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Novel Synthetic Approach to the 8,10-Dimethyl *anti-syn-anti*-Perhydrophenanthrene Skeleton

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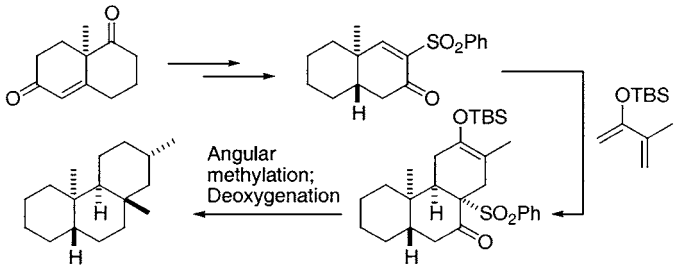
ABSTRACT



An efficient and highly stereocontrolled approach to the 8,10-dimethyl *anti-syn-anti*-perhydrophenanthrene carbon skeleton starting with the Wieland–Miescher ketone is described. The approach centers on a Diels–Alder–angular methylation–deoxygenation sequence.

The 8,10-dimethyl *anti-syn-anti*-perhydrophenanthrene carbon skeleton (**1**) is a substructure common to several important natural products.[1] As was recognized by W. S. Johnson many years ago,[2] a direct consequence of this particular backbone pattern and ring fusion is that *the central B ring cannot adopt a chair conformation*. Rather, the configurational elements virtually impose a boatlike disposition on the ring (see Figure 1). Synthetic approaches to this framework in the context of equilibrium control would be expected to result in more thermodynamically stable systems not possessing the obligatory B-ring boat conformer.[2] Clearly, tight kinetic control is required to reach **1**.

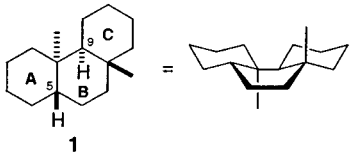


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Figure 1. 8,10-Dimethyl *anti-syn-anti*-perhydrophenanthrene skeleton (**1**).

Our interest in this structural motif arose from its incorporation into the novel tricyclic diterpenoid brasilicardin A (**2**, Figure 2).[1c] Aside from the challenge at the stereochemical level that this compound poses, its biological properties certainly add to its interest. Brasilicardin A was recently isolated as a metabolite from the culture broth of the patho-

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(1) See for example: (a) Godtfredsen, W. O.; Rastrup-Anderson, N.; Vangedal, S.; Ollis, W. D. *Tetrahedron* **1979**, *35*, 2419−2431. (b) Nishizawa, M.; Takenaka, H.; Hirotsu, K.; Higuchi, T.; Hayashi, Y. *J. Am. Chem. Soc*. **1984**, *106*, 4290−4291. (c) Shigemori, H.; Komaki, H.; Yazawa, K.; Mikami, Y.; Nemoto, A.; Tanaka, Y.; Sasaki, T.; In, Y.; Ishida, T.; Kobayashi, J. *J. Org. Chem*. **1998**, *63*, 6900−6904. (d) Matsuda, H.; Kageura, T.; Murakami, T.; Kishi, A.; Yoshikawa, M. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 3081−3086.

(2) Johnson, W. S. *J. Am. Chem. Soc*. **1953**, *75*, 1498−1500.

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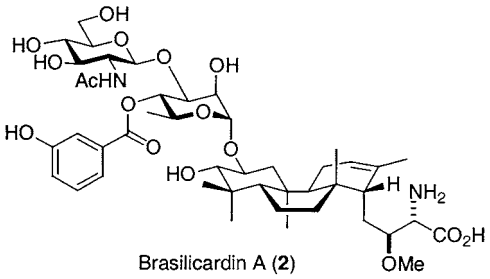
genic actinomycete *Nocardia brasiliensis*.[1c] It displays potent immunosuppressive activity,[3] having an IC_{50} of 0.05 nM, and also exhibits a broad range of cytotoxic activity against a variety of cell lines,[4] with an IC_{50} range of 0.07−96 nM.

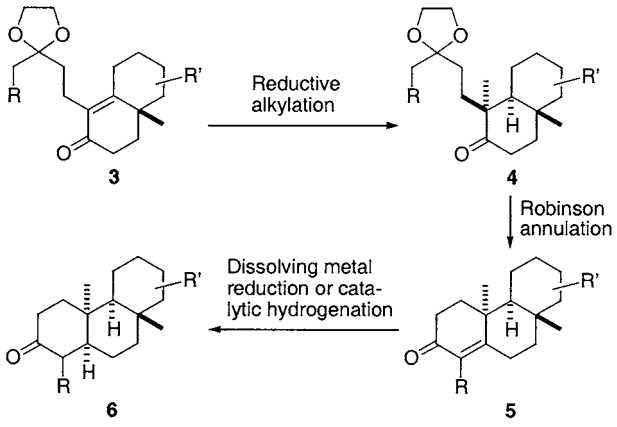


Brasilicardin A (**2**)

Figure 2. Structure of brasilicardin A (**2**).

We noted that access to the generic anti-syn-anti carbon skeleton had previously been attempted by first constructing an appropriately substituted BC ring system (**3**, Scheme 1).

Scheme 1

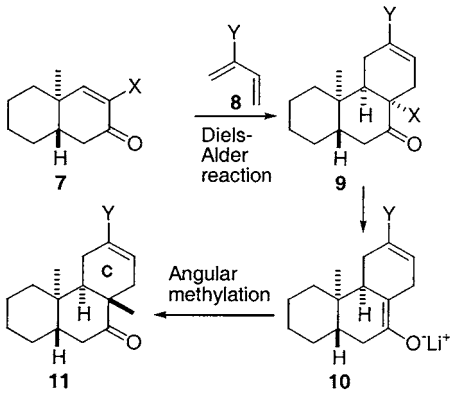


Following reductive methylation and Robinson annulation, compound **5** was formed.[5] Remarkably, both dissolving metal and catalytic hydrogenation reduction of **5** apparently led, predominantly, to the undesired syn relative stereochemistry at the AB juncture (see compound **6**).[5a,6]

To overcome this type of difficulty, several *indirect* approaches have been devised to reach system type **1**.[5,7] Herein, we describe an approach to the target system (cf. **1**). The approach exploits the stereochemical character of precursor structures to anneal the syn-anti BC substructure to an anti AB precursor.

The logic is encapsulated in Scheme 2. Central to the plan was the proper selection of X (see structure **7**). This function

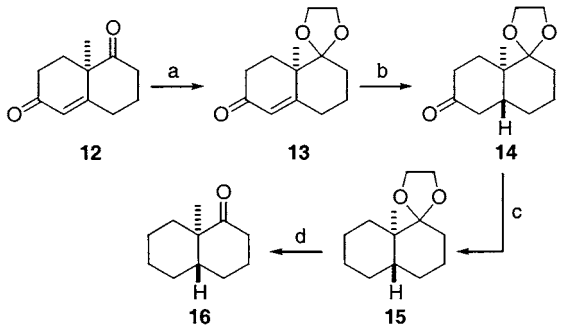
Scheme 2



had to favor, in the first instance, a Diels−Alder reaction, which would hopefully solve the syn backbone relationship.[8] Having provided this guidance, X must then facilitate access to the site-specific bridgehead enolate **10**, which, following methylation from the less hindered β-face, could afford **11**. This strategy carried with it the collateral feature that, with appropriate foresight as to the nature of the Diels−Alder diene (**8**), the C ring in a structure of type **11** might be well equipped to allow for progress toward **2**. As we show below, utilization of a phenylsufonyl group as the X function at the stage of **7** meets the former needs (see compound **21**).[9]

Our route to dienophile **21** is outlined in Schemes 3 and 4. Commercially available (±)-**12**[10] was subjected to chemose-

Scheme 3 [a]



[a] Key: (a) ethylene glycol, *p*-TsOH·H_2O, 4 Å MS, 85%; (b) Li, NH_3, *t*-BuOH, THF, −78 °C to reflux, 84%; (c) H_2NNH_2·H_2O, KOH, tri(ethylene glycol), 200 °C, 82%; (d) 35% $HClO_4$, THF, 99%.

lective ketalization to provide compound **13**.[11] Conjugate reduction of **13** was carried out using well-established

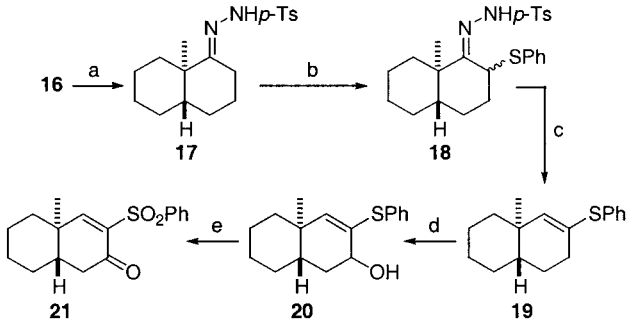
(3) Komaki, H.; Nemoto, A.; Tanaka, Y.; Takagi, H.; Yazawa, K.; Mikami, Y.; Shigemori, H.; Kobayashi, J.; Ando, A.; Nagata, Y. *J. Antibiotics* **1999**, *52*, 13−19.

(4) Komaki, H.; Tanaka, Y.; Yazawa, K.; Takagi, H.; Ando, A.; Nagata, Y.; Mikami, Y. *J. Antibiotics* **2000**, *53*, 75−77.

(5) (a) Ireland, R. E.; Beslin, P.; Giger, R.; Hengartner, V.; Kirst, H. A.; Maag, H. *J. Org. Chem.* **1977**, *42*, 1267−1275. (b) Corey, E. J.; Virgil, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 6429−6431.

(6) In a related system having a 9,11 olefin, the desired anti AB ring product was obtained in low (20%) yield. No mention was made regarding formation of the corresponding syn product. See: Dauben, W. G.; Ahlgren, G.; Leitereg, T. J.; Schwarzel, W. C.; Yoshioko, M. *J. Am. Chem. Soc.* **1972**, *94*, 8593−8594.

Scheme 4 [a]



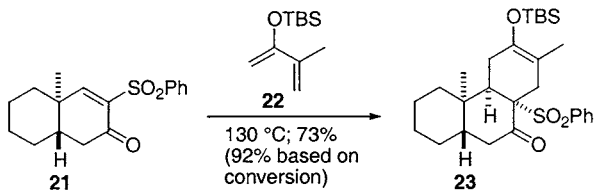
[a] Key: (a) *p*-TsNHNH$_2$, PPTS, THF, 92%; (b) *n*-BuLi, THF, PhSSPh, −78 to −40 °C, 94%; (c) *n*-BuLi, −78 to −20 °C, 42% (74% based on conversion); (d) SeO_2, pyridine, 95:5 EtOH−H_2O, reflux, 78%; (e) *m*-CPBA, CH_2Cl_2, 0 °C to rt; DMP, pyridine, CH_2Cl_2, 0 °C to rt, 91%.

procedures to afford ketone **14**,[12] thus establishing the anti fusion required of the AB ring junction. The ketone function was then reduced using the Huang−Minlon modification of the Wolff−Kischner reaction, thereby generating compound **15**.[12] Deketalization of this product gave **16**.

The stage was set for incorporation of the enabling dienophilic functionality (see Scheme 4). Accordingly, tosylhydrazone **17** was prepared. α-Sulfenylation of this material efficiently provided **18** as an approximately 2:1 mixture of diastereomers. These converged, via a Shapiro olefination reaction, to thioenol ether **19**.[13] Selenium dioxide-mediated allylic oxidation of this compound gave alcohol **20**[14] in good yield. Adjustment of the oxidation level to that required was best carried out by first converting the thioether to a sulfone, followed by oxidation of the resulting crude alcohol to the corresponding ketone, thus providing compound **21**.

Compound **21** served as the dienophile component in a Diels−Alder reaction using, for the purposes of demonstration, the readily accessible diene **22**[15] (Scheme 5). In the

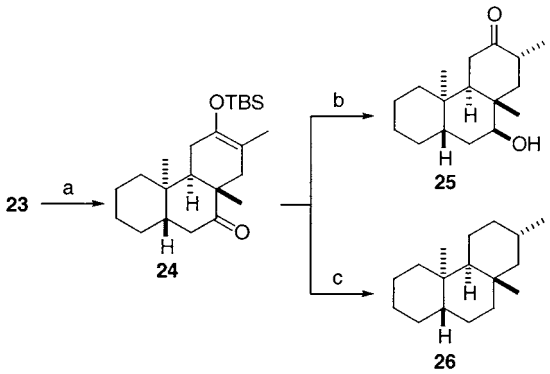
Scheme 5



event, the resulting cycloadduct exhibited spectral characteristics consistent with ketosulfone **23**. The ^{1}H and ^{13}C assignment was conducted using a combination of COSY, HMQC, DEPT, and NOE difference spectroscopy. Especially noteworthy in the NOE measurements was that the angular methyl substituent and the phenyl sulfone *ortho* protons each displayed a strong contact with H-9. Thus, as expected,[8] the stereochemical course of the cycloaddition reaction featured approach of the diene from the β-face of the dienophile. Cycloadducts resulting from other modes of addition were not detected. Hence, the desired relationship between C-9 and C-10 is established during the Diels−Alder reaction with apparent complete stereochemical control.

Ketosulfone **23** was treated with lithium naphthalenide[16] to generate the required enolate, which was methylated through the action of methyl iodide (see Scheme 6).

Scheme 6 [a]



[a] Key: (a) $Li^+(C_{10}H_8)^-$, THF, −78 °C ; MeI, −78 °C to rt, 66%; (b) $LiAlH_4$, Et_2O, −78 to 0 °C; TBAF, THF, 0 °C to rt, 86%; (c) $H_2NNH_2 \cdot H_2O$, KOH, tri(ethylene glycol), 200 °C, 77%.

C-Alkylated material (**24**) was obtained in reasonable yield, along with the corresponding O-alkylated compound (approximately 2.3:1, respectively). At this stage, we were unable to establish unambiguously the critical stereochemistry at C-8, due to the lack of resolution of relevant proton signals at 500 MHz. We were, however, able to deduce this information using a derivative of this compound. Hence, the C-alkylated compound (now known to be **24**) was treated with lithium aluminum hydride, followed by exposure of the product to TBAF, thereby affording keto alcohol **25**.

The key signals in keto alcohol **25** were suitably resolved in its ^{1}H NMR spectrum at 500 MHz. A number of useful

(7) Approaches involving different strategies have also been reported. See: Dauben, W. G.; Kessel, C. R.; Kishi, M.; Somei, M.; Tada, M.; Guillerm, D. *J. Am. Chem. Soc*. **1982**, *104*, 303−305. Wiebel, J.-M.; Heissler, D. *Tetrahedron Lett*. **1994**, *35*, 473−476.

(8) For leading studies on stereoselective Diels−Alder addition to 4a-methyl-*trans*-4a,5,6,7,8,8a-hexahydro-1*H*-naphthalen-2-ones, see: Grieco, P. A.; Garner, P.; He, Z. *Tetrahedron Lett*. **1983**, *24*, 1897−1900. Sicherer-Roetman, A.; Jansen, B. J. M.; de Groot, A. *Tetrahedron Lett*. **1984**, *25*, 2593−2596.

(9) For leading studies on synthesis via vinyl sulfones, see: Meyers, D. J.; Fuchs, P. L. *J. Org. Chem*. **2002**, *67*, 200−204 and other papers in that series.

(10) Available from Aldrich, catalog number M6,515−7.

(11) Ciceri, P.; Demnitz, J. *Tetrahedron Lett*. **1997**, *38*, 389−390.

(12) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem*. **1989**, *54*, 3449−3462.

(13) Cf.: Nakai, T.; Mimura, T. *Tetrahedron Lett*. **1979**, 531−534.

(14) A single diastereomer of undetermined relative configuration at C-7 was obtained.

(15) Ireland, R. E.; Thompson, W. J. *J. Org. Chem*. **1979**, *44*, 3041−3052.

(16) Cf.: Azuma, T.; Yanagida, S.; Sakurai, H.; Sasa, S.; Yoshino, K. *Synth. Commun*. **1982**, *12*, 137−140.

NOEs served to unambiguously establish the orientation of the new angular methyl substituent and, correspondingly, the C-ring stereochemistry (see Figure 3).

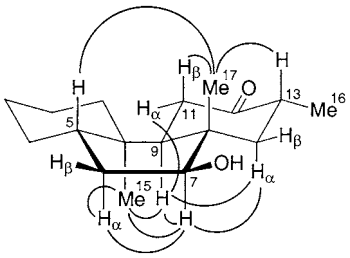


Figure 3. Structure of compound **25** with selected NOEs shown.

In summary, ^{1}H and ^{13}C resonances were assigned from COSY, HMQC, NOSEY, and DEPT data.[17] The configuration at C-7 was clearly revealed by NOE interactions involving H-6α, H-7, H-9, and H_3-15. The orientations of the new angular methyl substituent and the C-ring were established on the basis of NOE interactions involving H-5, H-11$_\beta$, H-13, and H_3-17 and those between H-7, H-9, H-11$_\alpha$, and H-14$_\alpha$. The most significant of these were the strong NOEs detected between H-5 and H_3-17 and between H-9 and H-14$_\alpha$. Thus, angular methylation had indeed occurred in a fashion anti to the face bearing the C-10 methyl substituent, thereby leading to the BC anti junction.

Parenthetically, access to the corresponding fully deoxygenated carbon skeleton was readily accomplished using the Huang−Minlon reduction of **24**, thereby providing hydrocarbon **26** in good yield (see Scheme 6).[18] We note that the carbonyl and silyl enol ether functions at C-7 and C-12, respectively, of **24** could well serve to provide exploitable reactivity.

In conclusion, we have established a novel and effective approach to the 8,10-dimethyl *anti-syn-anti*-perhydrophenanthrene carbon skeleton beginning from the Wieland−Miescher ketone. The synthetic route devised is efficient and proceeds in a highly stereocontrolled fashion. *Significantly, formation of each of the three new ring junction-stereogenic centers is dominated by the C-10 angular methyl substituent.* The route should be readily amenable to the incorporation of additional functionality. Investigations in this vein are organized about two central goals, namely, a total synthesis and biological evaluation of brasilicardin A.

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Supporting Information Available: Experimental procedures and characterization data for compounds **16**−**21** and **23**−**26**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) H-1, H-2, H-3, and H-4 protons could not be unambiguously assigned at 500 MHz due to signal overlap.

(18) A single diastereomer was obtained from this process. The relative configuration at C-13 is assumed to be as indicated, but this could not be confirmed by ^{1}H NMR at 500 MHz due to signal overlap.