ORGANIC LETTERS

2010
Vol. 12, No. 4
776−779

Enantioselective Total Synthesis of (+)-Conicol via Cascade Three-Component Organocatalysis

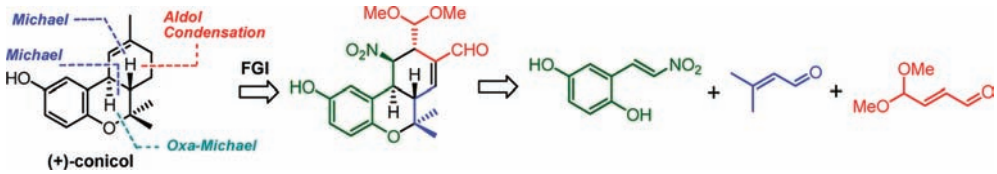
Bor-Cherng Hong,* Prakash Kotame, Chih-Wei Tsai, and Ju-Hsiou Liao

Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi, 621, Taiwan, R.O.C.

chebch@ccu.edu.tw

Received December 9, 2009

ABSTRACT



The first asymmetric total synthesis of (+)-conicol has been achieved via a key step reaction involving the organocatalytic domino oxa-Michael−Michael−Michael−aldol condensation of 2-((*E*)-2-nitrovinyl)benzene-1,4-diol and α,*β*-unsaturated aldehydes. Structures of the three-component domino reaction adducts, 20 and 21, including their absolute configurations, were confirmed unambiguously by X-ray analysis. Through this work, the absolute configuration of (+)-conicol was thereby elucidated.

The hexahydro-6*H*-benzo[*c*]chromene system occurs widely in a variety of natural products exhibiting various biological activities, such as heterophylol,[1] nabilone,[2] murrayamine P, murrayamine O,[3] machaeriol A, machaeriol B,[4] sauchinone A,[5] bisabosqual A,[6] clusiacitran A, clusiacitran B,[7] palodesangrens E,[8] and the cannabinoids[9] (Figure 1). Most of these meroterpenoids were isolated from higher plants, although recently some species were isolated from marine organisms. For example, (+)-conicol was isolated from a marine invertebrate, the ascidian *Aplidium conicum*,[10] and (+)-epiconicol,[11] a marine metabolite, was isolated from *Aplidium aff. densum* and exhibited antiproliferative activity against human acute lymphoblastic leukemia CEM-WT cells as well as antibacterial activity against the Gram-positive bacterium *Micrococcus luteus*. In addition, epiconicol, an isomer of conicol, displays

(1) A naturally occurring phenolic compound, which was isolated from root bark of *Artocarpus heterophyllus*, see: Lin, C.-N.; Lu, C.-M. *Tetrahedron Lett.* **1993**, *34*, 8249.

(2) Nabilone, also known as cesamet, is a synthetic cannabinoid with therapeutic use as an antiemetic and as an adjunct analgesic for neuropathic pain, see: (a) Notcutt, W.; Price, M.; Chapman, G. *Pharmacol. Sci.* **1997**, *3*, 551. (b) Skrabek, R. Q.; Galimova, L.; Ethans, K.; Perry, D. *J. Pain* **2008**, *9*, 164.

(3) Two novel cannabinol skeletal carbazole alkaloids, murrayamine-O and -P, were isolated from the root bark of *Murraya euchrestifolia*. See: Wu, T.-S.; Wang, M.-L.; Wu, P.-L. *Tetrahedron Lett.* **1995**, *36*, 5385.

(4) Machaeriol A and B were isolated from shrubs and the lianas *Machaerium multiflorum*. Both compounds showed in vitro antimalarial activity against a *Plasmodium falciparum* W-2 clone. Other derivatives showed antimicrobial and antiparasitic activities, see: (a) Muhammad, I.; Li, X.-C.; Dunbar, D. C.; ElSohly, M. A.; Khan, I. A. *J. Nat. Prod.* **2001**, *64*, 1322. (b) Muhammad, I.; Li, X.-C.; Jacob, M. R.; Tekwani, B. L.; Dunbar, D. C.; Ferreira, D. *J. Nat. Prod.* **2003**, *66*, 804.

(5) Sauchinone A was isolated from the herb *Saururus chinensis*. Incubation of cultured rat hepatocytes, intentionally injured by CCl_4, with sauchinone A significantly reduced the levels of glutamic pyruvic transaminase released by the damaged hepatocytes. See: Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2000**, *63*, 1019.

(6) Minagawa, K.; Kouzuki, S.; Nomura, K.; Yamaguchi, T.; Kawamura, Y.; Matsushima, K.; Tani, H.; Ishii, K.; Tanimoto, T.; Kamigauchi, T. *J. Antibiot.* **2001**, *54*, 890.

(7) The two citrans were isolated from an extract of the fruit from *Clusia multiflora*, see: Gonzalez, J. G.; Olivares, E. M.; Monache, F. D. *Phytochemistry* **1995**, *38*, 485.

(8) Shirota, O.; Takizawa, K.; Sekita, S.; Satake, M. *J. Nat. Prod.* **1997**, *60*, 997.

(9) For a recent structure−activity study of antibacterial cannabinoids from *Cannabis sativa*, see: Appendino, G.; Gibbons, S.; Giana, A.; Pagani, A.; Grassi, G.; Stavri, M.; Smith, E.; Rahman, M. M. *J. Nat. Prod.* **2008**, *71*, 1427.

(10) Garrido, L.; Zubía, E.; Ortega, M. J.; Salvá, J. *J. Nat. Prod.* **2002**, *65*, 1328.

(11) Simon-Levert, A.; Arrault, A.; Bontemps-Subielos, N.; Canal, C.; Banaigs, B. *J. Nat. Prod* **2005**, *68*, 1412.

10.1021/ol902840x
Published on Web 01/15/2010

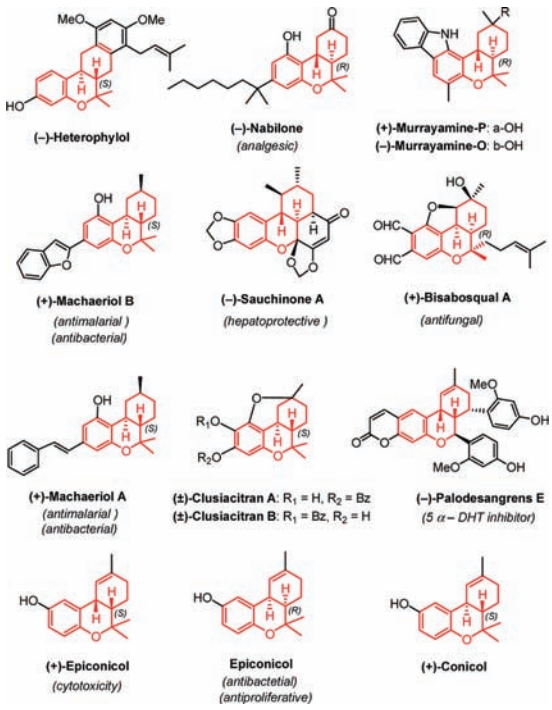


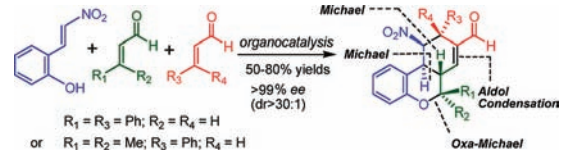
Figure 1. Selected naturally occurring hexahydro-6*H*-benzo[*c*]-chromenes.

cytotoxicity against P388 (murine leukemia), A549 (human lung carcinoma), HT29 (human colon carcinoma), and CV1 (monkey kidney fibroblast) cells.[12]

However, as shown in Figure 1, both absolute configurations at the core of hexahydro-6*H*-benzo[*c*]chromenes have been reported from nature sources,[13] and the absolute stereochemistries of some compounds are not clear. The absolute configurations of these compounds shown in the literature structures have been arbitrary. For instance, both enantiomers of epiconicol have been presented in the literature, and no attempts have been made to determine the absolute configurations of conicol and epiconicol, vide infra, as well as some other natural hexahydro-6*H*-benzo[*c*]chromens.[14] Large discrepancies in optical rotation for the same compound have been reported, e.g., epiconicol.[15] Several rationalizations have been suggested, including racemization of the compounds during isolation, the coexistence of enantiomers in nature, and the presence of an enantiomeric excess in the opposite sense. Despite these speculations, the solution to this discrepancy remains elusive.

Several elegant approaches have been implemented successfully to achieve synthesis of the natural tetrahydro-6*H*-benzo[*c*]chromenes, for example, the total synthesis of (+)-machaeriol A, B,[16] and nabilone.[17] However, the key reaction in these synthetic approaches used optically active starting compounds or involved reactions with chiral substrates, e.g., citronellal or geranyl aldehyde. The key reactions were not innately enantioselective, and the synthetic strategies lacked diversity. Consequently, despite the success of the previous synthetic strategies toward hexahydro-6*H*-benzo[*c*]chromenes, the development of an efficient and highly enantioselective as well as diversity-oriented synthetic strategy toward this skeleton remained an appealing challenge. Recently, we developed a concise synthesis of the skeleton of hexahydro-6*H*-benzo[*c*]chromenes via a quadruple cascade[18] organocatalytic[19] multicomponent reaction, with control over five stereocenters, in a one-pot operation (Scheme 1).[20,21] The diversity of the protocol was demonstrated by the chemo-differentiating three-component reaction (ABC type) with 3-methylbut-2-enal and β-aryl-α,β-unsatur-

Scheme 1



(12) Carroll, A. R.; Bowden, B. F.; Coll, J. C. *Aust. J. Chem.* **1993**, *46*, 1079.

(13) For example, both enantiomers of sauchinone have been found in nature, see: (a) Wang, E.-C.; Shih, M.-H.; Liu, M.-C.; Chen, M.-T.; Lee, G.-H. *Heterocycles* **1996**, *43*, 969. (b) Seo, C.-S.; Lee, Y.-K.; Kim, Y.-J.; Jung, J.-S.; Jahng, Y.; Chang, H.-W.; Song, D.-K.; Son, J.-K. *Biol. Pharm. Bull.* **2008**, *31*, 523. (c) Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2000**, *63*, 1019. (d) Hwang, B. Y.; Lee, J.-H.; Jung, H. S.; Kim, K.-S.; Nam, J. B.; Hong, Y. S.; Paik, S.-G.; Lee, J. J. *Planta Med.* **2003**, *69*, 1096.

(14) (a) Refer to footnote 6 in ref 10. (b) Both the enantiomers of epiconicol have been drawn in the literature. See refs 10, 11, and 12.

(15) (a) Optical rotation data for epiconicol: +58° (*c* 0.09) in ref 12 and +1.2° (*c* 0.6, $CHCl_3$) in ref 10. (b) Refer to the footnote 13 in ref 10.

(16) (a) Chittiboyina, A. G.; Reddy, C. R.; Watkins, E. B.; Avery, M. A. *Tetrahedron Lett.* **2004**, *45*, 1689. (b) Huang, Q.; Wang, Q.; Zheng, J.; Zhang, J.; Pan, X.; She, X. *Tetrahedron* **2007**, *63*, 1014. (c) Xia, L.; Lee, Y. R. *Synlett* **2008**, 1643. (d) Wang, Q.; Huang, Q.; Chen, B. O.; Lu, J.; Wang, H.; She, X.; Pan, X. *Angew. Chem., Int. Ed.* **2006**, *45*, 3651. (e) Lee, H. J.; Lee, Y. R.; Kim, S. H. *Helv. Chim. Acta* **2009**, *92*, 1404.

(17) (a) Huffman, J. W.; Joyner, H. H.; Lee, M. D.; Jordan, R. D.; Pennington, W. T. *J. Org. Chem.* **1991**, *56*, 2081. (b) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277.

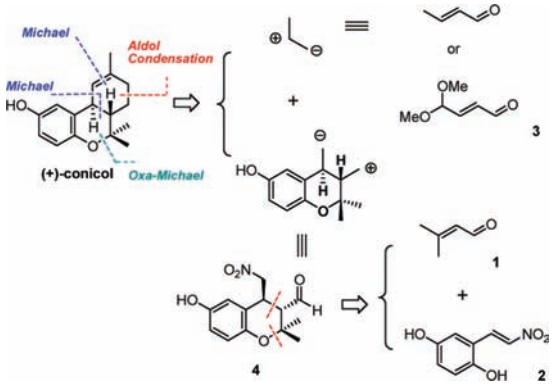
(18) For selected recent examples of organocatalytic domino reactions, see: (a) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem.—Eur. J.* **2009**, *15*, 6815. (b) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgenson, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (c) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467. (d) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2008**, *14*, 4788. (e) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304. (f) Marigo, M.; Schulte, T.; Franzén, J.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 15710. (g) Zu, L.; Zhang, S.; Xie, H.; Wang, W. *Org. Lett.* **2009**, *11*, 1627. (h) Franzén, J.; Fisher, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 787.

(19) For recent reviews in organocatalysis, see: (a) Palomo, C.; Oiarbide, M.; López, R. *Chem. Soc. Rev.* **2009**, *38*, 632. (b) Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev.* **2009**, *38*, 1187. (c) Lattanzi, A. *Chem. Commun.* **2009**, 1452. (d) Xu, L. W.; Luo, J.; Lu, Y. *Chem Commun.* **2009**, 1807. (e) Enders, D.; Wang, C.; Liebich, J. X. *Chem.—Eur. J.* **2009**, *15*, 11058. (f) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178. (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (h) Carlos, F. B., III. *Angew. Chem., Int. Ed.* **2008**, *47*, 42. (i) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (j) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (k) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (l) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (m) Kano, T.; Maruoka, K. *Chem. Commun.* **2008**, 5465. (n) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857. (o) Connon, S. J. *Chem. Commun.* **2008**, 2499.

ated aldehyde (3-arylacrylaldehyde), which afforded highly functionalized tetrahydro-6*H*-benzo[*c*]chromenes. Herein, we have expanded the methodology beyond the β-aryl-α,β-unsaturated aldehyde system to the β-alkyl variant (an aldehyde tends to undergo self-condensation via [4 + 2] and [3 + 3] annulations)[22] and achieved the first total synthesis of (+)-conicol and have also defined its absolute configuration.

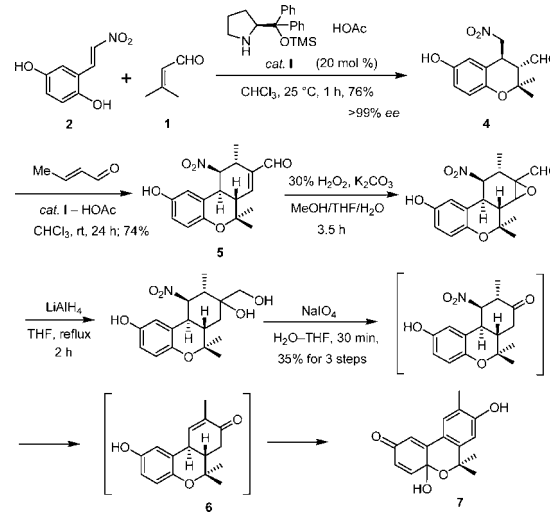
Initially, we envisioned that (+)-conicol could be assembled from 3-methylbut-2-enal (**1**), (*E*)-2-(2-nitrovinyl)-benzene-1,4-diol (**2**), and crotonaldehyde, or 4,4-dimethoxybut-2-enal (**3**), via a cascade reaction of oxa-Michael−Michael−Michael−aldol condensation (Scheme 2). Our

Scheme 2



approach started from the tandem oxa-Michael−Michael reaction of **1** and **2** to yield **4** (cat. **I** − HOAc, $CHCl_3$, rt, 1 h; 76%), followed by a domino Michael−Aldol condensation with crotonaldehyde (cat. **I** − HOAc, $CHCl_3$, rt, 24 h; 74% yield), affording the hexahydro-6*H*-benzo[*c*]chromene **5** (Scheme 3). The successful cascade reaction with crotonaldehyde is especially noteworthy since crotonaldehyde has an active γ-hydrogen for γ-amination that could lead to competing side reactions.[23] Moreover, the two reactions could be achieved in one-pot, without the isolation of **4**, to give **5** in a 66% overall yield. Transformation of **5** to **6** proceeded through a sequence of reactions: hydrogen peroxide epoxidation (H_2O_2, K_2CO_3), reduction ($LiAlH_4$, THF),

Scheme 3



and oxidative cleavage reaction ($NaIO_4$, THF−H_2O). Unfortunately, phenolic **7**, instead of desired **6**, was obtained in a 35% overall yield for the three-consecutive-step reaction without isolation of the intermediates. Apparently, the instability of **6** resulted in a favorable aromatization and led to the formation of *para*-quinone hemiketal **7**.[24]

Consequently, aldehyde **3** was selected as a suitable surrogate for the zwitterionic propane synthon due to its commercial availability and its potential for offering stable synthetic intermediates. This alternative approach started from the domino oxa-Michael−Michael−Michael−aldol condensation of **4** and **3** (cat. **I** − HOAc, $CHCl_3$, rt, 35 h; 69%), affording the hexahydro-6*H*-benzo[*c*]chromene **8** (Scheme 4). The two-step reaction could be achieved in one pot from **1** and **2**, without isolation of the intermediate **4**, with a 55% overall isolated yield of **8**. Decarbonylation of **8** with the Wilkinson catalyst in refluxing toluene afforded the alkene **9** in 54% yield. Hydrogenation of **9** with Pd−C in methanol provided **10** in 72% yield. Hydrolysis of the dimethoxymethyl groups on **10** (Amberlyst 15, acetonitrile−H_2O (1:1), 80 °C, 4 h; 69% yield) gave **11** and a trace amount of aromatic aldehyde **12**. Subsequent denitration elimination of **11** (DABCO, CH_3CN, 0−20 °C, 2 h, 79% yield) afforded **14**. Additionally, hydrolysis of **9** in aqueous HCl solution (v/v 1:1, acetone−10% aq. HCl; 25 °C, 30 min) gave 71% yield of the aromatic aldehyde **12** which was converted to the bacteriostatic agent didehydroconicol,[11] **13**, via Wolff−Kishner reduction (N_2H_4−H_2O and KOH in diethylene glycol, 130 °C, 8 h, 63% yield). Attempts under the various conditions of Wolff−Kishner reduction of aldehyde **14** led to the aromatic aldehyde **13** or to decomposition. Accordingly, the elaboration of the aldehyde group to a methyl group was achieved by the following transformation: reduction of

(20) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704.

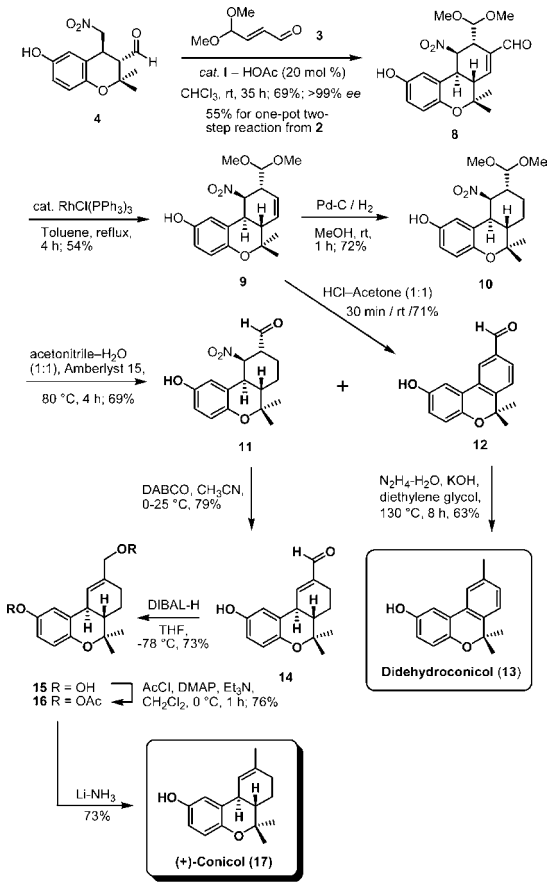
(21) For our previous efforts in exploring new annulations, see: (a) Hong, B.-C.; Jan, R.-H.; Tsai, C.-W.; Nimje, R. Y.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2009**, *11*, 5246. (b) Hong, B.-C.; Nimje, R. Y.; Liao, J.-H. *Org. Biomol. Chem.* **2009**, *7*, 3095. (c) Hong, B.-C.; Nimje, R. Y.; Sadani, A. A.; Liao, J.-H. *Org. Lett.* **2008**, *10*, 2345. (d) Hong, B.-C.; Nimje, R. Y.; Wu, M.-F.; Sadani, A. A. *Eur. J. Org. Chem.* **2008**, 1449. (e) Hong, B.-C.; Nimje, R. Y.; Yang, C.-Y. *Tetrahedron Lett.* **2007**, *48*, 1121. (f) Hong, B.-C.; Chen, F.-L.; Chen, S.-H.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2005**, *7*, 557. (g) Hong, B.-C.; Gupta, A. K.; Wu, M.-F.; Liao, J.-H. *Tetrahedron Lett.* **2004**, *45*, 1663. (h) Hong, B.-C.; Chen, Z. Y.; Chen, W. H. *Org. Lett.* **2000**, *2*, 2647.

(22) (a) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. *Org. Lett.* **2006**, *8*, 2217. (b) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Huang, G.-F.; Su, C.-F.; Liao, J.-H. *J. Org. Chem.* **2007**, *72*, 8459. (c) Hong, B.-C.; Tseng, H.-C.; Chen, S.-H. *Tetrahedron* **2007**, *63*, 2840.

(23) For examples of γ-amination of α,β-unsaturated aldehydes, see: (a) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (b) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536.

(24) For studies in the oxidation of chromenols to *para*-quinone hemiketals, see: (a) Patel, A.; Netscher, T.; Gille, L.; Mereiter, K.; Rosenau, T. *Tetrahedron* **2007**, *63*, 5312. (b) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230. (c) Lee, S. B.; Lin, C. Y.; Gill, P. M. W.; Webster, R. D. *J. Org. Chem.* **2005**, *70*, 10466.

Scheme 4



14 (DIBAL-H, THF, −78 °C, 1 h, 73% yield of **15**), followed by acetylation (Ac_2O, DMAP, $Et_3N-CH_2Cl_2$, 76% yield of **16**), and metallic reduction (Li, NH_3, 73% yield) to afford **17**. The ^1H and ^{13}C NMR spectroscopic data for synthetic **17** were identical to those described for the natural product (+)-conicol.[25]

To confirm the absolute configuration of the adducts in the cascade oxa-Michael−Michael−Michael−aldol condensation,[26] the one-pot domino reaction of 2-((*E*)-2-nitrovinyl)phenol (**18**) and 2 equiv of (*E*)-3-(4-bromophenyl)-acrylaldehyde (**19**) was carried out to afford the adduct **20** (>99% ee). The structure and absolute configuration of **20** were assigned unambiguously by X-ray analysis (Figure 2).[27] Moreover, the absolute configuration of the *gem*-dimethyl derivatives **21** (>99% ee), prepared from **18**, **1**, and **19**, was elucidated by single-crystal X-ray analysis (Figure 1).

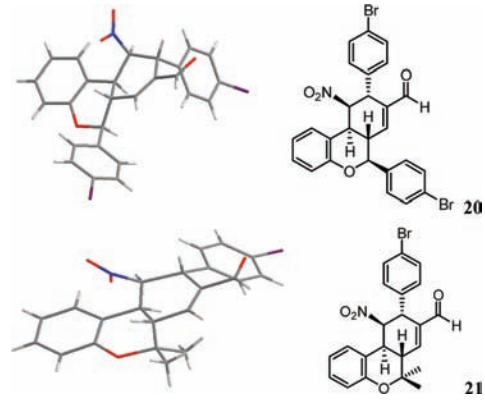


Figure 2. Stereo plots for X-ray crystal structures of **20** and **21**: C, gray; N, blue; O, red; Br, purple.

In summary, we described the first enantioselective total synthesis of the marine meroterpene (+)-conicol. This synthesis demonstrates the synthetic application of the new cascade oxa-Michael−Michael−Michael−aldol condensation of 2-((*E*)-2-nitrovinyl)benzene-1,4-diol and α,*β*-unsaturated aldehydes. The successful synthesis further expands the realm of the reactant of this three-component reaction beyond 3-arylacrylaldehyde to the α,*β*-unsaturated aldehydes bearing a *γ*-H. The structures as well as the absolute configurations of the products were confirmed by X-ray analysis of the appropriate cascade reaction adducts. The total synthesis successfully assigned the absolute configuration of (+)-conicol, which had previously been a mystery because the stereochemistry was difficult to determine by other means. Moreover, this methodology features the highly enantioselective and expeditious construction of the hexahydro-6*H*-benzo[*c*]chromene skeleton, a strategy that may be applied to the synthesis of other naturally occurring derivatives for use in bioassays or SAR studies. Extension of this methodology to the synthesis of other natural products is under active investigation.

Acknowledgment. We acknowledge the financial support for this study from the National Science Council, ROC. Thanks to the National Center for High-Performance Computing (NCHC) for their assistance in literature searching.

Supporting Information Available: Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compounds **20** and **21** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

OL902840X

(25) Synthetic **17**: $[\alpha]_D^{25}$ +51.8 (*c* 2, $CHCl_3$). Natural **17**: lit. $[\alpha]_D^{27}$ +1.0 (*c* 0.4, $CHCl_3$). The measured optical rotation differed from values reported for the natural product and raises earlier suspicions that the natural products were present in an enantiomeric excess in the opposite sense and were not isolated as pure single enantiomers. The lack of optical purity in the natural products may also be due to facile racemization and/or decomposition. We observed that storage of the neat enantiopure **17** at 25 °C for one week resulted in some decomposition products. Moreover, the compound completely decomposed in $CHCl_3$, and a complicated mixture was obtained after incubation in $CHCl_3$ for 24 h at ambient temperature. Refer to Supporting Information and ref 10, conclusion sentences on p 1330 and footnote 13 therein.

(26) The relative stereochemistry of the cascade reaction adduct was revealed by X-ray analysis of a product without heavy atoms. See ref 20.

(27)