrosymmetric Molecule in Natural Product Synthesis: Preparation of a Key Fragment in the Synthesis of Hemibrevetoxin B**

Joanne M. Holland, Mark Lewis, and Adam Nelson*

Many polyether marine natural products, such as the ciguatoxins, brevetoxins, and yessotoxins, have embedded centrosymmetric fragments.[1] For example, the AB ring system of hemibrevetoxin B (**1**) is a centrosymmetric dioxepane (see boxed fragment: **1**, Scheme 1). There are three reported syntheses of hemibrevetoxin B (**1**), but none of these approaches take advantage of this hidden symmetry.[2, 3]



Scheme 1. Retrosynthetic analysis.

Our approach to hemibrevetoxin B is outlined in Scheme 1. Desymmetrization[4] of the centrosymmetric diepoxide **3**, by selective hydrolysis[5] of one of its enantiotopic epoxides and protection, would give the known[3] acetonide **2**. The symmetry of **3** demanded that a two-directional strategy[6] be used, an approach which was expected to improve the efficiency of the synthesis of **2** considerably. The epoxide **2** has been prepared

[*] Dr. A. Nelson, J. M. Holland
School of Chemistry
University of Leeds
Leeds, LS2 9JT (UK)
Fax (+44) 113-233-6565
E-mail: adamn@chem.leeds.ac.uk
Dr. M. Lewis
Discovery Chemistry, Pfizer Central Research
Ramsgate Road, Sandwich, Kent, CT13 9NJ (UK)

[**] This work was supported by the University of Leeds (through a Brotherton Scholarship to J.M.H.) and Pfizer. We are extremely grateful to Professor T. Nakata of the Institute of Physical and Chemical Research (RIKEN), Saitama, Japan, for providing us with the NMR spectra of the epoxide **2**, the Royal Society for a grant, and AstraZeneca for strategic research funding.

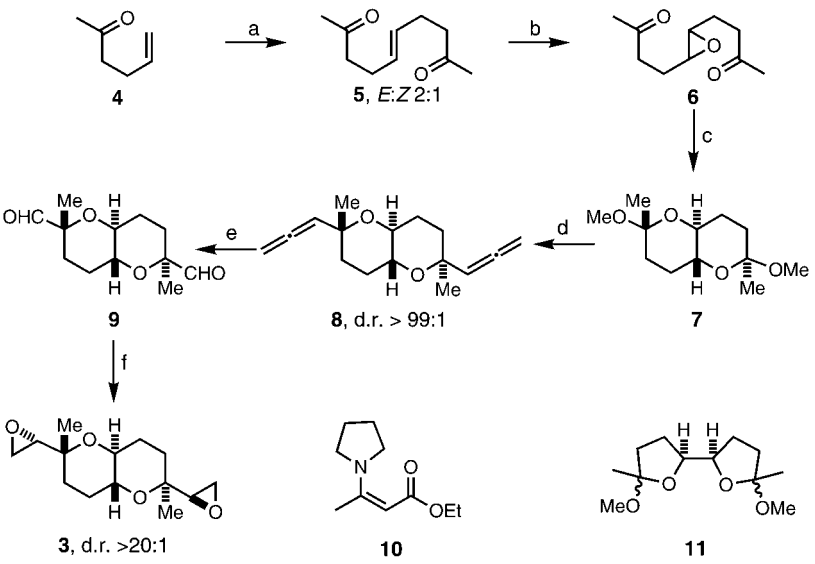
  0044-8249/01/11321-4206 $ 17.50+.50/0

from geranyl acetate in 22 steps and 14% overall yield, and is a key early intermediate in a total synthesis of hemibrevetoxin B: it has been converted in 32 steps into hemibrevetoxin B by means of an elegant double tetrahydropyran (THP) →oxepane ring expansion.[3]

The enedione **5** was prepared as a 2:1 mixture of *E*- and *Z*-geometric isomers by cross-metathesis of the available γ,δ-unsaturated ketone **4** (Scheme 2). An alternative approach to the enedione (*E*)-**5** involved reaction of the enamine **10** with (*E*)-1,4-dibromobut-2-ene, followed by hydrolysis and decarboxylation (70% yield). The enedione (*E*)-**5** was epoxidized with 3-chloroperoxybenzoic acid (*m*-CPBA) to give the epoxy diketone **6** in excellent yield.

The cyclization of the epoxy diketone **6**, catalyzed by pyridinium *p*-toluenesulfonate (PPTS), was central to the success of our synthesis;[7] participation of one of the ketones of **6** initially gave the diacetals **11** which equilibrated to give the di-THP **7**. The transformation **6** →**7**, therefore, exhibits an exquisite combination of thermodynamic and kinetic control: the stereochemistry of the ring junction derives from the stereospecific epoxide opening and the regiochemistry of the ring system and the stereochemistry of the anomeric centers are thermodynamically controlled.

Nucleophilic substitution of both acetals of **7** gave the centrosymmetric di-THP **8** in which both allenyl substituents had been introduced from an axial[8] direction; the relative stereochemistry was determined by using a series of NOE experiments (see Figure 1 for diagnostic NOE enhancements). In the context of two-directional synthesis, the isolation of a >99:1 mixture of diastereoisomers **8** reflects >200:1 stereoselectivity for each substitution reaction.



Scheme 2. Synthesis of the centrosymmetric bisepoxide **3**: a) 5 mol% $[(Cy_3P)_2RuCHPh]$, CH_2Cl_2, 92%; b) *m*-CPBA, 96%; c) PPTS, MeOH, 85%; d) propargyl trimethylsilane, cat. Me_3SiOTf, 92%; e) O_3, then Me_2S, 98%; f) $Me_3S(O)$ I, NaH, DMSO, 75%. Cy = cyclohexyl.

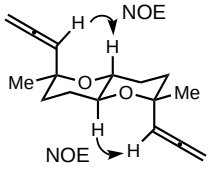


Figure 1. Proof of the stereochemistry of the bisallene **8**.

Ozonolysis of **8**, with reductive work-up, gave the dialdehyde **9** whose sulfur ylide-mediated epoxidation gave the diepoxide **3** as a 20:1 mixture of centrosymmetric and unsymmetrical isomers. The observation of a long-range coupling ($^4J = 1.6$ Hz) between the aldehyde proton (H^A) and the axial proton on C-3 (H^B) suggests that **9** largely populates a conformation **12** with a characteristic W-arrangement between H^A and H^B (Figure 2). The isolation of the diepoxide **3** is consistent with attack of the dimethylsulfoxonium ylide on the Felkin–Anh[9] conformation **13** (Figure 3).

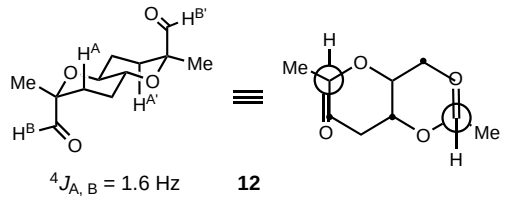


Figure 2. Ground-state conformation of the dialdehyde **9**.

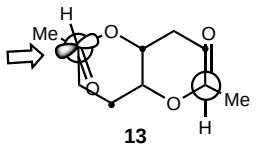
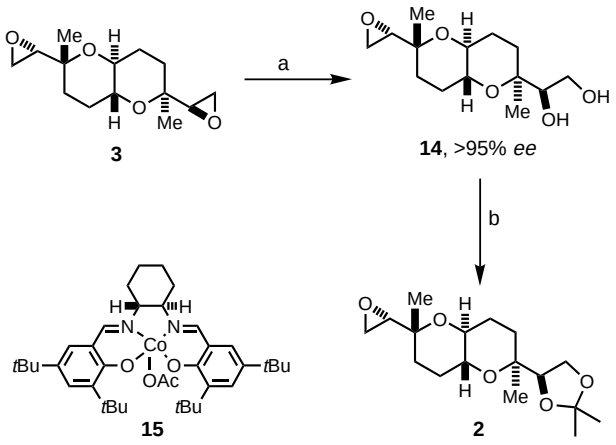


Figure 3. Diastereoselective epoxidation of the dialdehyde **9**.

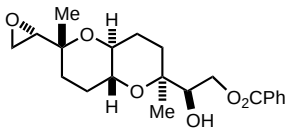
The centrosymmetric diepoxide **3** was desymmetrized by enantioselective epoxide hydrolysis[5] by using Jacobsen's chiral salen catalyst (*R*,*R*)-**15** (Scheme 3). Accordingly, treatment of a solution of **3** (1.0 M in 1:1 acetontrile/dichloromethane) with 1.1 equivalents of water and 20 mol% (*R*,*R*)-**15** gave the diol **14** in >98% yield, which was converted into the corresponding acetonide **2**. The epoxy



Scheme 3. Desymmetrization of the bisepoxide **3** and synthesis of the key intermediate **2**: a) 20 mol% **15**, 1.1 equiv H_2O, $MeCN/CH_2Cl_2$, >98%; b) $(MeO)_2CMe_2$, cat. PPTS, CH_2Cl_2, 98%.

  0044-8249/01/11321-4207 $ 17.50+.50/0

acetal **2**, $[\alpha]_D^{20} = -21.7$ ($c = 0.67$ in $CHCl_3$), was spectroscopically identical to that prepared previously[3] ($[\alpha]_D^{20} = -22.2$ ($c = 1.15$ in $CHCl_3$)[3]). The sense of asymmetric induction was the same as those observed in kinetic resolutions of terminal epoxides under similar reaction conditions. The enantiomeric excess of the desymmetrized product **14** was determined by chiral HPLC analysis of the corresponding benzoate **16**; comparison of **16** with a sample of low enantiomeric excess (prepared by mixing **16** with its enantiomer *ent*-**16**, also synthesized by desymmetrization of **3**) showed that the desymmetrized product **2** had >95% *ee*.



16

The key step of our synthesis was the desymmetrization of a centrosymmetric molecule, an approach which had not previously been exploited in natural product synthesis. This strategy has, however, been applied in the desymmetrization of a 2-pyridone [4+4] photodimer,[10] the asymmetric reduction of a diketone,[11] and in the preparation of syndiotactic polymers.[12] The use of a desymmetrization, rather than a kinetic resolution strategy, enabled the product **2** to be obtained in high yield without compromising its enantiomeric excess. Our two-directional approach allowed the synthesis of the established intermediate **2** in eight steps and 34% overall yield. The key features of our synthesis of **2** include a) the use of no protecting groups, b) the use of only achiral reagents to control relative stereochemistry, and c) the use of a single chiral catalyst to induce asymmetry. The desymmetrization of centrosymmetric molecules, combined with a two-directional synthetic approach, is a powerful strategy which will find further application in the synthesis of natural products and biologically active compounds.

Received: August 15, 2001 [Z17732]

[1] D. J. Faulkner, *Nat. Prod. Rep.* **2000**, *17*, 1.
[2] a) K. C. Nicolaou, K. Raja Reddy, G. Skokotas, F. Sato, X.-Y. Xiao, C.-K. Hwang, *J. Am. Chem. Soc.* **1993**, *115*, 3558; b) I. Kadota, P. Jung-Youl, N. Koumura, G. Pollaud, Y. Matsukawa, Y. Yamamoto, *Tetrahedron Lett.* **1995**, *36*, 5777.
[3] T. Nakata, *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 76.
[4] For a review concerning the desymmetrization of *meso* molecules, see: M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765.
[5] M. Tokunaga, J. F. Larrow, F. Kakiuchi, E. N. Jacobsen, *Science* **1997**, *277*, 936.
[6] C. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, *27*, 9.
[7] For the cyclization of epoxy ketones, see: a) H. H. Wasserman, T. Oku, *Tetrahedron Lett.* **1986**, *27*, 4913; b) I. Paterson, K. Fessner, M. R. V. Finlay, M. F. Jacobs, *Tetrahedron Lett.* **1996**, *37*, 8803.
[8] O. Gaertzen, A. M. Misske, P. Wolbers, H. M. R. Hoffmann, *Synlett* **1999**, 1041.
[9] a) M. Chérest, H. Felkin, N. Prudent, N. *Tetrahedron Lett.* **1968**, 2199; b) N. T. Anh, *Top. Curr. Chem.* **1980**, *88*, 145.
[10] A. C. Spivey, B. I. Andrews, A. D. Brown, C. S. Frampton, *Chem. Commun.* **1999**, 2523.
[11] D. R. Dodds, J. B. Jones, *J. Am. Chem. Soc.* **1988**, *110*, 577.
[12] T. M. Ovitt, G. W. Coates, *J. Am. Chem. Soc.* **1999**, *121*, 4072.

Discrete Mixed-Valence Metal Chains: Iridium Pyridonate Blues**

Cristina Tejel, Miguel A. Ciriano,* B. Eva Villarroya, Raquel Gelpi, José A. López, Fernando J. Lahoz, and Luis A. Oro*

Discrete chains of metal atoms are of current interest from both theoretical and practical points of view. One synthetic approach to this type of compounds is based on ligand-assisted reactions using polydentate ligands, which is exemplified by several families of metal string complexes supported by oligo-α-pyridylamido ligands.[1] A second approximation involves the formation of metal–metal bonds between partially oxidized d^8 square-planar complexes, for which the platinum blues are the most representative examples.[2] Most of the reported platinum blues have been prepared from disymmetric square-planar dinuclear complexes with two amidate N-C-O-type ligands as bridges, and it has been claimed[2a–c] that the head-to-head (HH) configurations are essential to achieve the tetrametallic platinum chains. Moreover, it has been argued that the head-to-tail (HT) structures do not dimerize for steric reasons. In fact, all the reported structures of platinum blues are based on HH dimers. Other metals, for which square-planar complexes are common, such as rhodium, iridium, and gold, are suitable for forming such metallic chains, but few examples for these metals are known.[3] Herein we describe two new tetrametallic mixed-valence iridium compounds, which substantiate that dinuclear complexes with HT configurations are actually able to participate in metallic chains, while those with HH configurations generate the thermodynamically stable compounds.

An appropriate precursor for the formation of iridium pyridonate blues is the binuclear complex $[\{Ir(\mu\text{-OPy})(CO)_2\}_2]$ (Opy = 2-pyridonate (**1**)). It was prepared, as purple microcrystals with metallic luster, by bubbling carbon monoxide through a solution of the complex $[\{Ir(\mu\text{-OPy})(cod)\}_2]$ (cod = 1,5-cyclooctadiene) in toluene.[4] While the HT configuration of the α-pyridonate ligands was found in the solid state and in solution for the diolefinic complex, a bridging ligand rearrangement occurs on carbonylation. Thus, complex **1** was found to be a 1:1 mixture of the HH and the HT isomers in solution (Scheme 1). Noteworthy, these configurational isomers were found to be in a chemical equilibrium, as shown by the ^1H two-dimensional exchange (EXSY) spectrum.

Oxidation of a solution of **1** in toluene with diiodine (in a 2:1 molar ratio) at 50 °C gives immediately an EPR-silent purple solution from which a crystalline blue solid (**2**) was isolated in excellent yield (95%) on addition of hexane.[5] This

[*] Dr. M. A. Ciriano, Prof. L. A. Oro, Dr. C. Tejel, Dr. B. E. Villarroya, R. Gelpi, Dr. J. A. López, Dr. F. J. Lahoz
Departamento de Química Inorgánica
Instituto de Ciencia de Materiales de Aragón
Universidad de Zaragoza-C.S.I.C., 50009-Zaragoza (Spain)
Fax: (+34) 976761143
E-mail: mciriano@posta.unizar.es
oro@posta.unizar.es

[**] The generous financial support from DGES and MCyT-PNI (Projects PB98-641 and BQU2000-1170) is gratefully acknowledged.

  0044-8249/01/11321-4208 $ 17.50+.50/0