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Asymmetric Synthesis of (+)- and (−)-Pauciflorol F: Confirmation of Absolute Stereochemistry

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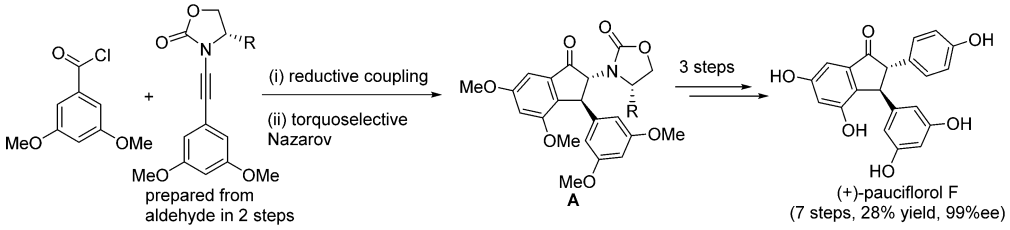
ABSTRACT



An efficient, formal enantioselective synthesis of (+)- and (−)-pauciflorol F has been achieved using a recently introduced oxazolidinone controlled torquoselective Nazarov reaction. The absolute stereochemistry of pauciflorol F and its biosynthetic precursors has been unambiguously confirmed using X-ray crystallography.

Resveratrol **1** is an important building block in nature that is used in the biosynthesis of a diverse array of bioactive polyphenols.[1] Key sources of these natural products are the plant families Vitaceae, Dipterocarpaceae, Gnetaceae, Cyperaceae, and Leguminosae. To date, several hundred such polyphenolic natural products have been isolated and characterized. Many of these exhibit valuable biological activity, such as antioxidant, antibiotic, anticancer, anti-inflammatory, anti-HIV, and antifungal activity.[2] Biosynthetically, the loss of an electron or addition of a proton reveals in **1** the complementary functionalities of a latent electrophilic quinone methide and nucleophilic 3,5-dihydroxyphenyl group **1a** (Scheme 1).[1a] These functionalities play key roles in the oligomerization of **1** and the further modification of these oligomers.[3] Oxidative dimerization of **1** to ε-viniferin (**2**)[3a] and quadrangularin A (**7**)[3f] are key first steps in this scaffold-divergent synthesis.[1a] As part of this biosynthetic divergence, **2** is converted into a regioisomer of **7**, ampelopsin D (**3**).[3b] There are a number of cyclization, redox, and oligomerization pathways available to **1**, **2**, **3**, and **7**, which, in combination with glycosylation, form the basis of much of the structural diversity seen in these natural products.[1] For example, protic activation of the alkene in regioisomers **3** and **7** results in cyclization onto the

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(1) For reviews on resveratrol and associated oligomers, see: (a) Snyder, S. A.; ElSohly, A. M.; Kontes, F. *Nat. Prod. Rep.* **2011**, *28*, 897–924. (b) Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 586–621. (c) Snyder, S. A. In *Biomimetic Organic Synthesis*; Poupon, E., Nay, B., Eds.; Wiley-VCH: Weinheim, 2011; pp 695−721. (d) Ito, T.; Tanaka, T.; Iinuma, M.; Iliya, I.; Nakaya, K.; Ali, Z.; Takahashi, Y.; Sawa, R.; Shirataki, Y.; Murata, J.; Darnaedi, D. *Tetrahedron* **2003**, *59*, 5347–5363.

(2) For reviews on the biological properties of resveratrol oligomers, see: (c) Pervaiz, S.; Holme, A. L.; Aggarwal, B. B.; Anekonda, T. S.; Baur, J. A.; Gojkovic-Bukarica, L.; Della Ragione, F.; Kim, A. L.; Pirola, L.; Saiko, P. *Antioxid. Redox Signal.* **2009**, *11*, 2851–2897. (d) Marques, F. Z.; Markus, M. A.; Morris, B. J. *Int. J. Biochem. Cell Biol.* **2009**, *41*, 2125–2128. See also: Wood, J. G.; Rogina, B.; Lavu, S.; Howitz, K.; Helfand, S. L.; Tatar, M.; Sinclair, D. *Nature* **2004**, *430*, 686–689 and references therein.

(3) For original papers describing the isolation of the resveratrol dimers depicted in Scheme 1, see: (a) **2**: Kurihara, K.; Kawabata, J.; Ichikawa, S.; Mizutani, J. *Agric. Biol. Chem.* **1990**, *54*, 1097–1099. (b) **3**: Oshima, Y.; Ueno, Y. *Phytochemistry* **1993**, *33*, 179–182. (c) **4**: Ito, T.; Tanaka, T.; Linuma, M.; Nakaya, K.; Takahashi, Y.; Sawa, R.; Murata, J.; Darnaedi, D. *J. Nat. Prod.* **2004**, *67*, 932–937. (d) **5** and **9** Luo, H.-F.; Zhang, L.-P.; Hu, C.-Q. *Tetrahedron* **2001**, *57*, 4849–4854. (e) **6**: Oshima, Y.; Ueno, Y. *Tetraherdron* **1993**, *49*, 5801–5804. (f) **7**: Adesanya, S. A.; Nia, R.; Martin, M.-T.; Boukamcha, N.; Montagnac, A.; Pais, M. *J. Nat. Prod.* **1999**, *62*, 1694–1695. (g) **8**: Khan, M. A.; Nabi, S. G.; Prakash, S.; Zaman, A. *Phytochemistry* **1986**, *25*, 1945–1948.

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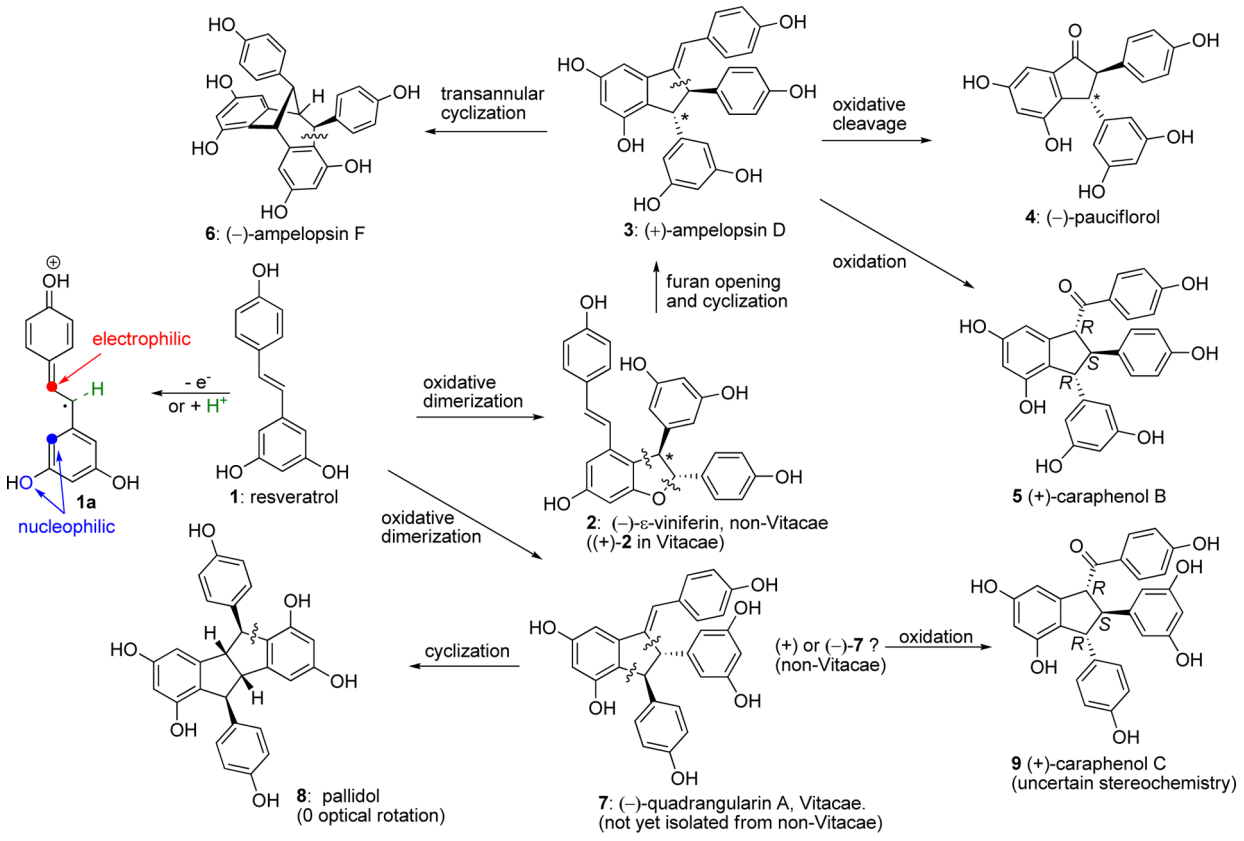
Scheme 1. Some Resveratrol Derived Natural Products[3]



pendant 3,5-dihydroxyphenyl unit: **3** → ampleopsin F (**6**)[3e] and **7** → pallidol (**8**).[3g] On the other hand, oxidation of this alkene in **3** and **7** gives caraphenols B (**5**) and C (**9**),[3d,4] respectively, and oxidative cleavage of the alkene in **3** gives pauciflorol F (**4**).[3c]

The absolute stereochemistry of (−)-**2** was assigned nearly 25 years ago based on its comparable circular dichroism (CD) spectra to other simpler 2-aryl-2,3-dihydrobenzofurans (not shown).[2,5] This assignment has been extended to the many biosynthetic products derived from **2**.[6] It has also been extended to **7** and related biosynthetic products by comparing the CD spectra of (−)-**3** and (−)-**7** (both from Vitacae), which are almost identical.[6b] Interestingly, while (−)-**2** is present in Dipterocarpaceae, Gnetaceae, Cyperaceae, and Leguminosae, (+)-**2** occurs in Vitacae.[6] This stereochemical switch also extends to the many biosynthetic products derived from **2**. At this stage it is not yet known if **7** also switches its absolute stereochemistry in different plant families, as it has only been isolated from *Cissus quadrangularis* L. (Vitaceae) as the (−)-enantiomer.[3f] Nonetheless, its presence in other plant families can be deduced from the isolation biosynthetic products, such as **8** and (+)-**9** from *Caragana sinica* (Leguminosae).[3d,g,7] While **8** has been isolated from both Vitaceae and Leguminosae, it cannot be used to inform on changes in absolute stereochemistry of **7**, as it has no optical rotation and **9** has only been isolated from Leguminosae. Since *Caragana sinica* also yielded (−)-**6** we can deduce that (+)-**3** is present in this plant (as expected for Leguminosae) and that (+)-**5** has the depicted *RSR*-stereochemistry (not previously assigned). Since **9** has a very similar structure to **5** (differing only in the location of OH groups), it is probable that (+)-**9** has the same *RSR*-stereochemistry as (+)-**5**. On this basis we could conclude that (+)-**7** is present in Leguminosae and that, like **2**, **7** also switches stereochemistry in Vitacae relative to other plant families. However, notwithstanding their structural similarity, some uncertainty exists in assigning the same stereochemistry to **5** and **9** based on the same optical rotation. Moreover, the current basis for the assignment of absolute stereochemistry of all resveratrol dimers, comparison of the CD spectra of **2** to other simpler 2-aryl-2,3-dihydrobenzofurans,

(4) For a structural revision of the relative stereochemistry of the caraphenols B and C, see: Snyder, S. A.; Brill, Z. G. *Org. Lett.* **2011**, *13*, 5524–5527.

(5) (a) Lins, A. P.; Yoshida, M.; Gottlieb, O. R.; Gottlieb, H. E.; Kubitzki, K. *Bull. Soc. Chim. Belg.* **1986**, *95*, 737–748. (b) Lima, O. A.; Gottlieb, O. R.; Magalhaes, M. T. *Phytochemistry* **1972**, *11*, 2031–2037.

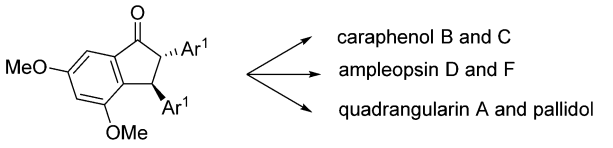
(6) (a) Takaya, Y.; Yan, K.-X.; Terashima, K.; Ito, J.; Niwa, M. *Tetrahedron* **2002**, *58*, 7259–7265. (b) He, S.; Wu, B.; Pan, Y.; Jiang, L. *J. Org. Chem.* **2008**, *73*, 5233–5241. (c) Ito, T.; Abe, N.; Oyama, M.; Iinuma, M. *Tetrahedron Lett.* **2009**, *50*, 2516–2520.

(7) Choi, C. W.; Choi, Y. H.; Cha, M.-R.; Yoo, D. S.; Kim, Y. S.; Yon, G. h.; Choi, S. U.; Kim, Y. H.; Ryu, S. Y. *Bull. Korean Chem. Soc.* **2010**, *31*, 3448–3450.

(8) (a) Polavarapu, P. *Chirality* **2012**, *24*, 909–920. (b) Sandstrom, J. *Chirality* **2000**, *12*, 162–171.

also has its limitations.[5,8] Confirmation of the absolute stereochemistry of these natural products can come from total synthesis, so long as the absolute stereochemistry of relevant substrates and/or synthetic intermediates can be unambiguously assigned using chiral pool substrates and/or X-ray crystallography. Such syntheses can also facilitate investigations into the bioactivity of specific antipodes. To this end, diarylindanones **10a** and **10b** are valuable synthetic targets for asymmetric synthesis. Snyder and others have synthesized racemic versions of these and converted them into **3**–**5**, **7**, **8**, **10**, and **11** (Scheme 2).[4,9] Recently, Heo and co-workers reported an elegant enantioselective synthesis of (+)-**10a** and (+)-**4**.[10,11] A key step in this synthesis was the baker's yeast reduction of indenone **11** to (*R*)-(+)-**12** (Scheme 3). This

Scheme 2. Use of Indanones in Resveratrol Dimer Synthesis[4,9]



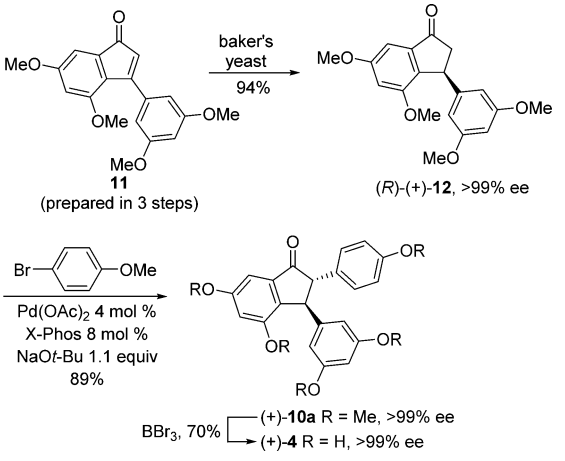
10a Ar^1 = 4-methoxyphenyl, Ar^2 = 3,5-dimethoxyphenyl
10b Ar^1 = 3,5-dimethoxyphenyl, Ar^2 = 4-methoxyphenyl

was followed by α-arylation to give (+)-**10a** and demethylation to (+)-**4**. While elegant, two limitations attend this approach to (+)-**4**: the inability to unequivocally verify the absolute stereochemistry of the product and the inability to prepare the correct enantiomer, since there is no reliable alternative to baker's yeast for this purpose. Herein, we describe the use of Evans' oxazolidinones as chiral auxiliaries in the asymmetric synthesis of both antipodes of **10a** and **4**. This approach provides rigorous assignment of the absolute stereochemistry of pauciflorol F through X-ray crystal structure analysis and formal, enantiodivergent, entry into a range of other related resveratrol dimers.

Our enantioselective approach to **4** utilizes our recently introduced oxazolidinone controlled Nazarov cyclization process.[12,13] This synthesis commences with the conversion of the aldehyde **13** into ynamides **15a**–**c** in two steps (Scheme 4). Initial conversion of **13** into the *gem*-dibromostyrene **14** (95%)[14] was followed by a one-pot HBr elimination and coupling (bromoalkyne and oxazolidinone) to give ynamides **15a**–**c** in good yield (78–91%).[15,16] We elected to use three different, readily available oxazolidinone auxiliaries, Aux^{1-3}, to evaluate which performs better and to enable the in-parallel generation of opposite enantiomers of our target product **4** (note: the antipodes of all three auxiliaries Aux^{1-3} are readily available). Reductive coupling of the ynamides **15a**–**c** with acid chloride **16** gave the arylvinyl ketones **17a** (68%), **17b** (73%), and **17c** (49%). The yield of this reaction was in part limited by the regioselectivity of hydrostannylation (Bu_3Sn group α or β to the oxazolidinone), which varied somewhat for the three auxiliaries used: the α:β ratio for Aux^1 (2.7:1); Aux^2 (4.6:1); Aux^3 (3.5:1).[17] The yield of **17c** (49%) was further compromised by the difficulty in separating the regioisomers of the coupled product upon chromatography.

Nazarov cyclization of **17a**–**c** under our standard conditions (10 equiv of $MeSO_3H$, CH_2Cl_2, 18 °C) gave the *trans*-indanones **18a**–**c** in good yields (79–94%). The stereochemical induction was highest in the case of Aux^1 and Aux^3, which both gave diastereomeric ratios (dr) of >40:1 and lower for Aux^2 (dr = 20:1), favoring the

Scheme 3. Heo Approach to **4**[10]



depicted diastereomers.[18] The isolated yield for **18a** (79%) and **18b** (87%) is for the major diastereomer, after chromatographic separation of the diastereomic mixture. The isolated yield for **18c** (94%) is for the diastereomeric

(9) (a) Snyder, S. A.; Zografos, A. L.; Lin, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 8186–8191. (b) Snyder, S. A.; Breazzano, A. G.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753–1765. (c) Zhong, C.; Zhu, J.; Chang, J.; Sun, X. *Tetrahedron Lett.* **2011**, *52*, 2815–2817.

(10) Lee, B. H.; Choi, Y. L.; Shin, S.; Heo, J.-Y. *J. Org. Chem.* **2011**, *76*, 6611–6618.

(11) For a racemic synthesis of **4** involving Nazarov cyclization, see: (a) Yang, Y.; Philips, D.; Pan, S. *J. Org. Chem.* **2011**, *76*, 1902–1905. For other racemic syntheses of **4**, see ref 9a and: (b) Jeffrey, J. L.; Sarpong, R. *Org. Lett.* **2009**, *11*, 5450–5453. (c) Bo, C.; Lu, J.-P.; Xie, X.-G.; She, X.-G.; Pan, X.-F. *Chin. J. Org. Chem.* **2006**, *26*, 1300–1302.

(12) (a) Kerr, D. J.; Miletic, M.; Chaplin, J. H.; White, J. M.; Flynn, B. L. *Org. Lett.* **2012**, *14*, 1732–1735. (b) Flynn, B. L.; Manchala, N.; Krenske, E. H. *J. Am. Chem. Soc.* **2013**, *135*, 9156–9163. (c) Kerr, D. J.; Flynn, B. L. *J. Org. Chem.* **2010**, *75*, 7073–7084.

(13) For reviews on enantioselective Nazarov cyclizations, see: (a) Vaidya, T.; Eisenberg, R.; Frontier, A. J. *ChemCatChem* **2011**, *3*, 1531–1548. (b) Shimada, N.; Stewart, C.; Tius, M. A. *Tetrahedron* **2011**, *67*, 5851–5870.

(14) Xia, Y.; Jin, Y.; Kaur, N.; Choi, Y.; Lee, K. *Eur. J. Med. Chem.* **2011**, *46*, 2386–2396.

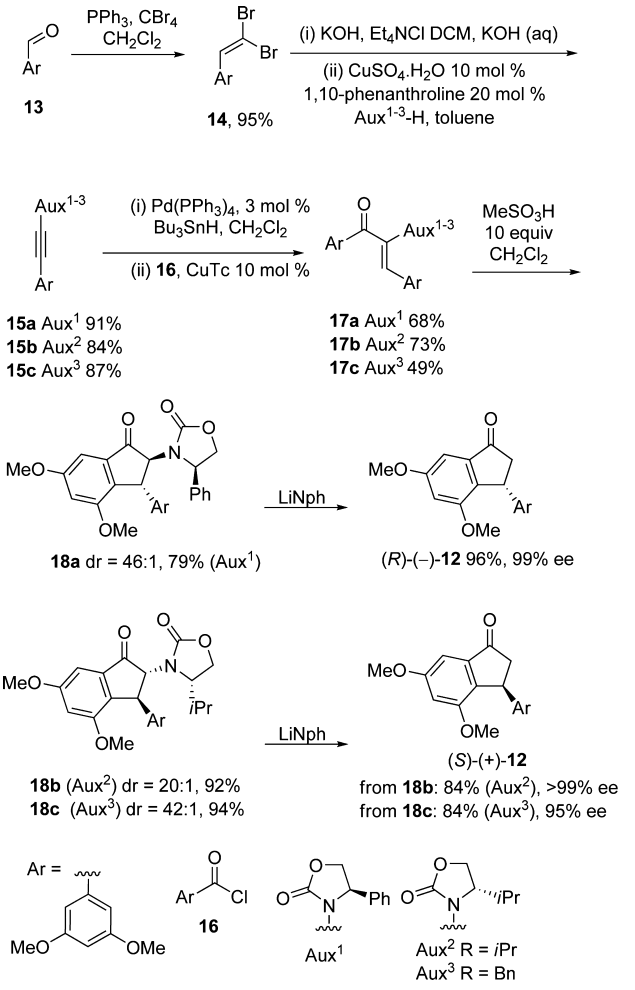
(15) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170–4177.

(16) For an alternative method of converting *gem*-dibromoalkenes to ynamides, see: Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381–4385.

(17) See Supporting Information.

(18) The diastereomeric ratios were determined by cleaving the auxiliary from a crude diastereomeric mixture, followed by chiral HPLC of the resultant enantiomeric mixture of **12**; see Supporting Information.

Scheme 4. Synthesis of (+)- and (−)-**12**



mixture obtained directly from the Nazarov reaction (base wash, no chromatography). Reductive cleavage of the auxiliaries (Aux$^{1-3}$) from **18a**−**c** using lithium naphthalenide (LiNph) produced indanones (*R*)-(−)-**12** and (*S*)-(+)-**12** in good yield (84−92%). While the enantiomeric purity of (*S*)-(+)-**12** obtained from **18c** was 95% ee (reflecting the dr of 42:1), higher enantiomeric purity (≥99% ee) was obtained for (*R*)-(−)-**12** and (*S*)-(+)-**12**, obtained from **18a** and **18b**, which had undergone prior chromatographic purification of the major diastereomers.

The stereochemical assignment of diastereomers **18a**−**c** was based on the X-ray crystal structure analysis of **18a** (Figure 1). Accordingly, we assigned (+)-**12** the *S*-stereochemistry. This conflicts with Heo and co-workers who assigned (+)-**12** the *R*-stereochemistry based on analogous baker's yeast reductions of indanones performed by Clark et al.[19] To help clarify the source of this discrepancy we subjected our sample of (−)-**12** ($[\alpha]_D$ = −5.1) to the steps of α-arylation and demethylation described in Scheme 2 and noted that it gave (+)-**10a** ($[\alpha]_D$ = +136) and (+)-**4** ($[\alpha]_D$ = +77),[17] whereas Heo had reported their sample of (+)-**12** ($[\alpha]_D$ = +8.9) gave (+)-**10a** ($[\alpha]_D$ = +137) and (+)-**4** ($[\alpha]_D$ = +86).[10,20] Thus, the most likely explanation for this discrepancy is that a mistake had been made in noting the optical rotation of **12** obtained from the baker's yeast reduction of **11** and that it had been incorrectly assigned the dextrorotary (+)-stereochemistry (no explanation is given for the variation in magnitude of rotation between equivalent compounds of similar ee).

In conclusion, the oxazolidinone controlled Nazarov reaction has been applied to a formal synthesis of both antipodes of **4** (Aux^2: 7 steps, 28%, 99% ee). This is comparable in overall efficiency to the recent synthesis of the unnatural enantiomer, (+)-**4**, by Heo and co-workers (6 steps, 33%, 99% ee).[10] Of the three oxazolidinones used in this study, Aux^1 and Aux^2 appear the most useful, with Aux^3 being less efficient in the reductive coupling step. This synthesis has confirmed the absolute stereochemistry of (−)-**4** and is consistent with earlier CD studies on **2** and on it being the biosynthetic source of **4**. This methodology has the potential to provide enantiodivergent access to many resveratrol oligomers, based on earlier described approaches using racemic **10a** and **10b** (Scheme 1).[4,9]

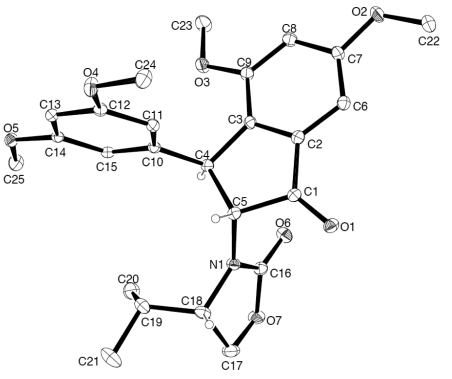


Figure 1. ORTEP of **18a** (arbitrary numbering).

Supporting Information Available. X-ray crystal structure data for **18a**, preparative procedures and spectroscopic data for all compounds, and chiral HPLC traces for different samples of (+)- and (−)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

(19) (a) Clark, W. M.; Kassick, A. J.; Plotkin, M. A.; Eldridge, A. M.; Lantos, I. *Org. Lett.* **1999**, *1*, 1839–1842. (b) Clark, W. M.; Tickner-Eldridge, A. M.; Huang, G. K.; Pridgen, L. N.; Olsen, M. A.; Mills, R. J.; Lantos, I.; Baine, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 4550–4551.

(20) All optical rotations were performed in MeOH (*c* = 0.4 or 0.5) at 20 °C.

The authors declare no competing financial interest.