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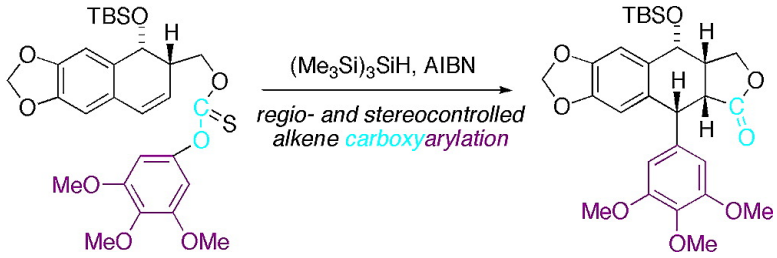

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The Intramolecular Carboxyarylation Approach to Podophyllotoxin

Aaron J. Reynolds,[‡] Andrew J. Scott,[†] Craig I. Turner,[†] 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

Received July 31, 2003; E-mail: sherburn@rsc.anu.edu.au

The aryl tetrahydronaphthalene lignan lactones have retained the interest of synthetic, medicinal, and biological chemists for over 50 years.[1,2] Whereas the natural product podophyllotoxin **1** (Figure 1) is a potent tubulin binding antimitotic agent, semisynthetic derivatives such as etoposide **2** are effective topoisomerase II poisons.[3] Both **1** and **2** are currently in clinical use, the former for the treatment of warts, with the latter being used extensively in cancer chemotherapy. In addition, new derivatives displaying improved water solubility and bioavailability are emerging, for example, GL 331 (**3**).

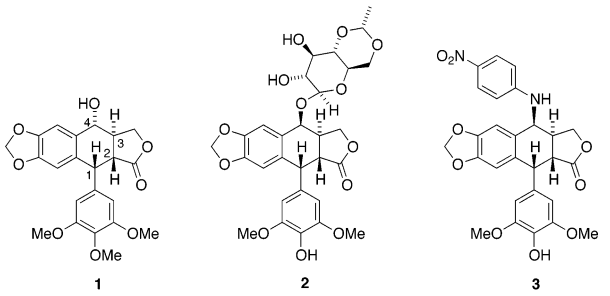


Figure 1. Selected aryl tetrahydronaphthalene lactones.

Over the years, many imaginative routes have been delineated for the stereoselective synthesis of aryltetrahydronaphthalene lignans.[1,4,5] C−C bond-forming events in these established routes involve Friedel−Crafts, Diels−Alder, Michael, and aldol reactions. Herein, we describe concise, highly convergent, and conceptually novel approaches to (−)-podophyllotoxin **1** and (+)-podophyllotoxin *ent*-**1** using a cascade radical reaction as the key step.

The natural product isopicropodophyllone[6] **4** (Figure 2) served as the primary goal for synthesis because methanolysis of the lactone would furnish a hydroxy ester which has previously been converted into podophyllotoxin.[5d] Aryl tetrahydronaphthalene lactone **5**, carrying a masked C-4 hydroxyl group *P*, would originate from thionocarbonate **6** as a result of intramolecular delivery of a carboxyl carbon to C-2 and an aromatic residue to C-1. This transformation requires a convoluted diversion from the traditional course of Robins' variation of the Barton−McCombie reaction.[7] Geometrical constraints on the two intramolecular C−C bond-forming events would control the stereochemistry at the two new stereocenters (i.e., syn- to the existing substituent at C-3), and the regiochemistry of substitution at the migrating aromatic group would be secured through an *ipso*-aromatic substitution phase in the mechanism (viz., **8** → **9** → **10**).

Two general approaches to thionocarbonates **6** were developed, one involving an asymmetric aldol/ring-closing metathesis sequence (Scheme 1), and the other involving a Meyers-type nucleophilic addition to a naphthyl oxazoline (Scheme 2). The former begins with an Evans *syn*-aldol reaction[8] between the dibutylboron

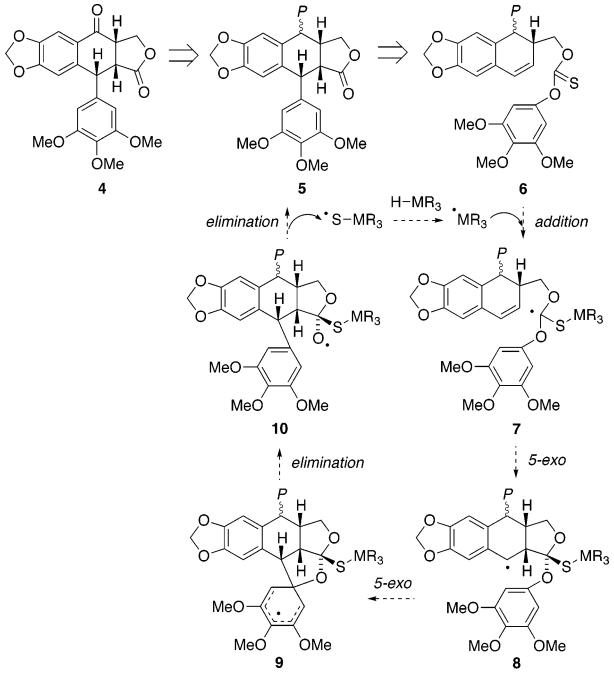
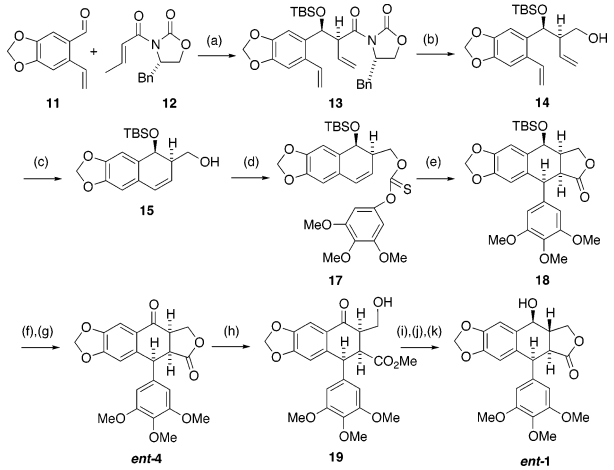


Figure 2. The intramolecular carboxyarylation route to podophyllotoxin.

Scheme 1. Evans Aldol-RCM Approach to (+)-Podophyllotoxin[a]



[a] (a) **12** (1.0 equiv), *n*-Bu_2BOTf (1.3 equiv), NEt_3 (1.7 equiv), CH_2Cl_2, then **11** (0.6 equiv), −78 °C → 0 °C, 1 h, then H_2O_2, pH 7.2 buffer, Et_2O, 25 °C, 14 h, then TBSOTf (1.0 equiv), 2,6-lutidine (1.5 equiv), CH_2Cl_2, 25 °C, 0.5 h, 78% overall, dr = 96:4; (b) $NaBH_4$ (15 equiv), THF−H_2O, 25 °C, 12 h, 94%; (c) Grubbs catalyst (0.10 equiv), CH_2Cl_2, 25 °C, 2 h, 91%; (d) pyridine (4 equiv), 3,4,5-$(OMe)_3C_6H_2OC(=S)Cl$ (**16**) (2 equiv), CH_2Cl_2, 25 °C, 2.5 h, 89%; (e) $(Me_3Si)_3SiH$ (1.1 equiv), AIBN (0.5 equiv added over 6 h), PhH, 80 °C, 8 h, 38%; (f) *n*-Bu_4NF (10 equiv), AcOH (10 equiv), THF, 25 °C, 8 h, 96%; (g) PCC (5.0 equiv), CH_2Cl_2, 25 °C, 5 h, 100%; (h) MeOH, H_2SO_4 (4 equiv), 25 °C, 2 h, **4**:**19** = 1:2; 89% isolated yield of **19** based upon recovered **4**; (i) DBU (1.0 equiv), THF, 25 °C, 6 h, 92%; (j) $LiEt_3BH$ (1.0 equiv), THF, −78 °C, 1 h; then SiO_2, MeOH, 56 °C, 2 h, 96%; (k) $ZnCl_2$, (2.0 equiv), 4 Å sieves, THF, 66 °C, 2.5 h, 81%.

[†] Australian National University.
[‡] University of Sydney.

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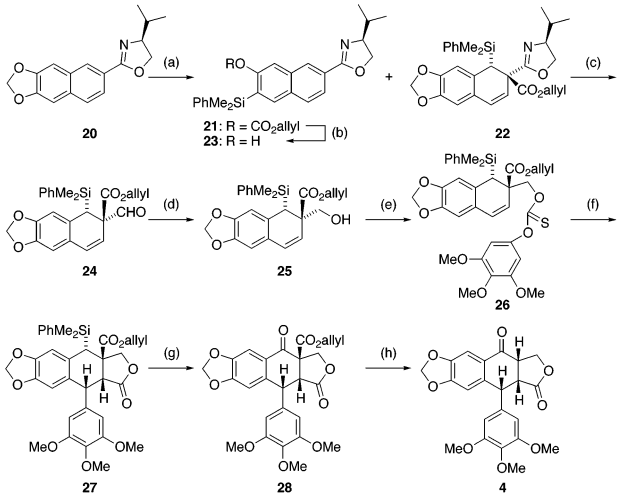
Scheme 2. Meyers Dearomatization Approach to (−)-Podophyllotoxin[a]



[a] (a) $PhMe_2SiLi$ (5.0 equiv), THF, −78 °C, 3 h, then allylchloroformate (7.5 equiv), −78 °C → 25 °C; (b) $KHCO_3$ (0.7 equiv), K_2CO_3 (2.5 equiv) MeOH−H_2O, 25 °C, 55 min, 30% of **23**, 57% of **22** over two steps; (c) MeOTf (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, then $NaBH_4$ (4.0 equiv) THF−MeOH, 25 °C, 30 min, then $(COOH)_2 \cdot 2H_2O$ (5.1 equiv), THF−H_2O, 25 °C, 16 h, 100% over three steps; (d) Bu_3SnH (2.0 equiv), SiO_2, PhMe, 80 °C, 10 h, 79%; (e) **16** (1.1 equiv), pyridine (2.0 equiv), CH_2Cl_2, 25 °C, 2 h, 99%; (f) $(Me_3Si)_3SiH$ (1.1 equiv), AIBN (0.6 equiv added over 14 h), PhH, 80 °C, 14 h, 40%; (g) $BF_3 \cdot 2AcOH$ (9.0 equiv), CH_2Cl_2, sealed tube, 50 °C, 27 h, then *m*-CPBA (6.9 equiv), KF (1.2 equiv), DMF, 25 °C, 1 h, then Dess−Martin periodinane (1.8 equiv), CH_2Cl_2, 25 °C, 30 min, 60% based on recovered **27** over three steps; (h) $Pd(OAc)_2$ (4 equiv), PPh_3 (8.0 equiv), HCO_2H (40 equiv), NEt_3 (50 equiv), THF, 25 °C, 43 min, 100%.

dienolate of crotonyl oxazolidinone **12** and 6-vinyl piperonal **11**.[9] After protection as the corresponding silyl ether **13** and reductive removal of the auxiliary, ring-closing metathesis of alcohol **14** with first generation Grubbs catalyst[10] gave the dihydronaphthalene-2-methanol **15** in excellent yield. Exposure to the chlorothionoformate derivative of 3,4,5-trimethoxyphenol **16**[11] proceeded smoothly. We were delighted to find that tris(trimethylsilyl)silane promoted the conversion of thionocarbonate **17** into alkene carboxyarylation product **18** in 38% yield.[12] Desilylation with buffered TBAF and oxidation with PCC gave (+)-isopicropodophyllone, which underwent acid-catalyzed transesterification to give methyl ester **19**. This compound was converted into (+)-podophyllotoxin *ent*-**1** through the reported[5d] three-step sequence involving selective epimerization at C-3, stereoselective ketone reduction, and *trans*-lactone formation.

The enantiomeric series was accessed by Meyers' elegant naphthalene dearomatization chemistry.[13] Thus, stereoselective nucleophilic addition of dimethylphenylsilyl-lithium to valine-derived 2-naphthyl oxazoline **20**,[14] followed by aza-enolate trapping with allyl chloroformate, furnished adduct **22** as a single diastereoisomer, within the limits of detection. This reaction was unexpectedly accompanied by C-6 S_NAr product **21**. Oxazoline **22** was converted into aldehyde **24**,[15] which was in turn reduced[16] to alcohol **25**. Following conversion into thionocarbonate **26**, exposure to tris(trimethylsilyl)silane gave aryl tetrahydronaphthalene lactone **27** in 40% yield. Fleming−Tamao oxidation[17] of the benzyl silane gave the alcohol, which was immediately oxidized to ketone **28**. Finally, Pd(0)-mediated deallylation-decarboxylation afforded (−)-isopicropodophyllone **4**.

In summary, an efficient and conceptually novel strategy for the stereocontrolled synthesis of aryl tetrahydronaphthalene lactone lignans has been developed. The late point of convergence instills true modularity in this approach, thereby facilitating SAR studies and inviting the application of combinatorial protocols. Work toward this end, in addition to optimization studies on the carboxyarylation reaction and further applications of this methodology, is under investigation in this laboratory.

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Supporting Information Available: Key experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra of new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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