Natural Product Synthesis

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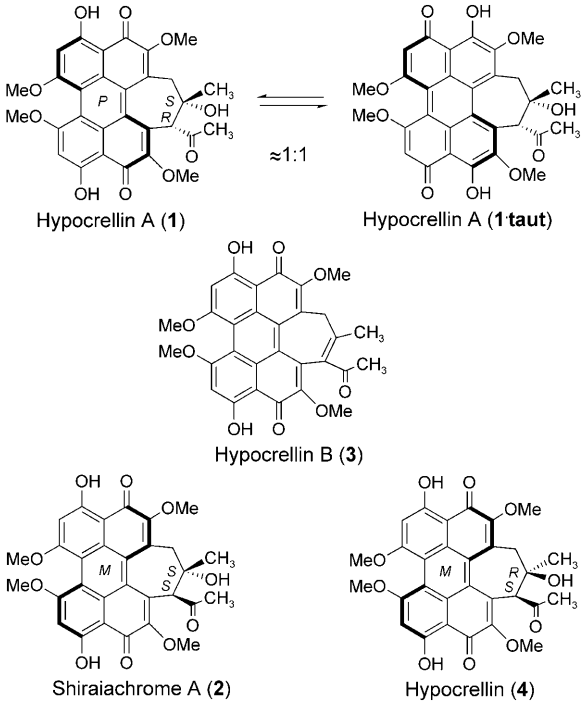
Dynamic Stereochemistry Transfer in a Transannular Aldol Reaction: Total Synthesis of Hypocrellin A**

*Erin M. O'Brien, Barbara J. Morgan, and Marisa C. Kozlowski**

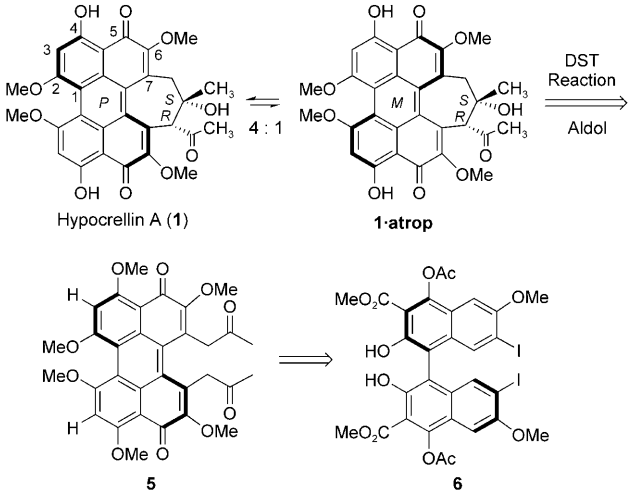
Hypocrellin A (**1**), shiraiachrome A (**2**), hypocrellin B (**3**), and hypocrellin (**4**) are members of a growing class of natural products called perylenequinones (Scheme 1). Hypocrellin A,



Scheme 1. Hypocrellin A and related perylenequinone natural products. *M* and *P* are the helical configurations, taut = tautomer.

shiraiachrome A, and hypocrellin B are isolates of *Shiraia bambusicola*.[1] Interestingly, a different source, *Hypocrella bambusae*, gave rise to hypocrellin (**4**), the enantiomer of hypocrellin A (**1**), along with the racemic hypocrellin B.[2] The perylenequinones have attracted considerable attention because of their potent biological activity, including light-induced activity against tumor cell lines,[3,4] antiviral activity,[5] and immunotherapeutic properties,[6] and elegant approaches to the calphostins have been reported.[7] The more architecturally complex perylenequinones are exciting targets for photodynamic cancer therapy (PDT)[3,4,8] but have not succumbed to total syntheses. Notably, hypocrellin A (**1**) with a seven-membered ring that contains two stereogenic centers, one of which is quaternary, remains a challenging synthetic target. Herein, we report the first total synthesis of hypocrellin A (**1**) through a dynamic stereochemistry transfer reaction.

There has been much confusion in the literature regarding the naming of these structurally distinct members of the perylenequinone natural products.[9] One contributing factor lies in the tautomerization available within the perylenequinone moiety (**1** and **1·taut**; Scheme 1). The major tautomer of each perylenequinone varies depending on the planarity of the naphthalene core and the strength of the intramolecular hydrogen bonds.[9,10] For hypocrellin A (**1**), the two tautomers are present in almost equal amounts. A second issue centers on atropisomerization of the helical configuration in the perylenequinone. Although the structurally related calphostins are atropisomerically stable, the additional seven-membered ring in hypocrellin A lowers the atropisomerization barrier. As a result, hypocrellin A exists as an equilibrium mixture of atropisomers (**1** and **1·atrop**),[11] with **1** favored (Scheme 2).



Scheme 2. Proposed dynamic stereochemistry transfer (DST) reaction to give hypocrellin A. atrop = atropisomer.

[*] E. M. O'Brien, B. J. Morgan, Prof. M. C. Kozlowski
Department of Chemistry, Roy and Diana Vagelos Laboratories
University of Pennsylvania
Philadelphia, PA 19104-6323 (USA)
Fax: (+1) 215-573-7165
E-mail: marisa@upenn.edu
Homepage: http://www.sas.upenn.edu/chem/

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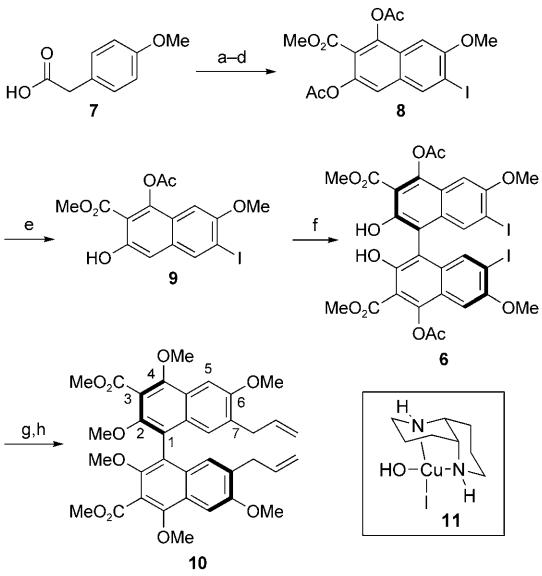
Given the facile atropisomerization of **1**, it is unclear which stereochemistry elements are established first in the biosynthesis, that is, the helical axis or the stereocenters of the seven-membered ring. For the synthesis of hypocrellin A, our research group envisioned a potentially biomimetic, dynamic stereochemistry transfer (DST) reaction (Scheme 2).[12] Such DST reactions that satisfy the following requirements are rare: 1) there is a directing stereocenter that is not involved in any bond-forming or bond-breaking processes; 2) diastereocontrol occurs from this directing stereocenter in the formation of a new stereocenter; and 3) a loss of the integrity in the original directing stereocenter occurs subsequent to the transformation.

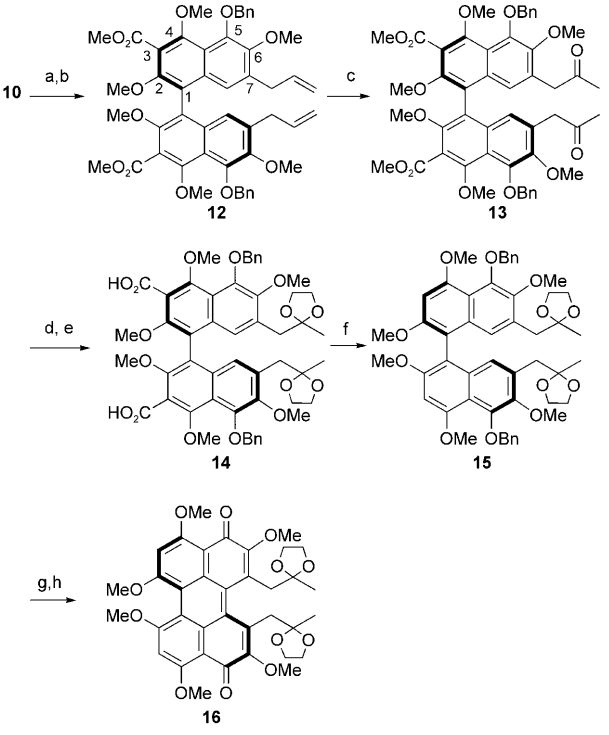
To implement this plan, the helical configuration, as found in enantiomerically pure perylenequinone **5**, would be synthesized first. The helical configuration would be used to direct the stereochemistry of an intramolecular 1,8-diketone aldol cyclization that forms the seven-membered ring and establishes the key centrochiral stereocenters, including the quaternary center (Scheme 2). From a biosynthetic viewpoint, such an ordering explains the genesis of all the perylenequinone compounds, including the calphostins and elsinochromes, from a common precursor similar to **5**.[13] Helically chiral perylenenquinone **5** would in turn be synthesized from axially chiral **6**.

Previous synthetic approaches toward less complex perylenequinone natural products (calphostins) have employed oxidative coupling reactions of enantiopure, chiral 2-naphthols; unfortunately, low diastereoselection was usually observed, with the undesired atropdiastereomer predominating.[7] As such, it seems unlikely that the biosynthetic route to these compounds relies on a similar diastereoselective coupling. The fact that certain enzymes exhibit enantioselectivity in the oxidative coupling of 2-naphthol[14] provides support for an enantioselective oxidative coupling of an achiral naphthol as a possible biogenesis. In our approach we employed such an enantioselective oxidative coupling of **9**, which was readily prepared in five steps from commercially available **7** (Scheme 3). The enantioselective biaryl coupling with our copper diaza-*cis*-decalin catalyst (**11**)[15] further highlights the utility of this method, and gave **6** with 81% *ee* (>99% *ee* after one trituration) and good yield. Deacylation of the C4,C4′-positions and subsequent methylation of the free hydroxy groups on the naphthalene ring was followed by a highly efficient Suzuki coupling reaction (96%) to install the C7,C7′ allyl groups, which afforded **10**.

With a viable route to large quantities of enantiopure biaryl **10**, our attention turned to the synthesis of diketone perylenequinone intermediate **5** (Scheme 2). Hydroxylation at the C5,C5′-positions was accomplished in 73% yield followed by benzylation to give dibenzyl ether **12** (Scheme 4). Wacker oxidation of **12** to the diketone **13** proceeded smoothly (75%). Protection of **13** as the bisketal was required because of the basic nature of the subsequent steps. An anionic displacement reaction was necessary to cleave the unreactive C3,C3′ esters; the use of NaCN provided **14** in quantitative yield. Standard methods to conduct aromatic decarboxylations require high temperature (namely, copper/quinoline, 180 °C),[16] which would racemize



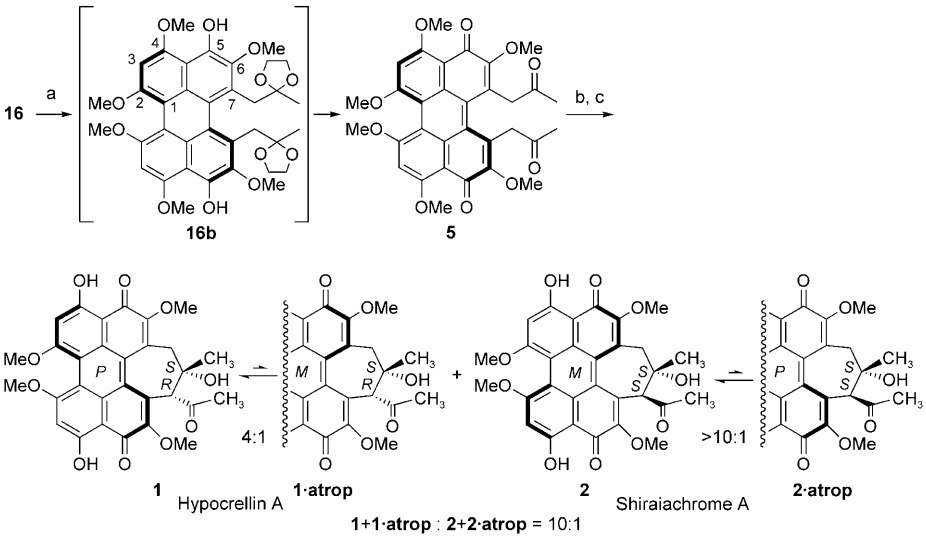
Scheme 3. Reagents and conditions: a) ICl, AcOH, 85%; b) $SOCl_2$, benzene; $NaCH(CO_2Me)_2$, THF; c) CH_3SO_3H, P_2O_5; d) Ac_2O, pyridine, 40% (over 3 steps); e) K_2CO_3, MeOH, CH_2Cl_2, 87%; f) (*R*,*R*)-**11** (20 mol%), CH_3CN, RT, 80%, 81% *ee* (>99% *ee*, EtOAc/hexanes trituration); g) MeI, NaH, DMF, 94%; h) allylB(pin), $[Pd(PPh_3)_4]$ (20 mol%), CsF, toluene, 96%. allylB(pin) = allylboronic acid pinacol ester, DMF = *N*,*N*-dimethylformamide.



Scheme 4. Reagents and conditions: a) $PhI(OCOCF_3)_2$, $(CF_3)_2CHOH$; then aq NaOH, 73%; b) BnBr, nBu_4NI, NaH, DMF, 78%; c) $PdCl_2$, CuCl, H_2O, DMF, 75%; d) $HC(OEt)_3$, $HOCH_2CH_2OH$, cat. TsOH, 90%; e) NaCN, DMSO, H_2O, 110 °C, 100%; f) $Pd(OCOCF_3)_2$, Ag_2CO_3, 5% DMSO/DMF, 70 °C; then $NaBH_4$, 60%; g) H_2, Pd/C, MeOH, 100%; h) MnO_2, NaOH, THF, EtOH, 88%. Bn = benzyl, DMSO = dimethyl sulfoxide, Ts = *para*-toluenesulfonyl.

the enantioenriched biaryl substrate **14**. To circumvent this problem we developed a new palladium-mediated decarboxylation that takes place at 70 °C and provided **15** without racemization.[17] After debenzylation of **15**, cyclization to perylenequinone **16** proved unexpectedly difficult with MnO_2,[7c,d] and gave rise to a hydroperylenequinone. However, addition of NaOH to facilitate deprotonation allowed smooth conversion into **16**.

Surprisingly, ketal hydrolysis of perylenequinone **16** was accompanied by decomposition. The sensitivity of the perylenequinone to acid was avoided by reducing **16** to the corresponding perylene (**16b**) and then treating with [$PdCl_2(CH_3CN)_2$] in acetone. Subsequent exposure to air oxidized the deprotected intermediate to furnish **5** (Scheme 5). With



Scheme 5. Reagents and conditions: a) $Na_2S_2O_4$, benzene; then [$PdCl_2(CH_3CN)_2$] (20 mol%), $(CH_3)_2CO$, 89%; b) $LiN(SiMe_2Ph)_2$, THF, −105 °C, 74% (d.r. 10:1); c) MgI_2, Et_2O, 57%.

key intermediate **5** in hand, the crucial intramolecular diketone aldol cyclization was investigated. To the best of our knowledge, the type of 1,8-diketone aldol reaction that we proposed to use had not been employed previously outside of bridged or macrocyclic architectures.[18,19]

Nonetheless, we hypothesized that such an aldol reaction must be involved in the biosynthesis of the hypocrellins. Encouragingly, the desired product of this aldol reaction corresponds to structure **1**, which is the most stable of the rapidly equilibrating atropisomeric (**1·atrop**; Scheme 2) and tautomeric (**1·taut**; Scheme 1) forms.[11] Furthermore, molecular modeling studies indicated that a *Z* enolate geometry of **5** would give rise to the *syn* aldol product, which corresponds to hypocrellin A (**1**), whereas the *E* enolate would produce the *anti* product, which corresponds to shiraiachrome A (**2**) via closed chairlike transition states. Analysis of the relevant transition states also revealed that the helical configuration of **5** would expose one diastereoface of the ketone, thus resulting in the required *S* tertiary alcohol configuration of both **1** and **2**. Simple MM2*[20] calculations reveal that of the two possible *Z* enolate transition states, transition state **A**, which corresponds to the configuration of **1**, is lower in energy (Figure 1). This approach requires that the helical configuration be sufficiently stable during the aldol reaction, even though it atropisomerizes freely thereafter. To investigate this proposal, silazide bases were chosen to effect deprotonation as they give predominantly *Z* enolates.[21]

After considerable optimization of the base, solvent, additive, and temperature, we discovered that aldol cyclization of **5** proceeded smoothly using $LiN(SiMe_2Ph)_2$ at −105 °C and provided the requisite seven-membered ring (Scheme 5). The resultant adduct was treated with MgI_2,[7b,e,f] which selectively removed the C4,C4′ methyl ethers, to yield the natural form of hypocrellin A (**1**:**1·atrop**) as the major product (*syn/anti* 10:1; *syn* diastereomer 92% *ee*). Spectroscopic data from our synthetic **1**:**1·atrop** were identical to that of hypocrellin (**4**) from natural sources, with the exception of the absolute configuration, as determined by direct comparison. The minor diastereomer **2** was separated by chromatography, and ^{1}H NMR spectroscopic analysis showed that it corresponds to shiraiachrome A, a natural product also isolated from *Shiraia bambusicola*.[1] Interestingly, in the case of shiraiachrome A, the atropisomeric equilibrium after the aldol reaction favors the opposite *M* helical configuration even though it originally arose from the same *P* helical configuration of **5** as hypocrellin A.

In summary, we have completed the first total synthesis of hypocrellin A in 19 steps (1.6% overall yield; average 82% per step). Key methods that were developed to enable this synthetic venture include: 1) a catalytic enantioselective coupling of highly functionalized naphthols;[15] 2) a low temperature aromatic decarboxylation protocol;[17] and 3) a 1,8-diketone aldol reaction to establish the seven-membered ring. In the aldol reaction, the two newly

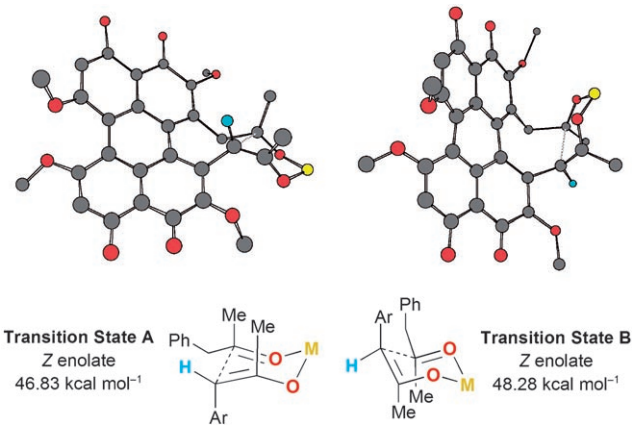


Figure 1. MM2* calculated Z enolate transition states. M = Li.

formed centrochiral stereocenters of the seven-membered ring were dictated by the stable perylenequinone helical configuration and the enolate geometry. After the aldol reaction, however, the helical configuration was labile as observed for the natural product (4:1 mixture of atropisomers). As such, we have shown that a dynamic stereochemical transfer is a viable approach here. The efficiency of this strategy will enable the synthesis of related structures and exploration of their biological chemistry and PDT properties.

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[1] a) T. Kishi, S. Tahara, M. Tsuda, C. Tanaka, S. Takahashi, *Planta Med.* **1991**, *57*, 376 – 379; b) H. Wu, X. F. Lao, Q. W. Wang, R. R. Lu, *J. Nat. Prod.* **1989**, *52*, 948 – 951 (hypocrellin A is called shiraiachrome B here, see Ref. [9]).

[2] W. S. Chen, Y. T. Chen, X. Y. Wang, E. Friedrichs, H. Puff, E. Breitmaier, *Liebigs Ann. Chem.* **1981**, 1880 – 1885.

[3] For reviews, see: a) J. W. Lown, *Can. J. Chem.* **1997**, *75*, 99 – 119; b) Z. Diwu, *Photochem. Photobiol.* **1995**, *61*, 529 – 539.

[4] a) M. Olivo, M. Ali-Seyed, *Int. J. Oncol.* **2007**, *30*, 537 – 548; b) J. B. Maxhimer, R. M. Reddy, J. Zuo, G. W. Cole, Jr., D. S. Schrump, D. M. Nguyen, *J. Thoracic and Cardiovascular Surg.* **2005**, *129*, 53 – 63; c) Z. Xiao, C. B. Hansen, T. M. Allen, G. G. Miller, R. B. Moore, *J. Pharm. Pharm. Sci.* **2005**, *8*, 536 – 543; d) B. Guo, S. L. Hembruff, D. J. Villeneuve, A. F. Kirwan, A. M. Parissenti, *Breast Cancer Res. Treat.* **2003**, *82*, 125 – 141; e) L. Ma, H. Tai, C. Li, Y. Zhang, Z.-H. Wang, W.-Z. Ji, *World J. Gastroenterol.* **2003**, *9*, 485 – 490; f) S. M. Ali, M. Olivo, *Int. J. Oncol.* **2002**, *21*, 1229 – 1237; g) S. M. Ali, M. Olivo, G. Y. Yuen, S. K. Chee, *Int. J. Oncol.* **2001**, *19*, 633 – 643; h) A. L. Vandenbogaerde, W. S. Delaey, A. M. Vantieghem, B. E. Himpens, W. S. Merlevede, P. A. De Witte, *Photochem. Photobiol.* **1998**, *67*, 119 – 125; i) J. Zhang, E.-H. Cao, J.-F. Li, T.-C. Zhang, W.-J. Ma, *J. Photochem. Photobiol. B* **1998**, *43*, 106 – 111.

[5] a) J. Hirayama, K. Ikebuchi, H. Abe, K.-W. Kwon, Y. Ohnishi, M. Horiuchi, M. Shinagawa, K. Ikuta, N. Kamo, S. Sekiguchi, *Photochem. Photobiol.* **1997**, *66*, 697 – 700; b) J. B. Hudson, V. Imperial, R. P. Haugland, Z. Diwu, *Photochem. Photobiol.* **1997**, *65*, 352 – 354.

[6] B. Leveugle (Altachem Pharma Ltd., Edmonton, CA), EP1357944, **2002**.

[7] a) C. A. Broka, *Tetrahedron Lett.* **1991**, *32*, 859 – 862; b) F. M. Hauser, D. Sengupta, S. A. Corlett, *J. Org. Chem.* **1994**, *59*, 1967 – 1969; c) R. S. Coleman, E. B. Grant, *J. Am. Chem. Soc.* **1994**, *116*, 8795 – 8796; d) R. S. Coleman, E. B. Grant, *J. Am. Chem. Soc.* **1995**, *117*, 10889 – 10904; e) C. A. Merlic, C. C. Aldrich, J. Albaneze-Walker, A. Saghatelian, *J. Am. Chem. Soc.* **2000**, *122*, 3224 – 3225; f) C. A. Merlic, C. C. Aldrich, J. Albaneze-Walker, A. Saghatelian, J. Mammen, *J. Org. Chem.* **2001**, *66*, 1297 – 1309.

[8] a) N. Lane, *Sci. Am.* **2003**, *288*, 38 – 45; b) D. E. J. G. J. Dolmans, D. Fukumura, R. K. Jain, *Nat. Rev. Cancer* **2003**, *3*, 380 – 387; c) C. Hopper, *Lancet Oncol.* **2000**, *1*, 212 – 219; d) D. E. Brundish, W. G. Love, *IDrugs* **2000**, *3*, 1487 – 1508; e) J. S. McCaughan, Jr., *Drugs Aging* **1999**, *15*, 49 – 68; f) A. M. Rouhi, *Chem. Eng. News* **1998**, *76*(44), 22 – 26.

[9] Here, we employ the names and structural assignments suggested by: S. Mazzini, L. Merlini, R. Mondelli, L. Scagloni, *J. Chem. Soc. Perkin Trans. 2* **2001**, 409 – 416. Note: SciFinder indexes hypocrellin and hypocrellin A as identical compounds with the absolute configuration of hypocrellin.

[10] A. Arnone, L. Merlini, R. Mondelli, G. Nasini, E. Ragg, L. Scaglioni, U. Weiss, *J. Chem. Soc. Perkin Trans. 2* **1993**, 1447 – 1454.

[11] A. Smirnov, D. B. Fulton, A. Andreotti, J. W. Petrich, *J. Am. Chem. Soc.* **1999**, *121*, 7979 – 7988.

[12] For related examples involving axial to central chirality transfer, see: a) K. Ohmori, M. Kitamura, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1304 – 1307; *Angew. Chem. Int. Ed.* **1999**, *38*, 1226 – 1229; b) M. Kitamura, K. Ohmori, T. Kawase, K. Suzuki, *Angew. Chem.* **1999**, *111*, 1308; *Angew. Chem. Int. Ed.* **1999**, *38*, 1229 – 1232; c) K. Ohmori, M. Tamiya, M. Kitamura, H. Kato, M. Oorui, K. Suzuki, *Angew. Chem.* **2005**, *117*, 3939 – 3942; *Angew. Chem. Int. Ed.* **2005**, *44*, 3871 – -3874; d) A. Joncour, A. Décor, S. Thoret, A. Chiaroni, O. Baudoin, *Angew. Chem.* **2006**, *118*, 4255; *Angew. Chem. Int. Ed.* **2006**, *45*, 4149 – 4152; e) G. Stavrakov, M. Keller, B. Breit, *Eur. J. Org. Chem.* **2007**, 5726 – 5733; f) A. J. B. Lapierre, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2007**, *129*, 494 – 495; for a general review of chirality transfer within biaryl systems, see: g) G. Bringmann, A. J. Price Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518 – 5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384 – 5427.

[13] For reviews of the perylenequinone natural products, see: a) G. Bringmann, C. Günther, M. Ochse, O. Schupp, S. Tasler, *Prog. Chem. Org. Nat. Prod.* **2001**, *82*, 1 – 249; b) U. Weiss, L. Merlini, G. Nasini, *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1 – 71.

[14] a) M. Sridhar, S. K. Vadivel, U. T. Bhalerao, *Tetrahedron Lett.* **1997**, *38*, 5695 – 5696; b) M. Takemoto, Y. Suzuki, K. Tanaka, *Tetrahedron Lett.* **2002**, *43*, 8499 – 8501.

[15] a) X. Li, J. Yang, M. C. Kozlowski, *Org. Lett.* **2001**, *3*, 1137 – 1140; b) X. Li, J. B. Hewgley, C. A. Mulrooney, J. Yang, M. C. Kozlowski, *J. Org. Chem.* **2003**, *68*, 5500 – 5511; c) C. A. Mulrooney, X. Li, E. S. Divirgilio, M. C. Kozlowski, *J. Am. Chem. Soc.* **2003**, *125*, 6856 – 6857; d) E. S. DiVirgilio, E. C. Dugan, C. A. Mulrooney, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 385 – 388; e) M. C. Kozlowski, E. C. Dugan, E. S. DiVirgilio, K. Maksimenka, G. Bringmann, *Adv. Synth. Catal.* **2007**, *349*, 583 – 594.

[16] Examples of copper-catalyzed decarboxylation of aryl acids: a) M. Nakajima, I. Miyoshi, K. Kanayama, S.-I. Hashimoto, M. Noji, K. Koga, *J. Org. Chem.* **1999**, *64*, 2264 – 2271; b) T. Cohen, R. A. Schambach, *J. Am. Chem. Soc.* **1970**, *92*, 3189 – 3190.

[17] J. Dickstein, C. A. Mulrooney, E. M. O'Brien, B. J. Morgan, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 2441 – 2444.

[18] For selected examples, see: a) Y. Miyahara, *J. Org. Chem.* **2006**, *71*, 6516 – 6521; b) S. Davies, R. L. Sheppard, A. D. Smith, J. E. Thomson, *Chem. Commun.* **2005**, 3802 – 3804; c) E. Piers, K. A. Skupinska, D. J. Wallace, *Synlett* **1999**, 1867 – 1870.

[19] There is one report of an acyclic intramolecular aldol to yield the seven-membered ring through a reductive aldol reaction of the enone aldehyde: T. G. Baik, A. L. Luis, L. C. Wang, M. J. Krische, *J. Am. Chem. Soc.* **2001**, *123*, 5112 – 5113.

[20] W. C. Still, *MacroModel*, V4.0, V5.0, V6.0, V6.5; Columbia University.

[21] M. Gaudemar, M. Bellassoued, *Tetrahedron Lett.* **1989**, *30*, 2779 – 2782.

