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The Catalytic Enantioselective, Protecting Group-Free Total Synthesis of (+)-Dichroanone

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(−)-Dichroanone (**1**) is a 4*a*-methyltetrahydrofluorene norditerpenoid isolated from the flowering plant *Salvia dichroantha* STAPF, found in Turkey.[1] It belongs to a recently discovered yet growing class of natural products that bear a [6-5-6] tricyclic core, including dichroanal B (**2**),[1] taiwaniaquinol B (**3**),[2] standishinal (**4**),[3] among others (Figure 1).[1,2,4,5] The biological activities of these compounds are under investigation, and standishinal, which has been shown to inhibit aromatase,[6] could be used to develop agents targeting estrogen-dependent carcinomas.[5] Although the racemic total syntheses of dichroanone (**1**),[7] dichroanal B (**2**),[7,8] and taiwaniaquinol B (**3**)[9] have recently been completed, there have been no enantioselective syntheses of any member of this family. Our interest in dichroanone (**1**) was piqued upon inspection of its interesting structure, which includes a fully substituted quinone, the characteristic [6-5-6] tricyclic core, and a benzylic all-carbon quaternary stereocenter. Herein we report a concise, catalytic enantioselective synthesis of (+)-dichroanone that does not employ protecting groups and unambiguously confirms the absolute configuration of the molecule.

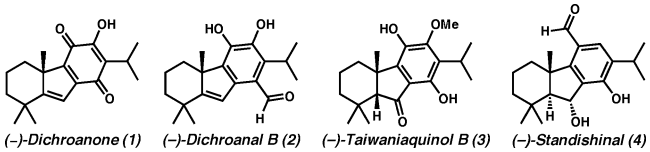
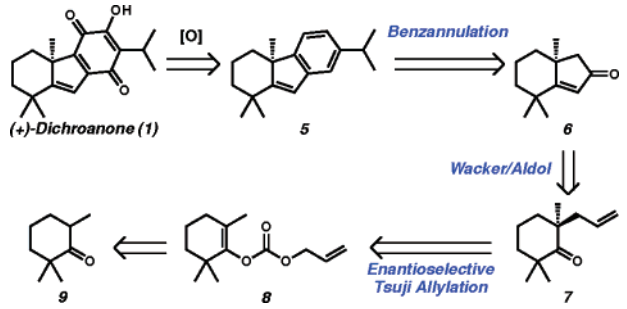


Figure 1. Dichroanone and related natural products (**1**−**4**).

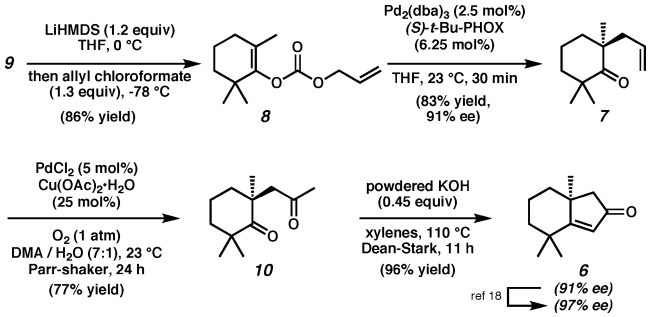
Our laboratory recently developed a powerful method for the enantioselective construction of quaternary centers by palladium-catalyzed allylation,[10] and we believed that this protocol could be employed to stereoselectively install the quaternary center of dichroanone (**1**). Specifically, our allylation method delivers cyclohexanones with stereogenicity α to the ketone. Prior to our work in this area, many of these simple cyclohexanone building blocks bearing all-carbon α-quaternary stereocenters centers were not readily available in an enantioselective fashion or had never been reported as single enantiomer substances.[10,11] In addition to employing our catalytic asymmetric allylation reaction, we planned to install the three oxygen atoms of dichroanone at a late synthetic stage, eliminating the need to protect any phenols or quinones during the synthesis (Scheme 1). Thus, dichroanone (**1**) could arise from arene **5**, which could be prepared via benzannulation of bicyclic enone **6**. Enone **6** could be prepared from allyl ketone **7** by sequential Wacker oxidation and aldol condensation.[10a] Either enantiomer of **7** is readily available from enol-carbonate **8** by application of our enantioselective Tsuji allylation.[10] Finally, **8** is available from commercial 2,2,6-trimethylcyclohexanone (**9**).

We began our synthesis of (+)-dichroanone (**1**) by enolization of **9** and trapping with allyl chloroformate, affording the enol carbonate **8** in high yield with minimal *C*-acylation (Scheme 2).[12,13] In the critical asymmetric Tsuji allylation, carbonate **8** was treated with catalytic $Pd_2(dba)_3$ (2.5 mol %) and (*S*)-*t*-Bu-PHOX (6.25 mol %) in THF to produce quaternary allyl ketone **7** in 83% yield and 91% ee.[14] Wacker oxidation[15] of keto-olefin **7** was performed in a Parr apparatus to afford complete conversion to diketone **10** in 77% yield.[16] Condensation of **10** using KOH in xylenes with azeotropic water removal provided bicyclic enone **6** in excellent yield.[17,18]

Scheme 1



Scheme 2



Elaboration of enone **6** to more advanced intermediates was challenging because of the propensity for most carbon electrophiles to react at oxygen preferentially to C(5a) (Scheme 3). Fortunately, Michael addition of the lithium enolate of **6** to methyl vinyl ketone (MVK) at low temperature formed the desired C−C bond of ketoenone **11** in good yield with high diastereoselectivity.[19] Given the success of this method, we pursued a Robinson annulation strategy to form the final ring of dichroanone. Aldol condensation furnished tricyclic enone **12** in 80% yield, albeit with partial epimerization of the C(5a) stereocenter. This stereochemical loss was of little consequence, as C(5a) is ultimately part of the quinone ring of **1**. Because attempts to oxidatively aromatize this newly formed ring to a phenol were hampered by poor yields, we took the opportunity to install the isopropyl group of the natural product, albeit as an isopropenyl moiety, with the hope that the higher oxidation level could be transposed into the ring. Hence, the kinetic enolate of tricyclic enone **12** was trapped with *N*-phenyltriflimide to give enol-triflate **13**, which was immediately subjected to Kumada coupling conditions with isopropenylmagnesium bromide. Interestingly, this coupling led to a mixture of isomeric products, which converted irreversibly to compound **5** upon exposure to acid. Gratifyingly,

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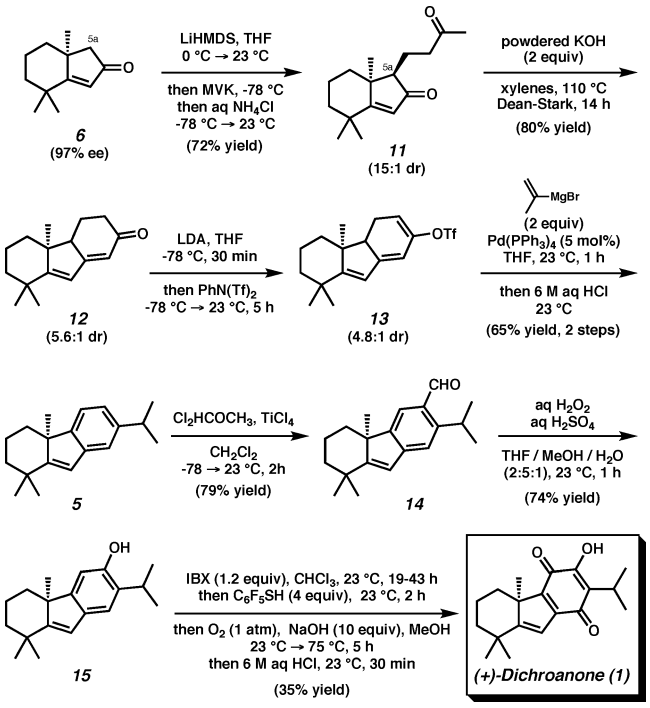
Scheme 3

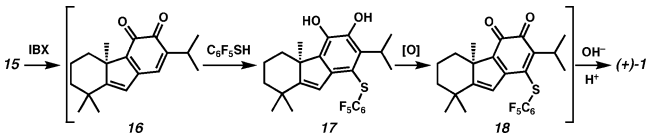


when the crude reaction mixture was treated with aqueous HCl, the major product isolated was aromatic hydrocarbon **5** in 65% overall yield from enone **12**.

Despite having completed the synthesis of the carbon skeleton of dichroanone, the oxidation of arene **5** to hydroxy-*p*-benzoquinone **1** was a significant hurdle. Toward this end, exposure of arene **5** to $TiCl_4$-mediated formylation conditions gave a 10:1 mixture of two separable benzaldehydes. The structure of the major aldehyde (i.e., **14**) was confirmed by nOe experiments and the absence of hyperfine coupling between the two remaining aryl protons. Baeyer−Villiger oxidation furnished phenol **15** in 74% yield. After extensive experimentation, the final oxidation sequence was carried out by treatment of phenol **15** with IBX,[20] followed by exposure to pentafluorothiophenol, then $NaOH/O_2$/MeOH, and finally 6 M HCl. To our delight, this protocol furnished (+)-dichroanone (**1**) in 35% yield. Synthetic (+)-dichroanone (**1**) proved spectroscopically identical to *nat*-(−)-dichroanone with the exception of the sign of rotation,[1] confirming the absolute configuration of *nat*-(*S*)-(−)-dichroanone.

Our analysis for the conversion of phenol **15** to (+)-dichroanone via the final sequence is as follows in Scheme 4. Oxidation of phenol **15** with IBX produces unstable *o*-quinone **16**, which was shown by ^{1}H NMR analysis to be formed in 36% yield. Despite extensive efforts to develop other oxidations, these conditions were superior to any others tested and were the most direct for the installation of the second oxygen atom. The crude *o*-quinone **16** was immediately treated with C_6F_5SH, which presumably undergoes 1,4-addition into the unsubstituted position, giving after tautomerization a highly reactive catechol (**17**). Attempts to isolate this catechol led to complex mixtures, including a second highly unstable *o*-quinone (**18**). We found that complete oxidation of catechol **17** to *o*-quinone **18** was cleanly promoted by molecular oxygen in the presence of base. Although isolation of *o*-quinone **18** was problematic, we reasoned that it could be hydrolyzed to dichroanone (**1**) in situ. Thus, base-mediated saponification of the activated vinylogous thioester **18**, followed by tautomerization, completed the reaction. Dichroanone (**1**) is produced as the sole isolable product through this novel sequence.

Scheme 4



(+)-Dichroanone (**1**) was prepared in 4.0% overall yield over 11 steps without the use of protecting groups. The synthesis is highlighted by the first use of our enantioselective Tsuji allylation in the context of a natural product, a novel Kumada aromatization of an enone, and a new method for generating a hydroxy-*p*-benzoquinone from a phenol in a single reaction sequence. Efforts directed toward the synthesis of other members of this interesting family of natural products are underway.

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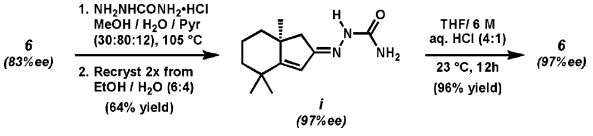
Supporting Information Available: Experimental details and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kawazoe, K.; Yamamoto, M.; Takaishi, Y.; Honda, G.; Fujita, T.; Sezik, E.; Yesilada, E. *Phytochemistry* **1999**, *50*, 493−497.
(2) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1995**, *40*, 871−873.
(3) Ohtsu, H.; Iwamoto, M,; Ohishi, H.; Matsunaga, S.; Tanaka, R. *Tetrahedron Lett.* **1999**, *40*, 6419−6422.
(4) (a) Lin, W.-H.; Fang, J.-M.; Cheng, Y.-S. *Phytochemistry* **1996**, *42*, 1657−1663. (b) Chang, C.-I.; Chien, S.-C.; Lee, S.-M.; Kuo, Y.-H. *Chem. Pharm. Bull.* **2003**, *51*, 1420−1422.
(5) Chang, C.-I.; Chang, J.-Y.; Kuo, C.-C.; Pan, W.-Y.; Kuo, W.-Y. *Planta Med.* **2005**, *71*, 72−76.
(6) (a) Iwamoto, M.; Ohtsu, H.; Tokuda, H.; Nishino, H.; Matsunaga, S.; Tanaka, R. *Bioorg. Med. Chem.* **2001**, *9*, 1911−1921. (b) Minami, T.; Iwamoto, M.; Ohtsu, H.; Ohishi, H.; Tanaka, R.; Yoshitake, A. *Planta Med.* **2002**, *68*, 742−745.
(7) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *Org. Lett.* **2003**, *5*, 3931−3933.
(8) Planas, L.; Mogi, M.; Takita, H.; Kajimoto, T.; Node, M. *J. Org. Chem.* **2006**, *71*, 2896−2898.
(9) (a) Fillion, E.; Fishlock, D. *J. Am. Chem. Soc.* **2005**, *127*, 13144−13145. (b) Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A. Kr. *J. Org. Chem.* **2006**, *71*, 2787−2796.
(10) (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044−15045. (b) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924−6927.
(11) Recently Trost has reported a related study, see: (a) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846−2847. (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180−17181.
(12) A minimal amount (3−5%) of *C*-acylation is observed. This material can be processed along with **8** in the asymmetric allylation without event.[10b]
(13) Aboulhoda, S. J.; Hénin, F.; Muzart, J.; Thorey, C. *Tetrahedron Lett.* **1995**, *36*, 4795−4796.
(14) We arbitrarily chose to pursue the (*S*)-enantiomer of **7** by using (*S*)-*t*-Bu PHOX as the ligand. In practice (*R*)-*t*-Bu PHOX is reasonably expensive.
(15) Smith, A. B., III; Cho, Y. S.; Friestad, G. K. *Tetrahedron Lett.* **1998**, *39*, 8765−8768.
(16) Without the use of a Parr apparatus, little or no oxidation was observed, presumably due to problems with molecular oxygen uptake by the solvent.
(17) Thomas, A. F.; Ozainne, M.; Guntz-Dubini, R. *Can. J. Chem.* **1980**, *58*, 1810−1820.
(18) The ee of enone **6** could be upgraded to 97% ee by preparation, recrystallization, and hydrolysis of its semicarbazone derivative **i**. For the experiment shown, a collection of multiple batches of **6** was used that had a composite ee of 83%. See Supporting Information for further details.



(19) The relative stereochemistry was confirmed by X-ray crystallography. See Supporting Information for details.
(20) Magdziak, D.; Rodriguez, A. A.; Van De Water, R. W.; Pettus, T. R. R. *Org. Lett.* **2002**, *4*, 285−288.

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