

## A Simple Total Synthesis of Viburtinal

Jean-Louis Brayer,<sup>a</sup> Jean-Pierre Alazard,<sup>b</sup> and Claude Thal<sup>\*b</sup>

<sup>a</sup> *Centre de Recherche Roussel-Uclaf, 102, route de Noisy, 93230, Romainville, France*

<sup>b</sup> *Institut de Chimie des Substances Naturelles du C.N.R.S., 91190, Gif-sur-Yvette, France*

Viburtinal (**2**) has been synthesised from 2-cyclopentadienylpropanol (**3**) *via* the dihydrocyclopenta[*c*]pyran (**1c**), which was itself prepared *via* regioselective formylation.

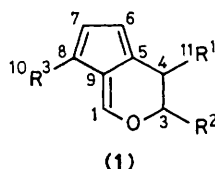
A direct and efficient synthesis of the dihydrocyclopenta[*c*]pyrans (**1a**) and (**1b**)<sup>1</sup> has been developed in our laboratory potentially providing access to three of the five families of cyclopentane monoterpenes: the iridoids, the secoiridoids, and the aminoterpene alkaloids.<sup>2</sup> All these products are known either for their role in the biogenesis of indole and Ipeca alkaloids<sup>3</sup> or for their interesting biological activities.<sup>4</sup>

To illustrate our approach to these interesting systems we

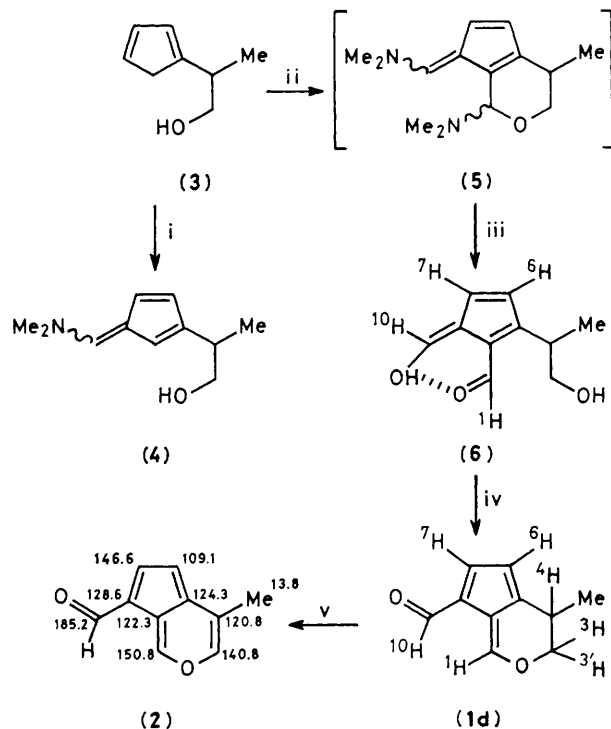
report here the first synthesis of viburtinal (**2**),<sup>5†</sup> a non-glucosidic iridoid isolated from the leaves of *Viburnum tinus*<sup>5</sup> and *Viburnum opulus*<sup>5</sup> Caprifoliaceae.

The dihydrocyclopenta[*c*]pyran (**1c**) was prepared by a

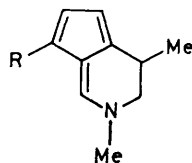
† This work was presented as a poster at the 8th Symposium on Heterocyclic Chemistry, 6–8th October 1982, Rennes, France.



- (1)  
 a;  $R^1 = \text{HC(OMe)}_2$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{H}$   
 b;  $R^1 = \text{HC(OMe)}_2$ ,  $R^2 = \text{Me}$ ,  $R^3 = \text{CHO}$   
 c;  $R^1 = \text{Me}$ ,  $R^2 = R^3 = \text{H}$   
 d;  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ,  $R^3 = \text{CHO}$



Compound (3) is a mixture of cyclopentadienyl-1-yl and -2-yl isomers. *Reagents*: i,  $\text{Me}_2\text{NCH(OMe)}_2$  (1.1 equiv.), 1,2-dimethoxyethane (DME), 40 °C; ii,  $\text{Me}_2\text{NCH(OMe)}_2$  (5 equiv.), DME, reflux, 24 h, concentration *in vacuo*; iii, 1 M-NaOH and  $(\text{CO}_2\text{H})_2$  in DME (pH 4); iv, anhydrous  $\text{C}_6\text{H}_6$  and anhydrous  $(\text{CO}_2\text{H})_2$  catalyst, reflux, 1 h; v, DDQ (1.5 equiv.), anhydrous  $\text{C}_6\text{H}_6$ , reflux, 4 h.



- (7)  $R = \text{H}$   
 (8)  $R = \text{CHO}$

short sequence of reactions from the cyclopentadienylpropanol (3) [itself prepared in two steps from sodium cyclopentadienide and ethyl 2-bromopropionate in tetrahydrofuran (THF) at -78 °C;  $\text{LiAlH}_4$ -THF, reflux]. Formylation of (3) with  $\text{HCO}_2\text{Et}$ - $\text{EtONa}$  in THF at -20 °C<sup>6</sup> proved to be highly regioselective giving after cyclization (oxalic acid and benzene) the triene (1c) in good yield. When dimethylformamide (DMF) dimethyl acetal<sup>7</sup> [ $\text{Me}_2\text{NCH(OMe)}_2$ ] was used however, regioselective  $\beta$ -formylation (*via* amino-formylation)<sup>8</sup> was observed leading to the amino-

fulvene (4).  $\alpha$ -Regioselectivity possibly arises *via* prior *O*-formylation followed by rearrangement to carbon, whereas DMF dimethyl acetal probably reacts differently formylating first at the  $\beta$ -position for steric reasons. These hypotheses will be discussed elsewhere.<sup>10</sup> Utilizing this interesting result, we found that when an excess of this reagent was used formylation at both the  $\alpha$ - and  $\beta$ -positions occurred leading *via* the unstable intermediate (5) to the hydroxy-fulvene (6).<sup>†</sup> Subsequent cyclization of this compound gave the desired triene (1d)<sup>‡</sup> [30% from (3)].

Dehydrogenation of the triene (1d) to the natural product viburtinal (2) was accomplished using dichlorodicyanobenzoquinone (DDQ) in refluxing benzene (55%). The physical constants observed for our synthetic product were identical with those published.<sup>§</sup>

Further applications of this transformation to the preparation of iridoids and secoiridoids will be published elsewhere,<sup>10</sup> and its extension to the synthesis of monoterpene alkaloids (like tecomanine) and analogues (7) and (8) will also be presented.<sup>9†</sup>

We thank Dr. P. Potier for his interest and advice and C.N.R.S. for financial assistance (J.L.B.).

Received, 29th November 1982; Com. 1369

## References

- (a) J. P. Alazard, J. L. Brayer, A. Tixidre, and C. Thal, poster presentation at the 7th Symposium on Heterocyclic Chemistry, 7-9th July, 1981, Marseille, France; (b) abstracted in part from the thesis of J. L. Brayer, Orsay University, France, 1982; (c) J. P. Alazard, J. L. Brayer, A. Tixidre, and C. Thal, full paper will be submitted for publication to *Tetrahedron*.
- R. Hegnauer, *Pharm. Acta Helv.*, 1966, **41**, 577; O. Stricher and U. Junod-Busch, *ibid.*, 1975, **50**, 127, and references therein.
- R. Thomas, *Tetrahedron Lett.*, 1961, 544; E. Wenkert, *J. Am. Chem. Soc.*, 1962, **84**, 98; 'Indole and Biogenetically Related Alkaloids,' eds. J. D. Philipson and M. H. Zenk, Academic Press, London, 1980.
- H. Wagner and P. Wolff, 'New Natural Products and Plant Drugs with Pharmacological, Biological, or Therapeutical Activity,' Springer Verlag, Berlin, Heidelberg, New York, 1977.
- (a) R. P. Godeau, J. C. Rossi, and I. Fouraste, *Phytochemistry*, 1977, **16**, 604; (b) R. P. Godeau, Y. Pelissier, and I. Fouraste, *Trav. Soc. Pharm. Montpelli.*, 1978, **38**, 343.
- For analogous conditions for formylation of cyclopentadiene itself see K. Hafner, G. Schultz, and K. Wagner, *Liebigs Ann. Chem.*, 1974, **678**, 39.
- For a recent review see R. F. Abdulla and R. S. Brinkmayer, *Tetrahedron*, 1979, **35**, 1675.
- For aminoformylation with DMF dimethyl acetal of cyclopentadiene itself see for example H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodte, and J. Spille, *Chem. Ber.*, 1956, **89**, 2060; H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Liebigs Ann. Chem.*, 1961, **641**, 1.
- J. L. Brayer, J. P. Alazard, and C. Thal, to be submitted for publication to *Tetrahedron Lett.*

<sup>†</sup> <sup>1</sup>H N.m.r.  $\delta$  ( $\text{CDCl}_3$ ;  $\text{SiMe}_4$ ;  $J$ -values in Hz): for (6), 1.30 (3H, d, Me), 2.89 (1H, s, OH), 3.08-3.76 (3H, m,  $\text{CH}_2$  and 4-H), 6.45 (1H, AB,  $J_{6,7}$  4, 6-H), 7.33 (1H, AB  $\times$  d,  $J_{6,7}$  4,  $J_{7,10}$  ca. 1, 7-H), 8.49 (1H, s, 10-H), 8.81 (1H, s, 1-H), and 16.25 (1H, s, O-H  $\cdots$  O); for (1d), 1.27 (3H, d,  $J$  6.5, Me), 3.17 (1H, m, 4-H), 3.89 (1H, ABX,  $J_{3,3'}$  11,  $J_{3',4}$  11, 3-H'), 4.39 (1H, ABX,  $J_{2,3}$  11,  $J_{3,4}$  5.25, 3-H), 6.15 (1H, AB  $\times$  d  $\times$  d,  $J_{6,7}$  2.6,  $J_{6,4}$  1.5,  $J_{6,1}$  1, 6-H), 7.15 (1H, AB,  $J_{6,7}$  2.6, 7-H), 8.21 (1H, s,  $J_{1,6}$  ca. 1, 1-H), and 9.65 (1H, s, 10-H).

<sup>§</sup> <sup>13</sup>C N.m.r. data ( $\delta$ ,  $\text{CDCl}_3$ ) for viburtinal (2) are indicated on the formula. For other physical constants see ref. 5b.