

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

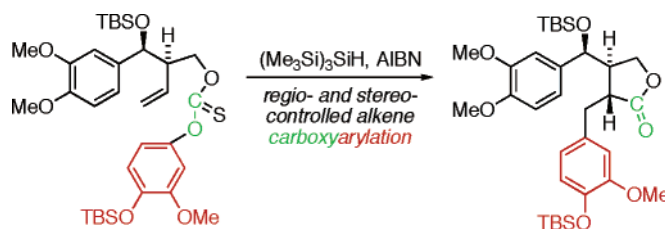
Joshua Fischer,[†] Aaron J. Reynolds,[†] Lisa A. Sharp,[‡] and Michael S. Sherburn^{*,†}

Research School of Chemistry, Australian National University, Canberra ACT 0200, Australia,
and School of Chemistry, University of Sydney, Sydney NSW 2006, Australia

sherburn@rsc.anu.edu.au

Received January 20, 2004

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 IC₅₀ 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

neuroprotective⁷ 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 matairesinol¹¹ 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-

[†] University of Sydney.

[‡] Australian National University.

(1) (a) Shinoda, J. *Yakugaku Zasshi* **1929**, 49, 1165–1169; *Chem. Abstr.* **1930**, 24, 12404. (b) Haworth, R. D.; Kelly, W. J. *Chem. Soc.* **1936**, 998–1003.

(2) Esterfield, T. H.; Bee, J. J. *Chem. Soc.* **1910**, 97, 1028–1032.

(3) (a) Hirano, T.; Gotoh, M.; Oka, K. *Life Sci.* **1994**, 55, 1061–1069. (b) Takasaki, M.; Konoshima, T.; Komatsu, K.; Tokuda, H.; Nishino, H. *Cancer Lett.* **2000**, 158, 53–59.

(4) (a) Eich, E.; Pertz, H.; Kaloga, M.; Schulz, J.; Fesen, M. R.; Mazumder, A.; Pommier, Y. J. *Med. Chem.* **1996**, 39, 86–95. (b) Yang, L.-M.; Lin, S.-J.; Yang, T.-H.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1996**, 6, 941–944.

(5) Meagher, L. P.; Beecher, G. R.; Flanagan, V. P.; Li, B. W. *J. Agric. Food Chem.* **1999**, 47, 3173–3180.

(6) Cho, J. Y.; Kim, A. R.; Yoo, E. S.; Baik, K. U.; Park, M. H. *J. Pharm. Pharmacol.* **1999**, 51, 1267–1273.

(7) (a) Jang, Y. P.; Kim, S. R.; Kim, Y. C. *Planta Med.* **2001**, 67, 470–472. (b) Jang, Y. P.; Kim, S. R.; Choi, Y. H.; Kim, J.; Kim, S. G.; Markelonis, G. J.; Oh, T. H.; Kim, Y. C. *J. Neurosci. Res.* **2002**, 68, 233–240.

(8) Asymmetric syntheses of arctigenin: (a) Brown, E.; Daugan, A. *Tetrahedron* **1989**, 45, 141–154. (b) Sibi, M. P.; Liu, P.; Ji, J.; Hajra, S.; Chen, J. J. *Org. Chem.* **2002**, 67, 1738–1745.

(9) Asymmetric synthesis of matairesinol: Daugan, A.; Brown, E. *J. Nat. Prod.* **1991**, 54, 110–118.

(10) Recent reviews on lignan synthesis: (a) Ward, R. S. In *Recent Advances in the Chemistry of Lignans*; Atta-ur-Rahman, Ed.; Studies in Natural Products Chemistry, Vol. 24: Bioactive Natural Products, Part E; Elsevier: Amsterdam, 2000; pp 739–798. (b) Ward, R. S. *Nat. Prod. Rep.* **1999**, 16, 75–96 and references therein.

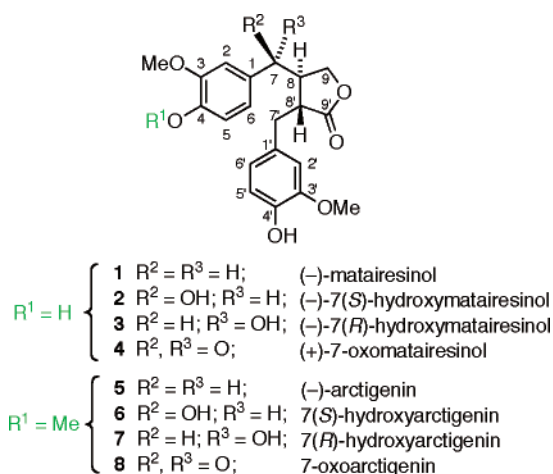


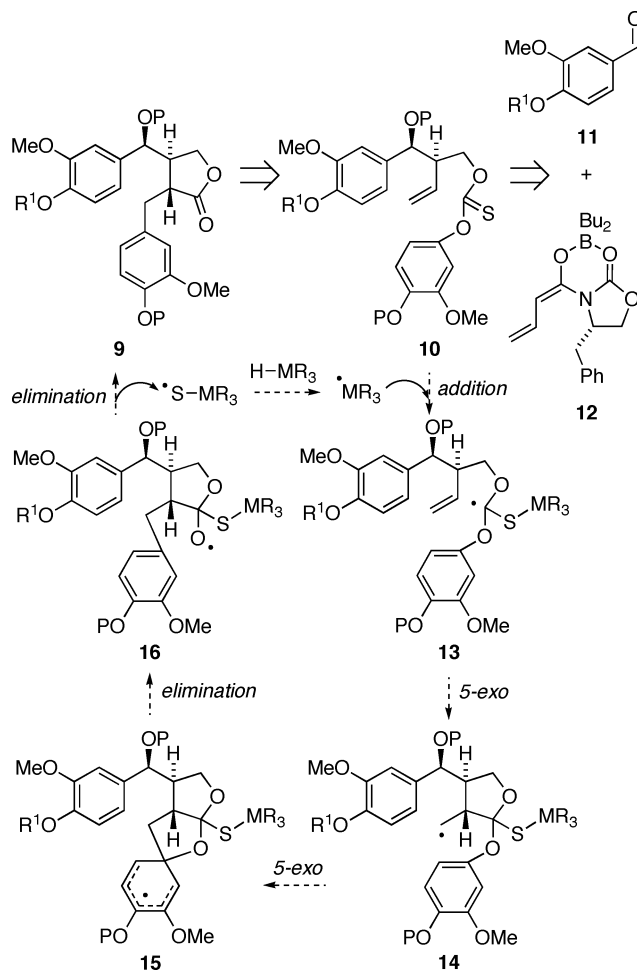
Figure 1. Dibenzyl butyrolactone lignan natural products and congeners under scrutiny.

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 ¹³C 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

Scheme 1. Intramolecular Alkene Carboxyarylation Approach to Dibenzyl butyrolactone Lignans



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

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

(12) Originally isolated from *Picea mariana* (black spruce): Freudenberg, K.; Knof, L. *Chem. Ber.* **1957**, *90*, 2857–2869.

(13) Marco, J. A.; Sanz, J. F.; Sancenón, F.; Susanna, A.; Rustiayan, A.; Saberi, M. *Phytochemistry* **1992**, *31*, 3527–3530.

(14) Nishibe, S.; Chiba, M.; Sakushima, A.; Hisada, S.; Yamanouchi, S.; Takido, M.; Sankawa, U.; Sakakibara, A. *Chem. Pharm. Bull.* **1980**, *28*, 850–860.

(15) Synthesis of racemic 7-oxygenated matairesinols: Makela, T. H.; Kaltia, S. A.; Wahala, K. T.; Hase, T. A. *Steroids* **2001**, *66*, 777–784.

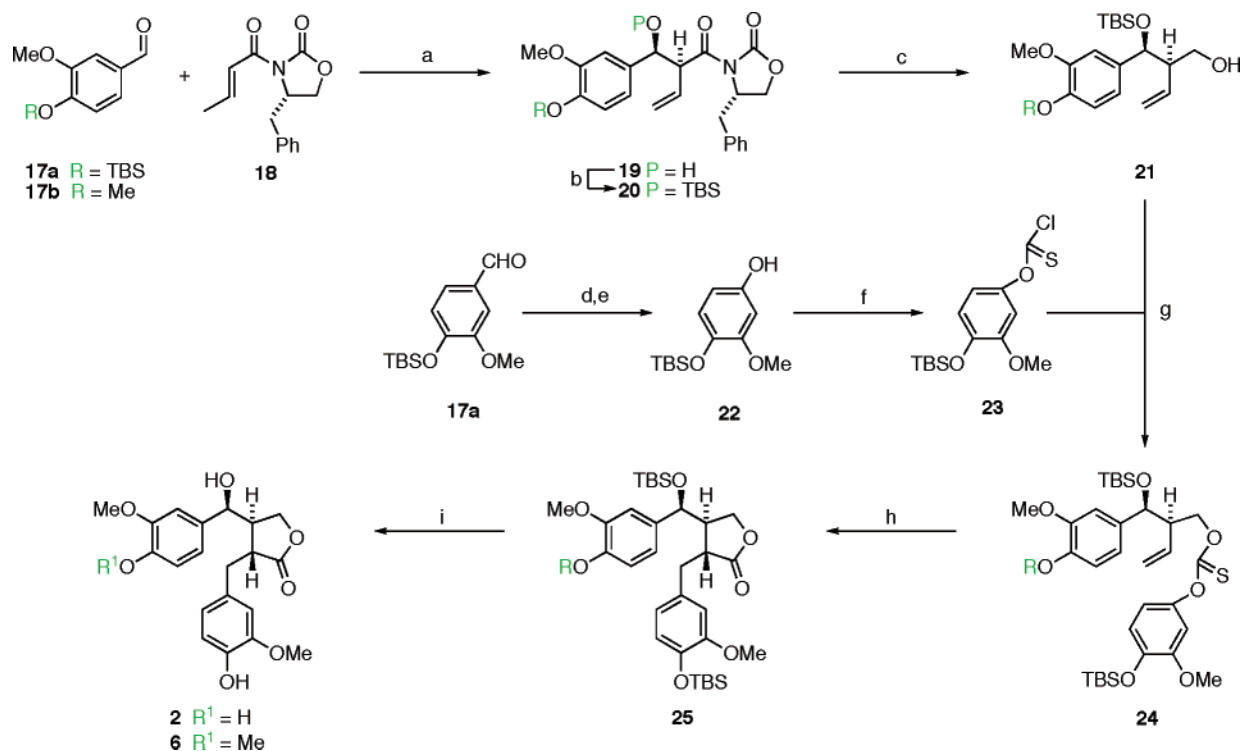
(16) Reynolds, A. J.; Scott, A. J.; Turner, C. I.; Sherburn, M. S. *J. Am. Chem. Soc.* **2003**, *125*, 12108–12109.

(17) Evans, D. A.; Sjogren, E. B.; Bartoli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957–4960.

(18) (a) Mander, L. N.; Sherburn, M. S. *Tetrahedron Lett.* **1996**, *37*, 4255–4258. (b) Bachi, M. D.; Bosch, M.; Denenmark, D.; Girsh, D. *J. Org. Chem.* **1992**, *57*, 6803–6810.

(19) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941.

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



^a Key: (a) **18** (1.8 equiv), *n*-Bu₂BOTf (2 equiv), NEt₃ (2.6 equiv), CH₂Cl₂, then **17** (1 equiv), -78 to 0 °C, 1 h, then H₂O₂, pH 7.2 buffer, Et₂O, 25 °C, 48 h; (b) TBSOTf (1.2 equiv), 2,6-lutidine (1.8 equiv), CH₂Cl₂, 25 °C, 0.5 h, overall yields from **17**: **20a**, 83%; **20b**, 92%; (c) NaBH₄ (10 equiv), THF–H₂O, 25 °C, 16 h, **21a**, 77%; **21b**, 85%; (d) *m*-CPBA (1.5 equiv), CH₂Cl₂, 40 °C, 2 h, 98%; (e) K₂CO₃ (1 equiv), MeOH, 25 °C, 10 min, 90%; (f) DBU (1.6 equiv), CH₂Cl₂, 25 °C, 0.5 h, then CSCI₂ (4.3 equiv), CH₂Cl₂, 0 °C, 20 min, 100%; (g) **21** (1 equiv), pyridine (2 equiv), **23** (1.2 equiv), CH₂Cl₂, 2 h, **24a**, 81%; **24b**, 88%; (h) (Me₃Si)₃SiH (1.1 equiv), AIBN (0.4 equiv added over 6 h), PhH, 80 °C, **25a**, 44%; **25b**, 44%; (i) *n*-Bu₄NF (15 equiv), AcOH (15 equiv), THF, 25 °C, 96 h, **2**, 90%; **6**, 86%.

(>95%) *trans*-diastereoselectivity with (Me₃Si)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 group²³ (**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

(23) Enders, D.; Lausberg, V.; Del Signore, G.; Berner, O. M. *Synthesis* **2002**, 515–522.

(24) Spectroscopic and physical data were in excellent agreement with literature data for (–)-arctigenin and (–)-matairesinol: Rahman, M. M.; Dewick, P. M.; Jackson, D. E.; Lucas, J. A. *Phytochemistry* **1990**, *29*, 1971–1980. See also refs 4a and 12.

(25) Nishibe, S.; Tsukamoto, H.; Hisada, S.; Yamanouchi, S.; Takido, M. *Chem. Pharm. Bull.* **1981**, *29*, 2082–2085. See also ref 12.

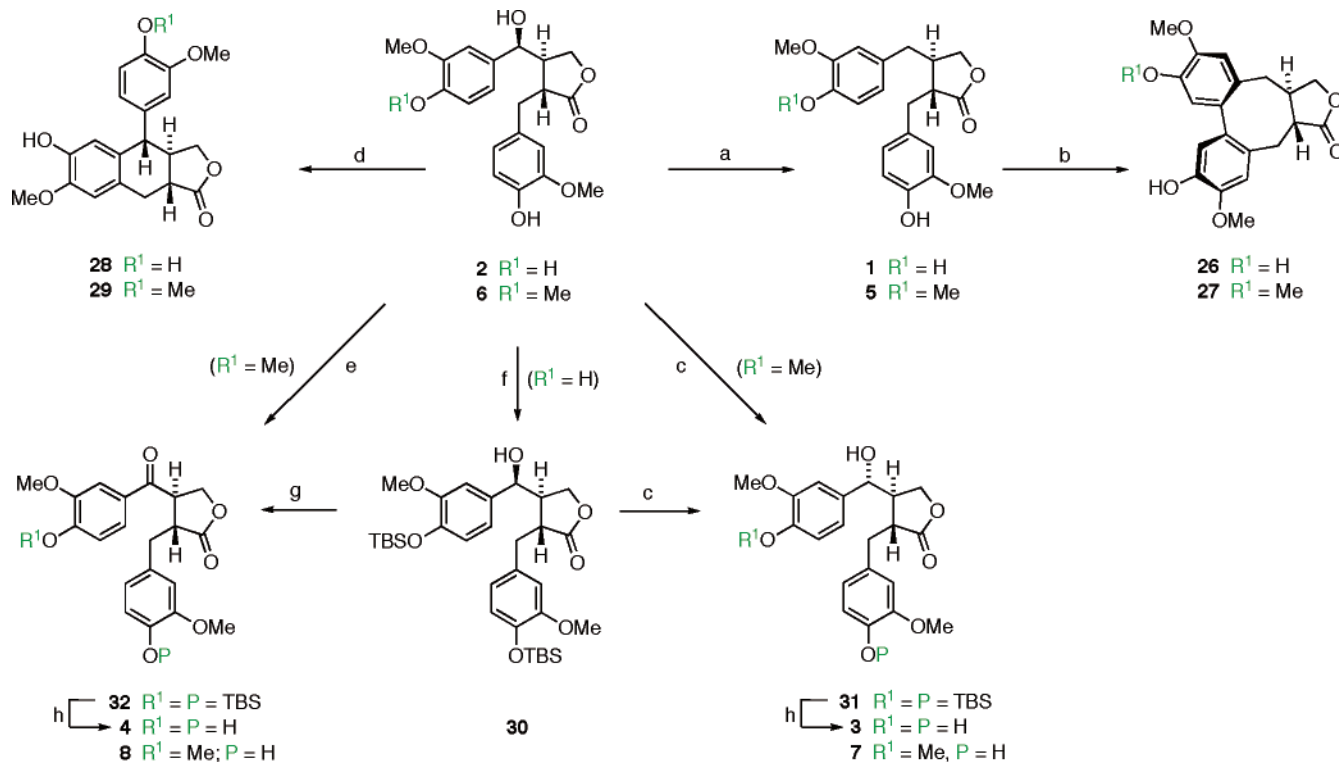
(26) Hughes, D. D.; Ward, R. S. *Tetrahedron* **2001**, *57*, 4015–4022.

(20) Mattinen, J.; Sjöholm, R.; Ekman, R. *ACH Models Chem.* **1998**, *135*, 583–590. The authors of this paper incorrectly assigned the configurations of the two 7-hydroxymatairesinol diastereoisomers. This error was recently corrected following X-ray analysis. See ref 11d.

(21) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017–3020.

(22) See the Supporting Information for full details.

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 carboxylation reaction are under way.

(27) Dhal, R.; Nabi, Y.; Brown, E. *Tetrahedron* **1986**, *42*, 2005–2016. See also refs 12 and 25.

Acknowledgment. We thank the Australian Research Council for funding.

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

OL049878B