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Total Synthesis of (−)-Anisatin

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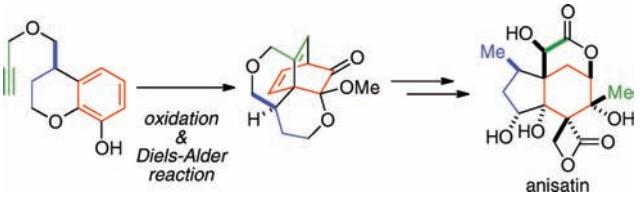
ABSTRACT



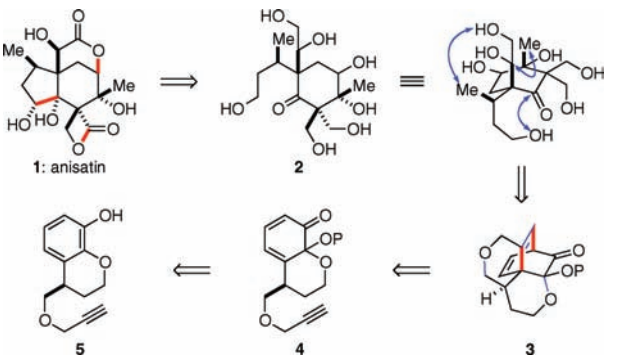
A novel synthetic route to (−)-anisatin has been developed. Our synthesis features a rhodium-catalyzed 1,4-addition of an arylboronic acid, an intramolecular Diels−Alder reaction of an *ortho*-quinone monoketal, a stereoselective [2,3]-Wittig rearrangement, and construction of the oxabicyclo [3.3.1] skeleton via cleavage of an epoxide by a primary amide.

Anisatin (**1**) was isolated as one of the toxic components of Japanese star anise (*Illicium anisatum*).[1] Structure elucidation revealed that anisatin is a sesquiterpene characterized by the eight contiguous stereogenic centers, the oxabicyclo [3.3.1] skeleton, and the spiro β-lactone.[2] The highly challenging structure of anisatin and its bioactivity as a strong $GABA_A$ antagonist[3] have attracted much attention in synthetic organic community. Despite numerous synthetic studies reported to date,[4] only one total synthesis has been achieved.[5] Herein, we report a completely stereoselective total synthesis of (−)-anisatin.

Our retrosynthesis is illustrated in Scheme 1. Cleavage of the three rings, including two lactone rings and a cyclopentane ring, would lead to a highly substituted cyclohexane **2**. To achieve stereoselective construction of the cyclohexane ring, three bonding pairs shown by arrows were connected to give a compound with a bicyclo [2.2.2] skeleton. The quaternary stereogenic center, which corresponds to the spiro carbon, would be constructed stereoselectively by utilizing the steric or electronic character of the bicyclic system. The key intermediate **3** could be synthesized by an intramolecular Diels−Alder reaction of **4**,[6] which would in turn be prepared by oxidation of phenol **5**.

Our synthesis commenced with a rhodium-catalyzed 1,4-addition[7] of known arylboronic acid **6**[8] to butenolide **7**,[9]

Scheme 1. Retrosynthesis



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(2) (a) Yamada, K.; Takeda, S.; Nakamura, S.; Hirata, Y. *Tetrahedron Lett.* **1965**, *6*, 4797. (b) Yamada, K.; Takada, S.; Nakamura, S.; Hirata, Y. *Tetrahedron* **1968**, *24*, 199.

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(4) (a) Lindner, D. L.; Doherty, J. B.; Shoham, G.; Woodward, R. B. *Tetrahedron Lett.* **1982**, *23*, 5111. (b) Kato, M.; Kitahara, H.; Yoshikoshi, A. *Chem. Lett.* **1985**, *14*, 1785. (c) Kende, A. S.; Chen, J. *J. Am. Chem. Soc.* **1985**, *107*, 7184. (d) Niwa, H.; Mori, T.; Hasegawa, T.; Yamada, K. *J. Org. Chem.* **1986**, *51*, 1015. (e) Charonnat, J. A.; Nishimura, N.; Travers, B. W.; Waas, J. R. *Synlett* **1996**, 1162. (f) Loh, T.-P.; Hu, Q.-Y. *Org. Lett.* **2001**, *3*, 279. For a recent review, see: (g) Urabe, D.; Inoue, M. *Tetrahedron* **2009**, *65*, 6271.

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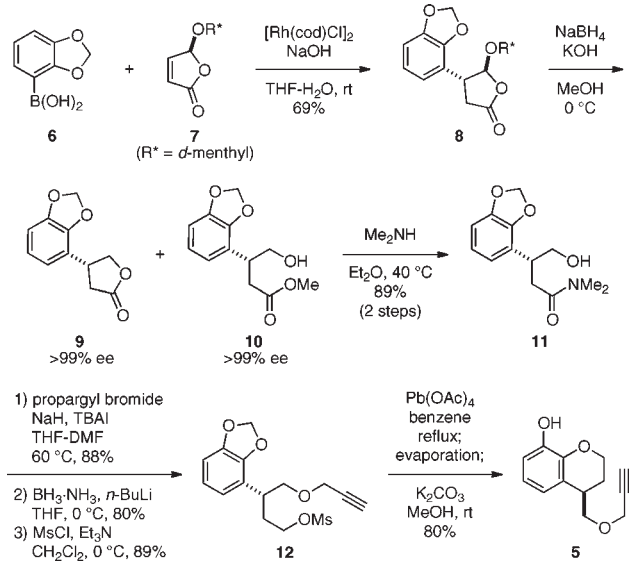
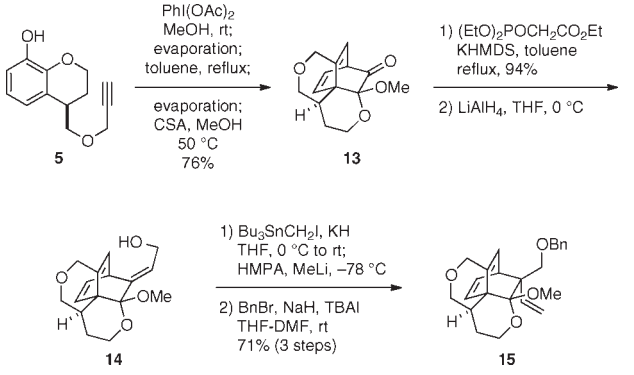
giving the desired adduct **8** with complete diastereoselectivity (Scheme 2). Treatment of **8** with potassium hydroxide and sodium borohydride in methanol provided a mixture of lactone **9** and ester **10** without loss of the enantiomeric purity. The mixture was subjected to aminolysis to provide dimethylamide **11**. Propargylation of the hydroxy group, reductive cleavage of the amide moiety,[10] followed by mesylation of the resulting alcohol, afforded **12**. Subsequent deprotection of the catechol was conducted in a two-step sequence.[11] Oxidation of the methylenedioxy moiety with lead tetraacetate provided an acetoxydioxolan. The ensuing methanolysis under basic conditions liberated the catechol, which underwent an intramolecular S_N2 reaction to give the desired phenol **5** in good yield.

Scheme 2. Synthesis of Phenol **5**



We next focused on the intramolecular Diels–Alder reaction to construct the bicyclo [2.2.2] skeleton (Scheme 3). Phenol **5** was treated with iodobenzene diacetate in methanol to give a 1:1 diastereomeric mixture of *ortho*-quinone monoketals **4** (P = Me). Upon heating in toluene to reflux, both diastereomers underwent a Diels–Alder reaction[6] to furnish tetracyclic adducts as a mixture of the epimers at the ketal moiety. The mixture could easily be converged into a single epimer by treatment with CSA in methanol to give **13**. We next pursued the construction of the other quaternary stereogenic center by utilizing the steric bias of the bicylclo [2.2.2] system. Homologation of the ketone moiety in **13** was effected using a Horner–Wadsworth–Emmons reaction to give an unsaturated ester as a single isomer.[12] This was then reduced with lithium aluminum hydride to provide **14**. After alkylation with iodomethyltributyltin,[13] a facile [2,3]-Wittig rearrangement[14] proceeded diastereoselectively, on treatment with methyllithium in the presence of HMPA, to give a homoallyl alcohol,[15] which was benzylated to furnish **15**.

Scheme 3. Construction of the Quaternary Stereogenic Centers



Having successfully constructed the quaternary stereogenic center, which corresponds to the spiro carbon, we turned our attention to cleaving the bicyclo [2.2.2] skeleton (Scheme 4). When **15** was subjected to careful ozonolysis, the most electron rich and constrained trisubstituted double bond underwent selective cleavage to give, after isomerization of the double bond by treatment with potassium carbonate, ketoaldehyde **16**. Thus, the highly substituted cyclohexane core of anisatin was established.

The ketoaldehyde was reduced to the corresponding diol whose primary alcohol was then protected with a TIPS group. Conversion of **17** to **18** by Chugaev elimination[16] set the stage for construction of the cyclopentene ring. Thus, acidic hydrolysis of the ketal was followed by conversion of the resulting primary alcohol to iodide **19**. Upon treatment with *tert*-butyllithium, Barbier-type cyclization took place to give a cyclopentanol, which was dehydrated with Burgess reagent[17] to afford **20**.

(6) For reviews, see: (a) Liao, C.-C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856. (b) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev.* **2004**, *104*, 1383. (c) Pouysegu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (d) Roche, S. P.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2011**, *50*, 4068.

(7) (a) Sakai, M.; Hayashi, H.; Miyaura, N. *Organometallics* **1997**, *16*, 4229. (b) Navarro, C.; Moreno, A.; Csáky, A. G. *J. Org. Chem.* **2009**, *74*, 466. For reviews of the rhodium-catalyzed 1,4-addition, see: (g) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (h) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(8) Caturla Javaloyes, J. F.; Vidal Gispert, L.; Lumeras Amador, W. WO2008/017461, 2008.

(9) Moradei, O. M.; Paquette, L. A. *Org. Synth.* **2003**, *80*, 66.

(10) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

(11) Ikeya, Y.; Taguchi, H.; Yoshioka, I. *Chem. Pharm. Bull.* **1981**, *29*, 2893.

(12) An X-ray crystallographic study of the α,β-unsaturated ester revealed that the bicyclo[2.2.2]octadiene skeleton was twisted by the ether and the ketal linkages, and the carbonyl group leaned to the opposite side of the methoxy group.

(13) Seitz, D. E.; Carroll, J. J.; Cartaya, M. C. P.; Lee, S.; Zapata, A. *Synth. Commun.* **1983**, *13*, 129.

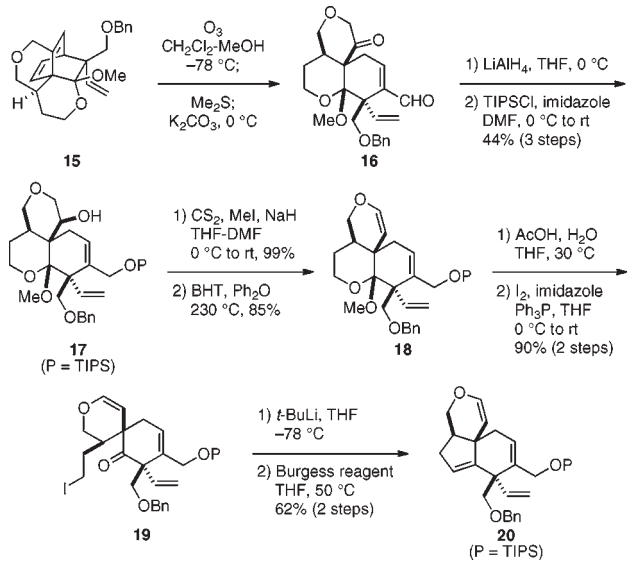
(14) (a) Depuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431. (b) Nace, H. R. *Org. React.* **1962**, *12*, 57.

(15) In addition to the steric bias of the bicyclo [2.2.2] system, the stereoselectivity of the [2,3]-Wittig rearrangement may be effected by coordination of both the methoxy group and the ether linkage to the lithium atom in the lithiated intermediate.

(16) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105.

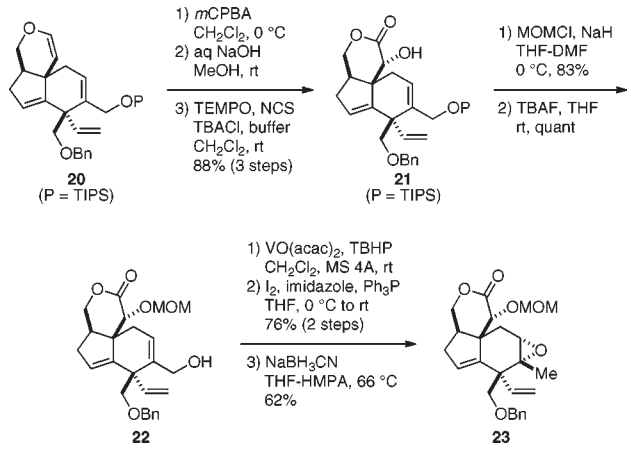
(17) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744.

Scheme 4. Construction of the Carbon Core of Anisatin



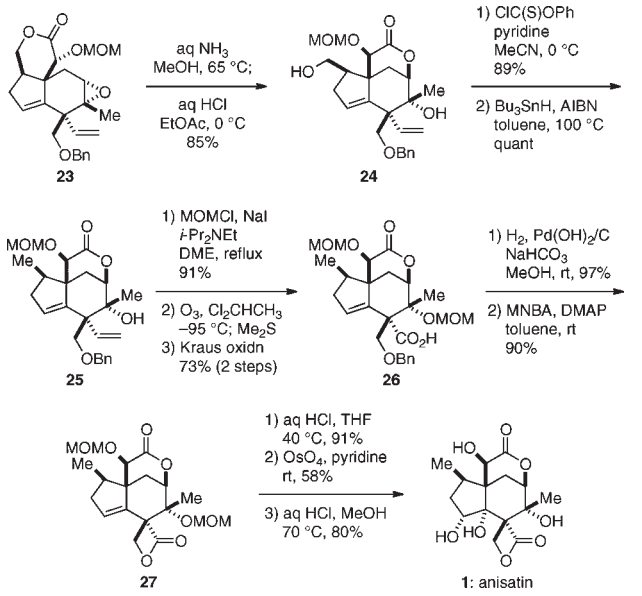
Sequential oxidation of the cyclic enol ether moiety in **20** provided α-hydroxylactone **21** (Scheme 5). After protection of the α-hydroxy group, cleavage of the TIPS ether with TBAF furnished allyl alcohol **22**. Subsequent Sharpless epoxidation[18] proceeded stereoselectively to yield an epoxyalcohol, the primary hydroxy group of which was reductively removed via an iodide to afford **23**.[19]

Scheme 5. Introduction of the Oxygen Functionalities



With the requisite substrate in hand, the crucial construction of the oxabicyclo [3.3.1] skeleton was investigated (Scheme 6). Treatment of **23** with ammonia yielded a primary amide, which upon heating, underwent an intramolecular S_N2 reaction between the carbonyl oxygen and the epoxide to provide a cyclic imidate. Acidic workup induced hydrolysis of the imidate to give the desired lactone **24** in good yield.[20] Radical-mediated deoxygenation of the primary alcohol afforded **25**. Thus, the core oxabicyclo [3.3.1] skeleton was constructed in a completely stereoselective manner.

Scheme 6. Completion of the Synthesis



The remaining tasks that had to be achieved were to construct the *β*-lactone and the *cis*-diol moiety. Prior to oxidative cleavage of the vinyl group, the tertiary alcohol was protected with a methoxymethyl group.[21] Ozonolysis of the resulting MOM ether at low temperature afforded an aldehyde, which was immediately converted to carboxylic acid **26**.[22] Hydrogenolysis of the benzyl group over Pearlman's catalyst proceeded without affecting the trisubstituted double bond. The crucial formation of the *β*-lactone was best carried out with MNBA.[23] After selective deprotection of the tertiary hydroxy group, dihydroxylation of the olefin was performed with OsO_4 and pyridine. Finally, removal of the MOM group under acidic

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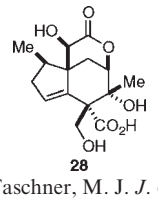
(20) For an example of the cleavage of an epoxide by a primary amide to provide a lactone, see:Wuts, P. G. M.; Ritter, A. R.; Pruitt, L. E. *J. Org. Chem.* **1992**, *57*, 6696.

(21) Protection of the tertiary alcohol was inevitable for the following reasons:(a) Without protection, ozonolysis of the vinyl group gave a complex mixture, presumably due to a retro-aldol reaction of the resulting *β*-hydroxyaldehyde. (b) Formation of the *β*-lactone from **28** occurred preferentially between the carboxylic acid and the tertiary alcohol.



(22) (a) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825. (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(23) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, *31*, 286.

conditions afforded (−)-anisatin, which was identical in every respect with an authentic sample.

In conclusion, we have accomplished a completely stereoselective total synthesis of anisatin, featuring an intramolecular Diels−Alder reaction, a stereoselective [2,3]-Wittig rearrangement, regioselective cleavage of the trisubstituted double bond, and construction of the oxabicyclo [3.3.1] skeleton via cleavage of an epoxide by a primary amide.

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Supporting Information Available. Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, and an X-ray crystallographic information file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.