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Radical Carboxyarylation Approach to Lignans. Total Synthesis of (–)-Arctigenin, (–)-Matairesinol, and Related Natural Products

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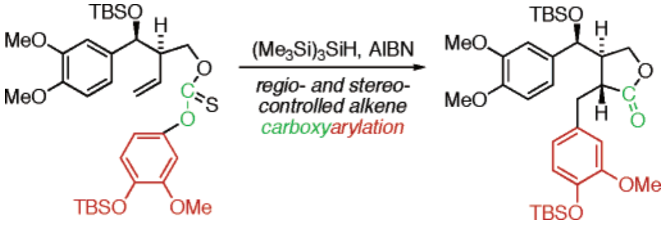
ABSTRACT



Total syntheses of seven biologically important lignan natural products, including (–)-arctigenin, (–)-matairesinol, and (–)-α-conidendrin, by way of a highly stereoselective domino radical sequence is presented. The reported stereochemistry of the natural product 7-hydroxyarctigenin is shown to be erroneous; a diastereoisomeric structure is assigned to the natural product.

Matairesinol (**1**) and arctigenin (**5**) (Figure 1) are naturally occurring dibenzylbutyrolactone lignans isolated from several plant sources.[1,2] Both compounds are potent cytostatic agents against human leukemic HL-60 cells, with IC_{50} values of less than 100 ng/mL.[3] Arctigenin and analogues have also been shown to be potent inhibitors of HIV Type-1 Integrase.[4] In addition to antitumor and antiviral activities, these compounds display phytoestrogenic,[5] immunoregulatory,[6]and neuroprotective[7] properties. Despite their modest size and structural complexity, surprisingly few synthetic studies have been reported on these compounds.[8−10]

Three C7-oxygenated analogues of matairesinol[11] and one of arctigenin have been reported as natural products: (−)-7(*S*)-hydroxymatairesinol **2**,[12] (−)-7(*R*)-hydroxymatairesinol **3**,[12] (+)-7-oxomatairesinol **4**,[12] and (+)-7(*S*)-hydroxyarcti-

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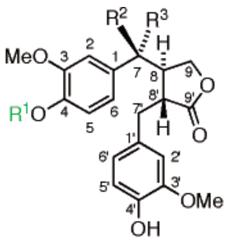
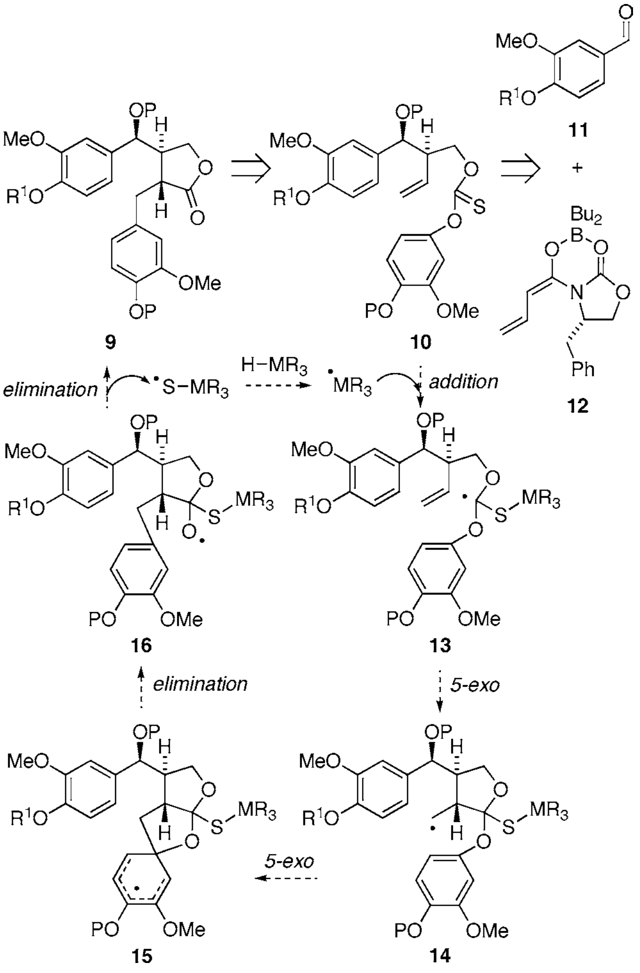


R1 = H
- **1** R2 = R3 = H; (−)-matairesinol
- **2** R2 = OH; R3 = H; (−)-7(*S*)-hydroxymatairesinol
- **3** R2 = H; R3 = OH; (−)-7(*R*)-hydroxymatairesinol
- **4** R2, R3 = O; (+)-7-oxomatairesinol

R1 = Me
- **5** R2 = R3 = H; (−)-arctigenin
- **6** R2 = OH; R3 = H; 7(*S*)-hydroxyarctigenin
- **7** R2 = H; R3 = OH; 7(*R*)-hydroxyarctigenin
- **8** R2, R3 = O; 7-oxoarctigenin

Figure 1. Dibenzyl butyrolactone lignan natural products and congeners under scrutiny.

Scheme 1. Intramolecular Alkene Carboxyarylation Approach to Dibenzyl butyrolactone Lignans



genin **6**.[13] The identity of the natural product isolated from the aerial parts of *Centaurea calcitrapa* was assigned structure **6** since the spectroscopic data for this compound matched that of a compound previously synthesized from arctigenin. The stereochemistry of the semisynthetic sample was assigned by comparing its ^{13}C chemical shifts with those of the two known 7-hydroxy matairesinol diastereomers.[14] The 7(*R*)-hydroxy and 7-oxo derivatives of arctigenin **7** and **8** have not been reported in the literature. Herein we disclose short asymmetric syntheses of the eight compounds depicted in Figure 1.

This work represents the first asymmetric total synthesis of the four naturally occurring C7-oxygenated lignans.[15]

Lignan natural products of this type lend themselves to disconnection (Scheme 1) involving an intramolecular alkene 1,2-carboxyarylation reaction (**10** → **9**)[16] and an Evans asymmetric crotonate aldol reaction.[17] The proposed radical sequence forms two C−C bonds, incorporating the lactone ring and an aromatic ring through a sequence involving an addition, two 5-*exo* cyclizations, and two elimination steps.[18] The *trans*-disubstituted lactone was expected to be the dominant product on the basis of Beckwith's models for stereoselectivity in radical cyclizations (cf. **13** → **14**).[19]

Syntheses of 7(*S*)-hydroxymatairesinol **2** and 7(*S*)-hydroxyarctigenin **6** via this strategy are depicted in Scheme 2. Thus, an aldol reaction between the requisite aromatic aldehyde **17a/b** and the dibutylboron dienolate derived from crotonyl oxazolidinone **18** gave the Evans *syn*-adduct **19** in >95% diastereoselectivity. These aldol adducts proved to be unstable toward chromatography, so they were immediately protected as the corresponding silyl ethers **20**. Reductive removal of the phenylalanine-derived oxazolidinone auxiliary gave homoallylic alcohol **21**, which was united with aryl chlorothionoformate **23** in high yield.

Thionocarbonates **24a** and **24b** underwent the desired domino radical reaction in acceptable yields and very high

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[11] 7-Hydroxymatairesinol has recently been shown to be a useful starting material: (a) Eklund, P. C.; Sjoholm, R. E. *Tetrahedron* **2003**, *59*, 4515−4523. (b) Eklund, P.; Lindholm, A.; Mikkola, J.-P.; Smeds, A.; Lehtilae, R.; Sjoeholm, R. *Org. Lett.* **2003**, *5*, 491−493. (c) Eklund, P. C.; Riska, A. I.; Sjoeholm, R. E. *J. Org. Chem.* **2002**, *67*, 7544−7546. (d) Eklund, P.; Sillanpaeae, R.; Sjoeholm, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1906−1910.

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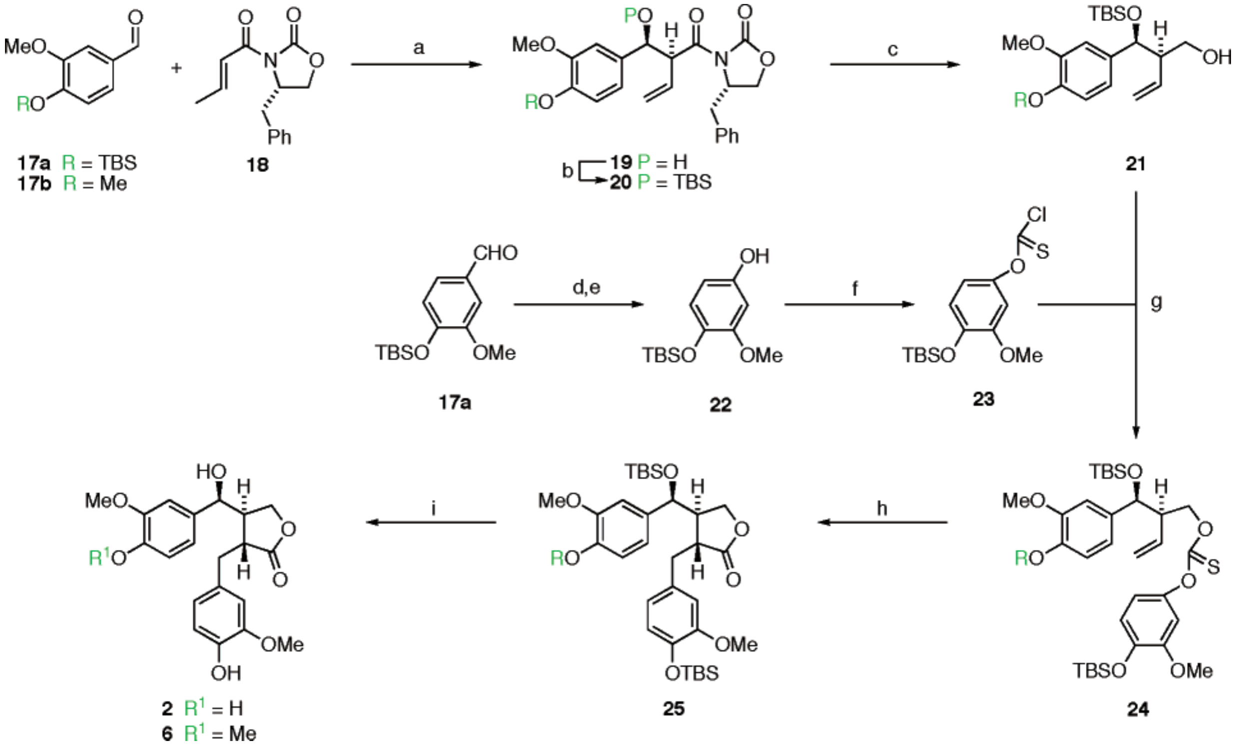
Scheme 2. Total Syntheses of 7(*S*)-Hydroxymatairesinol **2** and 7(*S*)-Hydroxyarctigenin **6**[a]



[a] Key: (a) **18** (1.8 equiv), *n*-Bu_2BOTf (2 equiv), NEt_3 (2.6 equiv), CH_2Cl_2, then **17** (1 equiv), −78 to 0 °C, 1 h, then H_2O_2, pH 7.2 buffer, Et_2O, 25 °C, 48 h; (b) TBSOTf (1.2 equiv), 2,6-lutidine (1.8 equiv), CH_2Cl_2, 25 °C, 0.5 h, overall yields from **17**: **20a**, 83%; **20b**, 92%; (c) $NaBH_4$ (10 equiv), THF−H_2O, 25 °C, 16 h, **21a**, 77%; **21b**, 85%; (d) *m*-CPBA (1.5 equiv), CH_2Cl_2, 40 °C, 2 h, 98%; (e) K_2CO_3 (1 equiv), MeOH, 25 °C, 10 min, 90%; (f) DBU (1.6 equiv), CH_2Cl_2, 25 °C, 0.5 h, then $CSCl_2$ (4.3 equiv), CH_2Cl_2, 0 °C, 20 min, 100%; (g) **21** (1 equiv), pyridine (2 equiv), **23** (1.2 equiv), CH_2Cl_2, 2 h, **24a**, 81%; **24b**, 88%; (h) $(Me_3Si)_3SiH$ (1.1 equiv), AIBN (0.4 equiv added over 6 h), PhH, 80 °C, **25a**, 44%; **25b**, 44%; (i) *n*-Bu_4NF (15 equiv), AcOH (15 equiv), THF, 25 °C, 96 h, **2**, 90%; **6**, 86%.

(>95%) *trans*-diastereoselectivity with $(Me_3Si)_3SiH$ as reagent. Removal of the silyl protecting groups furnished the 7(*S*)-hydroxy lignans. Spectroscopic and physical data for synthetic 7(*S*)-hydroxymatairesinol **2** were in good agreement with data reported for this compound.[20] In contrast, characterization data collected on synthetic 7(*S*)-hydroxyarctigenin **6** were not in accord with literature[13,14] figures. We suspected that the stereochemistry of this natural product had been incorrectly assigned in these previous investigations. To clarify this issue, we pursued the preparation of **7**, the 7(*R*)-diastereoisomer of **6**. The results of this and related chemistry is depicted in Scheme 3. Inversion of the C7-hydroxy group of **6** was achieved under modified Mitsunobu conditions.[21] Spectroscopic and physical data for synthetic 7(*R*)-hydroxyarctigenin **7** was in good agreement with literature data for natural 7-hydroxyarctigenin.[13,14] We therefore conclude that the stereochemistry of the natural product has been incorrectly assigned.[22]

Interestingly, whereas both Mitsunobu inversion and Parikh−Doering oxidation of the C7-hydroxyl group could be carried out in the presence of a free C4′ phenol (**6** → **7** and **6** → **8**, respectively), a free phenolic residue at C4 caused these reactions to fail. Thus, access to oxygenated matairesinol natural products **3** and **4** was by way of the silyl-protected compound **30**. Spectroscopic and physical data for synthetic 7(*R*)-hydroxymatairesinol **3** and 7-oxomatairesinol **4** were in good agreement with literature data.[12,20] Hydrogenolytic deoxygenation of the benzylic alcohol group[23] (**2** → **1**; **6** → **5**) afforded samples of (−)-matairesinol and (−)-arctigenin.[24]

The synthetic potential of these compounds was further exemplified by their ready conversion into aryl tetrahydronaphthalene (**2** → **28**; **6** → **29**)[25] and dibenzocyclooctane (**5** → **27**)[26] lignan skeletons. Once again, characterization data for (−)-α-conidendrin **28** (and the corresponding monomethyl ether **29**) prepared by this route matched those reported in the literature for the natural product.[27]

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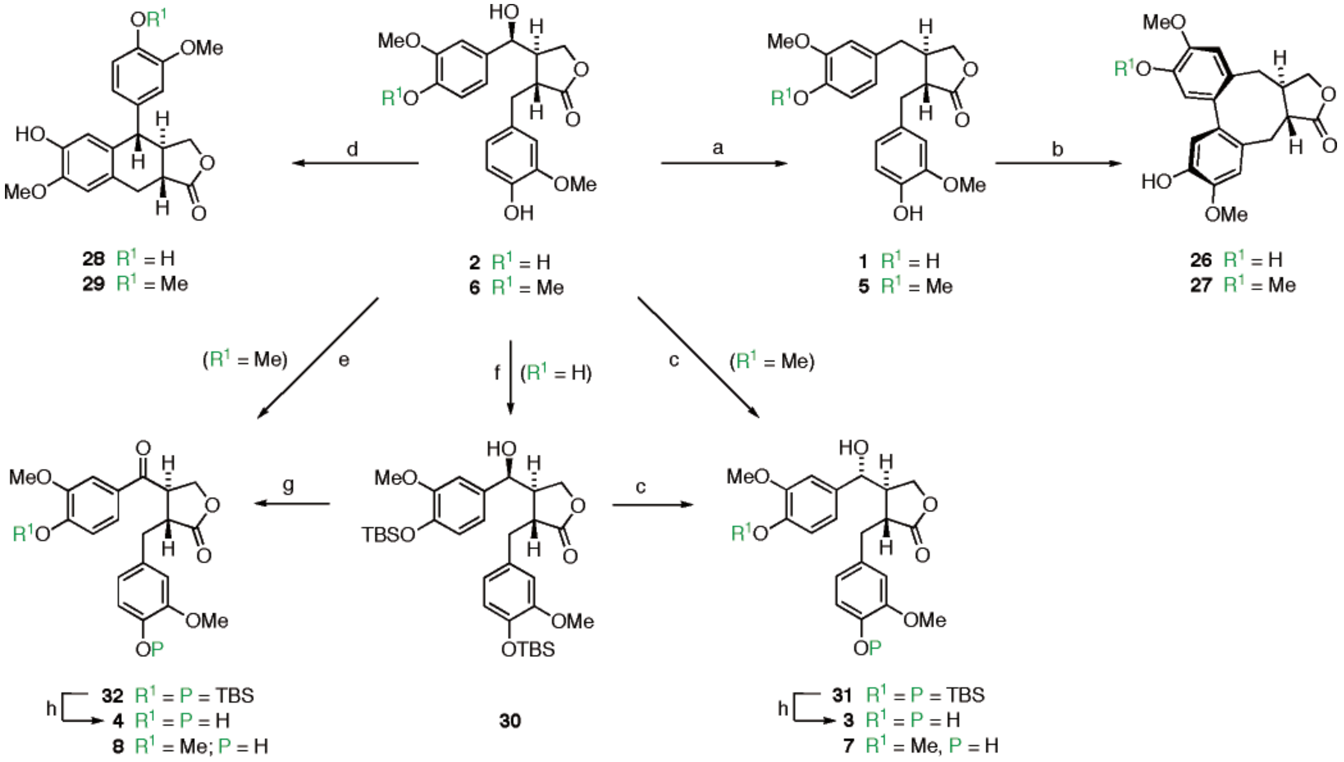
Scheme 3. Transformations of 7(*S*)-Hydroxy Lignans **2** and **6**[a]



[a] Key: (a) H_2 (4 atm), 10% Pd/C (0.1 equiv), $HClO_4$ (0.1 equiv), EtOH, 48 h, 25 °C, **2** → **1**, 78%; **6** → **5**, 80%; (b) $RuO_2{\cdot}2H_2O$ (2 equiv), CF_3CO_2H (54 equiv), $(CF_3CO)_2O$ (15 equiv), $BF_3{\cdot}Et_2O$ (7 equiv), CH_2Cl_2, 16 h, 25 °C, **1** → **26**, 0%; **5** → **27**, 80%; (c) PPh_3 (3 equiv), *p*-$NO_2C_6H_4CO_2H$ (3 equiv), DEAD (3 equiv), PhH, 25 °C, 48 h, then K_2CO_3 (2.5 equiv), $KHCO_3$ (0.7 equiv), MeOH−H_2O, 25 °C, 1 h, overall yields: **6** → **7**, 47%; **30** → **31**, 83%; (d) CF_3CO_2H (3.3 equiv), CH_2Cl_2, 25 °C, 1 h, **2** → **28**, 100%; **6** → **29**, 100%; (e) *i*-Pr_2NEt (6 equiv), $SO_3{\cdot}$pyr (3 equiv), DMSO, 25 °C, 1 h, **6** → **8**, 84%; (f) TBSCl (2.1 equiv). imidazole (2.1 equiv), DMF, 2 h, 25 °C, **2** → **30**, 77%; (g) PCC, CH_2Cl_2, 1 h, 25 °C, **30** → **32**, 77%; (h) TBAF (4 equiv), AcOH (4 eq) THF, 16 h, 25 °C, **31** → **3**, 72%; **32** → **4**, 84%.

In summary, a conceptually novel route to lignans has been developed. Many new analogues of biologically important compounds are now accessible due to the short and convergent nature of this approach. Optimization studies and further applications of the radical carboxyarylation reaction are under way.

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Supporting Information Available: Experimental procedures, product characterization data, and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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