

Total Synthesis of the Cytotoxic Guaipyridine Sesquiterpene Alkaloid (+)-Cananodine

Donald Craig*^[a] and Gavin D. Henry^[a]

Keywords: C–C coupling reactions / Catalysis / Claisen rearrangement / Microwave-assisted synthesis / Pyridine synthesis / Ring-closing metathesis

The enantiospecific total synthesis of the cytotoxic guaipyridine sesquiterpene alkaloid (+)-cananodine (**1**) is described. A chiral pool/chiral auxiliary based approach is described for the synthesis of a key oxazolidinone intermediate. Subsequent key steps involve diastereoselective oxazolidinone allylation, cycloheptenylmethanol formation using ring-closing

olefin metathesis, microwave-assisted decarboxylative Claisen rearrangement reaction, and use of a novel pyridine-forming method.

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Cananodine is a naturally occurring guaipyridine sesquiterpene alkaloid which shows sub-micromolar activity against Hep G2 human hepatocarcinoma cell lines. It was isolated from the perfumery tree *Cananga odorata* (ylang ylang) in 2001 by workers at the Kaohsiung Medical University in Taiwan, who assigned the structure **1** using NMR and MS techniques.^[1] Cananodine is structurally related to β -patchoulene (**2**),^[2] and patchouli pyridine (**3**).^[3]

We have recently initiated a major new programme for the development of methods for the de novo synthesis of polysubstituted arenes from unsaturated, acyclic precursors. Part of this strategy is based on the recognition that 1,5-dicarbonyl compounds bearing a C-3 leaving group are suitably disposed to enter into redox-neutral condensation reactions with ammonia, to provide pyridines. We have demonstrated the effectiveness of this approach for the synthesis of 2,4,6-trisubstituted pyridines, in which the requisite 1,5-dicarbonyl substrates possessing a 4-tolylsulfonyl substituent at C-3 were synthesised by oxidative cleavage of 1,6-dienes, using (allyl)Pd⁰ chemistry (Scheme 1).^[4] We were keen to apply the new pyridine-forming method to the synthesis of cananodine, because it would demonstrate the compatibility of the method with a multi-functional substrate. However, we were mindful that the 2,3,6-trisubstitution pattern present in the natural product was incompatible with the palladium(0)-based approach employed during method development,^[4] because it would require access to a 1,6-diene **4** in which one of the required C–C bond-forming reactions had taken place at the more substituted terminus

of the requisite allylic electrophile (Scheme 1). In light of this analysis, we chose instead to use the decarboxylative Claisen rearrangement (dCr) reaction recently uncovered in our laboratory.^[5] This is a new, catalytic variant of the classical Ireland–Claisen rearrangement, in which silyl ketene acetals generated in situ from allylic α -tosyl esters under weakly basic conditions undergo [3,3]-sigmatropic rearrangement followed by acetate-induced decarboxylation to give γ,δ -unsaturated sulfones directly.^[6] Unlike most (π -allyl)metal-based methods, this sigmatropic rearrangement mediated approach enables *regiospecific* allylation α to the arylsulfonyl moiety. This communication describes the application of the dCr reaction in conjunction with our new pyridine chemistry in the first total synthesis of (+)-cananodine.

The retrosynthetic analysis of **1** is depicted in Scheme 2. Diene **4** (R = CO₂Me) was envisaged to be the product of dCr reaction of the substituted (4-tolylsulfonyl)acetate **5**, which indicated the substituted cycloheptenylmethanol **6** as a key intermediate. This would be synthesised by ring-closing olefin metathesis of the diene **7**, the product of diastereoselective allylation of the *N*-acyloxazolidinone **8**.

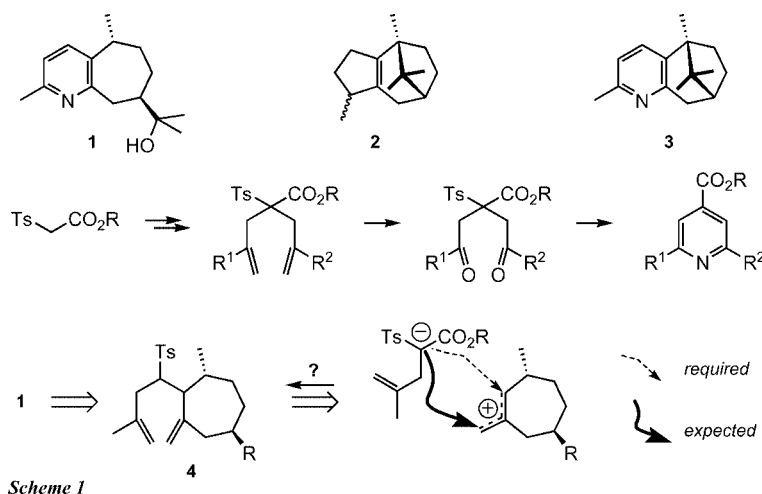
Compound **8** could be prepared in quantities viable for the planned total synthesis by the sequence depicted in Scheme 3. Straightforward regioselective oxidative cleavage^[7] of (*R*)-(-)-citronellene with reductive workup, followed by 4-tolylsulfonylation and cyanide displacement gave the nitrile **9**, which upon hydrolysis, acid chloride formation and condensation with the lithio salt of the (*S*)-valinol-derived oxazolidinone gave **8**.^[8]

With the *N*-heptenoyloxazolidinone **8** in hand, attention was turned to its diastereoselective allylation (Scheme 4). The requisite allylic bromide **12** was straightforwardly prepared from commercially available 2-methylenepropane-1,3-diol by NaH-mediated monosilylation^[9] using TBDPSCl,

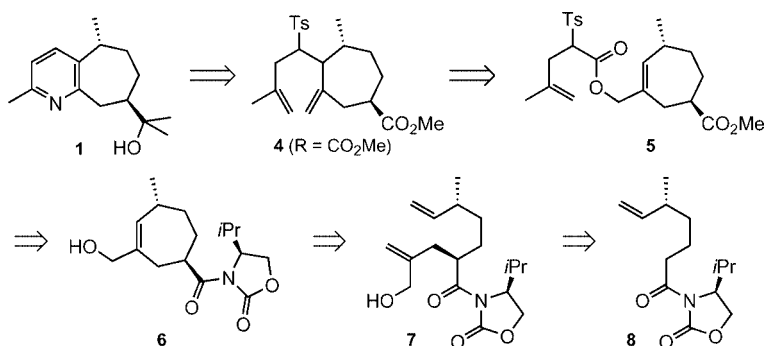
[a] Department of Chemistry, Imperial College London, South Kensington Campus, London SW7 2AZ, UK
Fax: +44-20-7594-5868

E-mail: d.craig@imperial.ac.uk

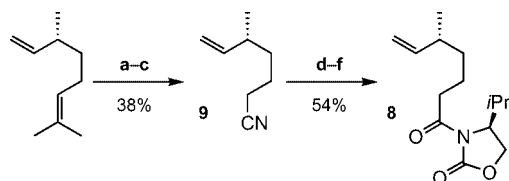
Supporting information for this article is available on the WWW under <http://www.eurjoc.org> or from the author.



Scheme 1.



Scheme 2.

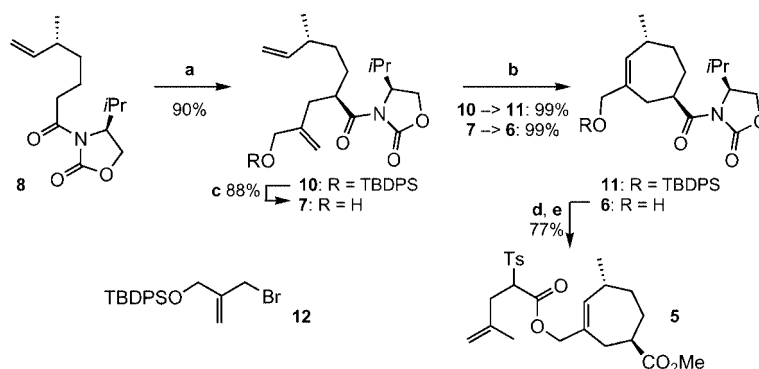


Scheme 3.

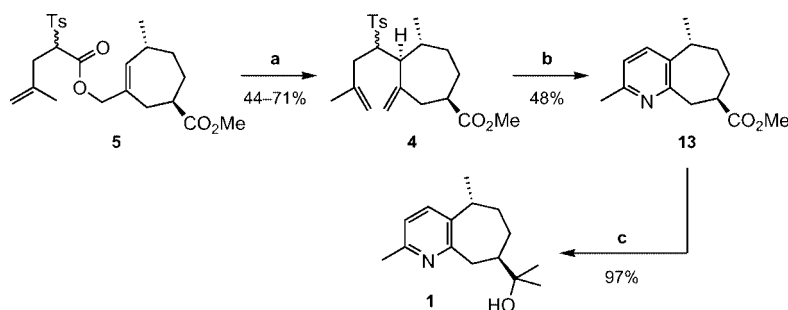
followed by 4-tolylsulfonylation and S_N2 reaction with lithium bromide in diethyl ether. Addition of this bromide to the lithium enolate of **8** in THF/DMPU at -78 °C to -20 °C resulted in diastereoselective allylation, providing the 1,7-diene **10** in 90% yield. Ring-closing olefin metathesis (RCM) could be carried out at this stage; cycloheptene **11** was formed in virtually quantitative yield upon reaction of **10** in the presence of 5 mol-% of Grubbs' second-generation catalyst in dichloromethane. However, problems were encountered with the subsequent desilylation: exposure of **11** both to acidic (methanolic HCl) and to basic (TBAF) conditions resulted in significant decomposition, and we had been concerned beforehand that basic reagents would lead to erosion of *de* by epimerisation of the stereocentre α to the acyl moiety. These problems led to the adoption of a sequence modified simply by reversing the order of the RCM and deprotection steps. Thus, treatment of **10** with methanolic HCl, and reaction of the product acyclic allylic

alcohol **7** with Grubbs' catalyst gave the cycloheptenylmethanol **6** in 88% yield over the two steps from **10**. Removal of the oxazolidinone auxiliary was accomplished at this stage by methanolysis under basic conditions, after which esterification of the primary alcohol with 4-methyl-2-(4-tolylsulfonyl)-4-pentenoic acid^[10] completed in 77% over two steps the assembly of dCr substrate **5** (Scheme 4).

The stage was now set to assess the effectiveness of the dCr reactions of substrate **5**. Initial studies carried out using conventional thermal conditions were discouraging; treatment of **5** with *N,O*-bis(trimethylsilyl)acetamide (BSA) and potassium acetate in toluene under reflux failed to yield any of the desired rearrangement/decarboxylation product. Instead, 3-methyl-1-(4-tolylsulfonyl)-3-butene was formed as the sole identifiable product in 52% yield, presumably by hydrolysis of the 4-tolylsulfonyl-substituted ester followed by decarboxylation of the product 4-methyl-2-(4-tolylsulfonyl)-4-pentenoic acid. In marked contrast, substrate **5** underwent highly stereoselective dCr reaction under microwave-irradiation conditions to give the 1,6-diene **4** in 44–71% yield as a mixture of two of the four possible diastereoisomers. Although we have not determined the stereochemistry of the two products, structures **4** are proposed based on the assumption that formation of the new C–C bond takes place *anti* to the vicinal methyl substituent. Ozonolysis of the dienes **4** with sequential addition of tri-



Scheme 4.



Scheme 5.

phenylphosphane and ethanolic ammonia gave the pyridine **13** in 48% yield. Finally, exposure of **13** to excess methylmagnesium bromide gave (+)-cananodine (**1**) in almost quantitative yield. The completion of the synthesis of **1** is depicted in Scheme 5.

Compound **1** prepared as described above gave ^1H and ^{13}C NMR spectra which are identical to ones kindly provided by Professor Yang-Chang Wu of Kaohsiung Medical University.^[11] Professor Wu and co-workers obtained their data from the isolated, natural sample; we have been unable to locate a source of the required plant material. However, the optical rotation value obtained by us $\{[\alpha]_D^{25} = +17.9$ ($c = 1.34$, CHCl_3) $\}$ differs significantly from that obtained by Professor Wu's team $\{[\alpha]_D^{25} = -76.2$ ($c = 0.06$, CHCl_3) $\}$; of particular concern to us was the different sign of the two specific rotation values. From the quoted specific rotation, concentration (0.6 mg mL^{-1}) and path length (0.1 dm)^[12] of the solution of natural **1** on which the optical activity was measured by Professor Wu's team, a measured rotation of -0.0046° may be inferred. Our rotation, measured on a solution having a concentration of 13.4 mg mL^{-1} with a path length of 0.25 dm was $+0.06^\circ$, and we suggest that the greater order of magnitude of our value makes it significantly less susceptible to experimental error.

In spite of the conflicting optical rotation values described above, the results described herein demonstrate that an unambiguous synthesis of structure **1** has been achieved: the spectroscopic homogeneity of late-stage material generated using the (–)-(R)-citronellene-based route shows that intermediates **4**, **5**, **6**, **7**, **10** and **13** together with cananodine **1** are formed as single stereoisomers. This clearly rules out

the possibility that optically impure (–)-(R)-citronellene gave rise to the discrepancy in optical behaviour, because (S)-valine was the ultimate source of the second of the two stereocentres present in the target structure; any erosion of the optical purity of either chiral pool source would have resulted in the formation of mixtures of diastereomers.

In summary, the first total synthesis of (+)-cananodine has been achieved using new Claisen rearrangement and pyridine chemistry developed within our laboratory. Current studies are underway to apply this powerful combination of methods to other natural and non-natural pyridine-containing structures. The results of these investigations will be reported in due course.

Supporting Information (see footnote on the first page of this article): Full experimental details and spectroscopic information are provided for compounds **1** and **4–13**.

Acknowledgments

We thank EPSRC and Aventis CropScience (supported Quota Studentship to G. D. H.) for financial support of this research. We extend our gratitude to Professor Yang-Chang Wu, Kaohsiung Medical University, Taiwan for valuable discussions and for providing copies of NMR spectra of authentic cananodine.

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- [8] Spectroscopic data for **8**: R_f = 0.29 (20% EtOAc/petroleum ether). $[\alpha]_D^{24}$ = +73.9 (c = 6.0, CHCl₃); IR (film): $\tilde{\nu}_{\max}$ = 2954, 2929, 2885, 1734, 1471, 1464, 1363, 1255, 1178, 1097, 837, 779, 669 cm⁻¹. ¹H NMR (400 MHz): δ = 5.68 (ddd, J = 17.5, 10.5, 7.5 Hz, 1 H, CH alkene), [4.96 (ddd, J = 17.0, 2.0, 1.0 Hz, 1 H), and 4.93 (ddd, J = 11.5, 2.0, 1.0 Hz, 1 H), CH₂ alkene $\times$ 2], 4.43 (ddd, J = 8.5, 3.5, 3.5 Hz, 1 H, CHN), [4.26 (dd, J = 9.0, 8.5 Hz, 1 H), and 4.20 (dd, J = 9.0, 3.0 Hz, 1 H), CH₂O $\times$ 2], 2.43–2.33 [m, 1 H, CH(CH₃)₂], 2.20–2.11 (1 H, m, δ amide), 1.67–1.62 (m, 2 H, β amide), 1.40–1.32 (q, J = 8.0 Hz, 2 H, γ amide), 1.00 (d, J = 7.0 Hz, 3 H, CH₃), [0.92 (d, J = 7.0 Hz, 3 H), and 0.88 (d, J = 7.0 Hz, 3 H), Me of isopropyl $\times$ 2]. ¹³C NMR (75 MHz): δ = 173.3 (C amide), 154.1 (C carbamate), 144.3 (CH alkene), 112.9 (CH₂ alkene), 63.3 (OCH₂), 58.4 (NCH), 37.7 (CH δ amide), [35.9, 35.6 (CH₂ α , γ amide $\times$ 2)], 28.4 [CH(CH₃)₂], 22.2 (CH₂ β amide), 20.2 (CH₃ Me), [18.0 and 14.7 (CH₃ of isopropyl $\times$ 2)]. MS(Cl): m/z = 271 [M + NH₄]⁺, 254 [MH]⁺, 184, 171, 130, 124, 84, 49; calcd. for C₁₄H₂₃NO₃ [MH]⁺ 254.1756, found 254.1750.
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- [11] See the Supporting Information for spectroscopic data for natural and synthetic **1**, and full experimental details and characterisation data for all synthetic intermediates.
- [12] Personal communication from Professor Yang-Chang Wu.

Received: May 11, 2006

Published Online: July 3, 2006