

may encourage formation of an intermediate where none exists in less highly stabilized systems.

These results do not provide any direct information about the electronic nature of the reaction intermediate. In particular, three likely possibilities exist: a biradical, which may be a singlet or a triplet, a zwitterion, or a hybrid showing properties intermediate between these two extremes. We are continuing to investigate the chemical properties of this species in order to characterize it more precisely.

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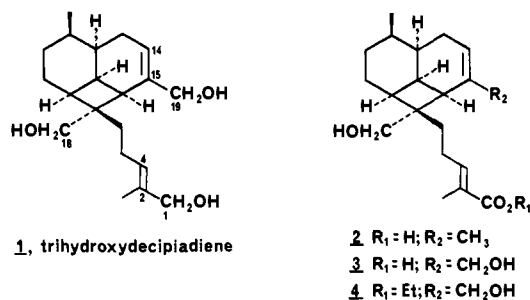
## Total Synthesis of ( $\pm$ )-Trihydroxydeciadiene

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The decipiene diterpenes (1-3) possess a structurally unique skeleton based on the tricyclo[5.3.1.0<sup>3,11</sup>]undecane ring system. These unusual compounds were isolated from the resinous coating of the Australian plant *Eremophila decipiens*, and their structures were established by a combination of chemical and X-ray studies.<sup>1,2</sup>



We describe an efficient approach to this novel tricyclic skeleton, and its application to the first total synthesis of a member of this interesting group of diterpenes, ( $\pm$ )-trihydroxydeciadiene (1).

Our strategy for the construction of the decipiene ring system is illustrated in Scheme I by the synthesis of the key intermediate 9. Cycloaddition of dichloroketene to the diene 5,<sup>3,4</sup> followed by

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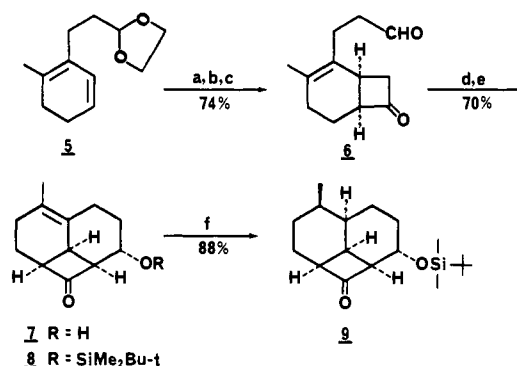
(1) (a) Ghisalbetti, E. L.; Jefferies, P. R.; Sheppard, P. *Tetrahedron Lett.* 1975, 1775. (b) Indem, *Tetrahedron* 1980, 36, 3253. (c) Maslen, E. N.; Sheppard, P. N.; White, A. H.; Willis, A. C. *J. Chem. Soc., Perkin Trans. 2* 1976, 263. (d) Recently, the structure of a new decipiene diterpene, which lacks the 2(4) unsaturation of 1-3, has been determined: Croft, K. D.; Ghisalbetti, E. L.; Jefferies, P. R.; Marshall, D. G.; Raston, C. L.; White, A. H. *Aust. J. Chem.* 1980, 33, 1529.

(2) The nomenclature for these compounds is based on the trivial name, decipiene, given to the parent hydrocarbon,<sup>1a</sup> and its assigned numbering system, which is shown (in part) in structure 1 of this paper. Thus, the complete name for 1 is 1,18,19-trihydroxydeci-2(4),14-diene.<sup>1b</sup> We omit the number designations hereafter for convenience.

(3) Prepared in five steps from 4-carboxy-3-methyl-2-cyclohexen-1-one (Hagemann's ester): (i) 2-(2-bromoethyl)-1,3-dioxolane,<sup>5</sup> KO-*t*-Bu, THF, reflux; (ii) 2 N aqueous NaOH (1.5 equiv), MeOH, 25 °C; (iii) 75 °C, 1 mm, 12 h; (iv) H<sub>2</sub>NNHTs, TsOH-Py, THF, 25 °C; (v) MeLi (2.5 equiv), Et<sub>2</sub>O, 0 °C.<sup>6</sup> The overall yield of 5 [bp 60-62 °C (0.03 mm); NMR (CDCl<sub>3</sub>)  $\delta$  5.79 (1 H, d,  $J$  = 9.7 Hz), 5.63 (1 H, m), 1.73 (3 H, br s)] was 35%.

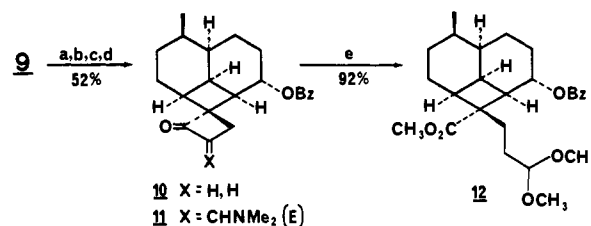
(4) All new compounds were fully characterized by spectroscopic means (NMR, IR, MS) and gave satisfactory elemental analysis (crystalline compounds) or precise mass measurement. All yields correspond to isolated amounts of purified products.

### Scheme I<sup>a</sup>



<sup>a</sup> Reagents: (a) Cl<sub>2</sub>, CHCOCl, Et<sub>3</sub>N, hexane, 25 °C, 16 h.<sup>7</sup> (b) Zn, NH<sub>4</sub>Cl, MeOH, 25 °C. (c) 2 N HCl, THF. (d) 0.1 M BaO/MeOH, 25 °C, 10 h. (e) *t*-BuMe<sub>2</sub>SiCl, 4-(dimethylamino)-pyridine (DMAP), DMF, 25 °C.<sup>11</sup> (f) H<sub>2</sub> (1 atm), 10% Pd/Al<sub>2</sub>O<sub>3</sub>, MeOH.

### Scheme II<sup>a</sup>



<sup>a</sup> Reagents: (a) 1-Lithiocyclopropyl phenyl sulfide, THF, -78 °C. (b) (1) MeOH, Dowex 50W-X8 resin; (2) benzoic anhydride, DMAP, CH<sub>2</sub>Cl<sub>2</sub>. (c) SnCl<sub>4</sub> (1 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 0 °C, 10 min. (d) (Me<sub>2</sub>N)<sub>3</sub>CHO-*t*-Bu, PhH, 60 °C. (e) *p*-TsOH (1 equiv), MeOH, 50 °C, 12 h.

dechlorination and hydrolysis afforded the aldehyde 6 [bp 93-95 °C (0.02 mm); NMR (CDCl<sub>3</sub>)  $\delta$  9.78 (1 H, t,  $J$  = 1.4 Hz), 1.67 (3 H, br s)] in 74% overall yield. Attempts to effect aldol cyclization of 6 were unsuccessful under a variety of conditions.<sup>8</sup> However, methanolic barium oxide was found to be a remarkably effective catalyst for this reaction, giving a single ketol 7,<sup>9</sup> which was isolated in 70% yield after protection as its *tert*-butyldimethylsilyl ether 8 [mp 50-51 °C; NMR (CDCl<sub>3</sub>)  $\delta$  4.08 (1 H, ddd,  $J$  = 4.5, 3.0, 3.0 Hz), 1.69 (3 H, d,  $J$  = 2.3 Hz); IR (neat)  $\nu_{\max}$  1770 cm<sup>-1</sup>]. Hydrogenation of 8 at atmospheric pressure occurred exclusively from the more accessible convex face of the molecule to give 9 [mp 59-60 °C; NMR (CDCl<sub>3</sub>)  $\delta$  4.25 (1 H,

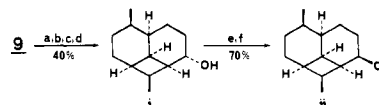
(5) Buchi, G.; Wuest, H. *J. Org. Chem.* 1969, 34, 1122.

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(8) Reaction of 6 under a number of aldol conditions led to either complex mixtures (e.g., KOH, NaOH, K<sub>2</sub>CO<sub>3</sub>, NaOMe, or Mg(OMe)<sub>2</sub> in MeOH; KO-*t*-Bu in Et<sub>2</sub>O) or no reaction (pyrrolidine/HOAc in PhH; DBN in CH<sub>2</sub>Cl<sub>2</sub>).

(9) The orientation of the hydroxyl was assigned on the basis of the following observations. The alcohol ii, prepared as indicated from its more polar isomer i, showed a distinct downfield shift (0.15 ppm relative to i) of its <sup>1</sup>H NMR signal corresponding to the methyl group on the cyclobutane ring.<sup>10</sup>

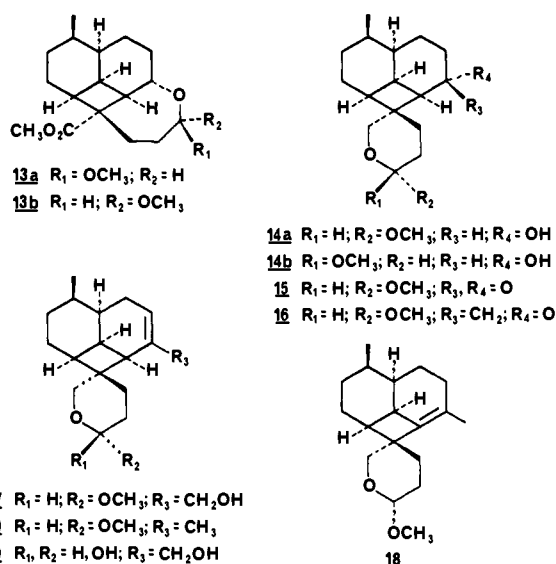


(a) MeLi, Et<sub>2</sub>O, -78 °C; (b) POCl<sub>3</sub>/DMAP, pyridine, 25 °C; (c) H<sub>2</sub>, Pd/C, EtOAc; (d) Dowex 50W-X8 resin, MeOH; (e) PCC, CH<sub>2</sub>Cl<sub>2</sub>; (f) DIBAL, Et<sub>2</sub>O, -78 °C.

(10) For a similar deshielding effect, see: Cimarusti, C. M.; Wolinsky, J. *J. Org. Chem.* 1971, 36, 1871. See also: Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed.; Pergamon Press: Oxford, 1969; p 71-72.

(11) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* 1979, 99.

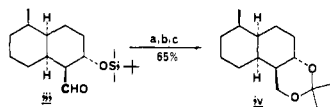
Chart I



ddd,  $J = 9.2, 7.8, 1.4$  Hz), 0.89 (3 H, d,  $J = 6.0$  Hz)] in 88% yield and a small amount (<5%) of an aldehyde resulting from hydrogenolysis of the four-membered ring.<sup>12,13</sup>

Having developed a convenient route to the cyclobutanone **9**, we turned our attention to the transformation of its carbonyl carbon into the quaternary center of **1**, as shown in Scheme II. While **9** failed to react satisfactorily with various Wittig-type reagents, the Trost spiroannulation procedure<sup>15</sup> provided a single spirocyclobutanone **10** [mp 91–92 °C; NMR (CDCl<sub>3</sub>)  $\delta$  5.24 (1 H, m), 2.84 (4 H, m), 0.91 (3 H, d,  $J = 5.5$  Hz); IR (neat)  $\nu_{\text{max}}$  1765, 1700 cm<sup>-1</sup>] in 52% yield. The orientation of the spirofusion was tentatively assigned to be as shown, by analogy to known examples.<sup>15</sup> Activation of the spirocyclobutanone toward fragmentation by substituting a formyl group at the  $\alpha$  position<sup>16</sup> proceeded in poor yield using standard procedures. However, treatment of **10** with *tert*-butoxybis(dimethylamino)methane<sup>17</sup> (PhH, 60 °C) afforded the crystalline vinylogous amide **11** [mp 178–181 °C; NMR (CDCl<sub>3</sub>)  $\delta$  6.86 (1 H, t,  $J = 1.5$  Hz), 2.85 (6 H, s), 0.88 (3 H, d,  $J = 5.5$  Hz); IR (neat)  $\nu_{\text{max}}$  1695, 1605 cm<sup>-1</sup>] in nearly quantitative yield. Heating **11** with 1 equiv of *p*-toluenesulfonic acid in methanol resulted in ring opening to give **12** [NMR (CDCl<sub>3</sub>)  $\delta$  4.08 (1 H, t,  $J = 5.5$  Hz), 3.72 (3 H, s), 0.90 (3 H, d,  $J = 5.2$  Hz); IR (neat)  $\nu_{\text{max}}$  1710 cm<sup>-1</sup>] in 92% overall yield from **10**. This reaction presumably proceeds via methanolysis of the enamide, followed by an acid-catalyzed retro-Claisen-type process.<sup>18</sup> The assigned stereochemistry was verified at this point

(12) The structure of the aldehyde has been assigned as **iii** on the basis of spectral data [NMR (CDCl<sub>3</sub>)  $\delta$  9.80 (1 H, d,  $J = 2.5$  Hz); IR (neat)  $\nu_{\text{max}}$  1730 cm<sup>-1</sup>] and the following transformation:



(a) DIBAH, Et<sub>2</sub>O; (b) MeOH, Dowex 50W-X8 resin; (c) dimethoxypropane, TsOH·Py, CH<sub>2</sub>Cl<sub>2</sub>.

(13) The amount of hydrogenolysis was substantial (15–20%) when 10% Pd/C was used as catalyst. While hydrogenolysis of strained cyclobutane bonds is well preceded,<sup>14</sup> we are not aware of another example of reduction of a cyclobutanone carbon-carbon bond.

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(15) (a) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Rigby, J. H. Bogdanowicz, M. *J. Am. Chem. Soc.* **1977**, *99*, 3080. (b) Trost, B. M.; Keeley, D. E.; Arndt, H. C.; Bogdanowicz, M. *J. Am. Chem. Soc.* **1977**, *99*, 3088.

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(18) See ref 16 for an analogous fragmentation of an  $\alpha$ -formylcyclobutanone and ref 17b for the observation of hydrolytic ring opening of a similar vinylogous amide.

by the transformation of **12** into the cyclic acetals **13a** and **13b** [(1) 0.1 N KOH/MeOH, 25 °C. (2) TsOH·Py, CH<sub>2</sub>Cl<sub>2</sub>; 71% yield]. Dreiding models reveal that with the alternative orientation at the quaternary center, formation of a cyclic acetal would not be possible.

With the desired configuration at the quaternary carbon established, we proceeded to elaborate the alkyl appendages. Reduction of **12** with excess diisobutylaluminum hydride (Et<sub>2</sub>O, 0 °C) and differentiation of the resulting diol by internal acetalization (Dowex 50W-X8 resin, MeOH) gave the epimeric acetals **14a** (mp 98–99 °C) and **14b** (mp 116–117 °C) in a combined yield of 93% (3:2 ratio) (Chart I).<sup>19</sup> Oxidation of **14a** with pyridinium chlorochromate<sup>20</sup> afforded the ketone **15** [mp 125–127 °C; NMR (CDCl<sub>3</sub>)  $\delta$  4.50 (1 H, t,  $J = 3.3$  Hz), 3.37 (3 H, s), 0.95 (3 H, d,  $J = 5.8$  Hz); IR (CHCl<sub>3</sub>)  $\nu_{\text{max}}$  1690 cm<sup>-1</sup>] in 94% yield. Conversion of **15** into the allylic alcohol **17** was accomplished in two different ways. Wittig olefination of **15** (Ph<sub>3</sub>P=CH<sub>2</sub>, DMSO/PhH, 70 °C) followed by epoxidation under carefully buffered conditions (MCPBA, 0.5 M aqueous NaHCO<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C)<sup>21</sup> yielded the labile epoxide **16**, which rearranged upon exposure to (isopropylcyclohexylamino)magnesium bromide (5 equiv., THF, 0 °C)<sup>22</sup> to give **17** [NMR (CDCl<sub>3</sub>)  $\delta$  5.90 (1 H, m), 3.99 (2 H, br s), 0.94 (3 H, d,  $J = 5.7$  Hz); IR (neat)  $\nu_{\text{max}}$  3390 cm<sup>-1</sup>] in 40% overall yield. On the other hand, addition of MeLi to **15**, followed by dehydration (POCl<sub>3</sub>, 4-(dimethylamino)pyridine, pyridine, 25 °C)<sup>23</sup> gave, remarkably, the strained olefin **18** [NMR (CDCl<sub>3</sub>)  $\delta$  1.59 (3 H, d,  $J = 2.3$  Hz), 0.95 (3 H, d,  $J = 6.5$  Hz)]<sup>24</sup> as the major product along with the desired isomer **19** [NMR (CDCl<sub>3</sub>)  $\delta$  5.57 (1 H, m), 1.65 (3 H, br s), 0.92 (3 H, d,  $J = 5.8$  Hz)] (4:1 ratio, 60% yield).<sup>25</sup> The strained nature of **18** was demonstrated by its complete isomerization to **19** in the presence of sulfur dioxide (CDCl<sub>3</sub>, 25 °C, 10 days; 77% yield).<sup>25,26</sup> Oxidation of **19** with selenium dioxide by using the Sharpless procedure<sup>27</sup> provided **17** in 50% yield.

Completion of the synthesis from **17** proceeded in a straightforward manner. Hydrolysis (1 N HCl, THF) afforded the hemiacetals **20** (87% yield) which reacted with (carboxyethylidene)triphenylphosphorane (PhCH<sub>2</sub>, 100 °C, 20 h) to give the trans ester **4** [NMR (CDCl<sub>3</sub>)  $\delta$  6.68 (1 H, br t,  $J = 7$  Hz), 5.84 (1 H, m), 1.76 (3 H, d,  $J = 1.0$  Hz), 0.91 (3 H, d,  $J = 5.6$  Hz); IR (neat)  $\nu_{\text{max}}$  1700, 1650 cm<sup>-1</sup>] in 68% yield and a small amount (8%) of the corresponding cis isomer. Reduction of **4** (DIBAH, Et<sub>2</sub>O, 0 °C) provided synthetic ( $\pm$ )-trihydroxydecipadiene (**1**) (mp 105–106 °C) in 94% yield, which was identical to the natural substance<sup>28</sup> by comparison of <sup>13</sup>C NMR (C<sub>5</sub>D<sub>5</sub>N), <sup>1</sup>H NMR (CDCl<sub>3</sub>), IR (CHCl<sub>3</sub>), MS, and TLC.

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**Supplementary Material Available:** Spectra (NMR, IR) of new compounds described in this paper (25 pages). Ordering information is given on any current masthead page.

(19) While the synthesis has been completed in comparable yield by using each acetal diastereomer as well as the mixture, the discussion here will be limited to the major isomer to simplify the presentation.

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(23) The rate of POCl<sub>3</sub> promoted dehydration was greatly enhanced by the addition of 1 equiv of 4-(dimethylamino)pyridine, allowing rapid elimination under very mild conditions (30 min, 25 °C).

(24) It is interesting to note that a similar methylene cyclobutane moiety is a prominent structural feature of the sesquiterpene, illudol (McMorris, T. C.; Nair, M. S. R.; Anchel, M. *J. Am. Chem. Soc.* **1967**, *89*, 4562).

(25) This ratio was measured by NMR analysis of the mixture.

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(28) We are grateful to Dr. P. R. Jefferies of the University of Western Australia for providing a sample of (–)-trihydroxydecipadiene from natural sources.