A Total Synthesis of (+)-Isovelleral. The Absolute Configuration of the Russulaceae Sesquiterpenes

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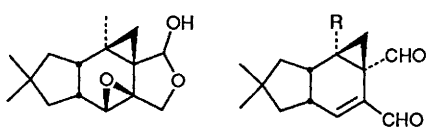
(+)-Isovelleral, an antibiotic and antifeedant sesquiterpene dialdehyde from Basidiomycetes, has been synthesised *via* a diastereoselective intramolecular Diels–Alder cyclisation of a chiral intermediate derived from D-ribonolactone.

Humulene-derived sesquiterpenes with a marasmane, lactarane, or secolactarane skeleton have been isolated from a number of Basidiomycetes.[1,2] However, it is known for several species that they appear to contain just one sesquiterpene, the very labile velutinal (**1**), esterified with fatty acids.[3] Physical damage of the mushroom induces a rapid enzymatic conversion of velutinal, *inter alia*, to unsaturated dialdehydes, *e.g.* isovelleral (**2**), with pronounced biological activity (antimicrobial, antifeedant),[2,4] and this may constitute a chemical defence system of the fungi.[4] We undertook a total synthesis of isovelleral (**2**), because of an expected need for structurally and isotopically modified analogues in connection with projected biological studies. This should also make isotopically labelled velutinal (**1**) available, since we have synthesised the latter from isovelleral.[5] Finally, an enantioselective synthesis of isovelleral would definitely establish the absolute configuration of this group of sesquiterpenes, many of which have been stereochemically correlated with each other[1] and recently also with isovelleral.[6] The absolute configuration indicated in the formulae is suggested by ORD and CD studies[7] and from an *X*-ray investigation of the related antibiotic marasmic acid (**3**).[8] A close biogenetic relationship between (**2**) and (**3**) is indicated by their co-occurrence in one organism.[2] Three syntheses of racemic (**3**) have been reported.[9a–c]

The synthesis is shown in Scheme 1.† The phosphorane from (**4**) was allowed to react with 2,3-*O*-isopropylidene-L-erythrouronic acid (**5**) (from D-ribonic acid γ-lactone[10]), yielding a non-separable mixture of the *E*- and *Z*-diene carboxylic acids (**6a**) and (**6b**) in a ratio of 2 : 3.‡ This ratio was raised to 19 : 1 by mercury(II) acetate-catalysed *cis–trans*-isomerisation,[12] and the *trans*-acid (**6a**) was isolated *via* chromatography of its methyl ester (**7**) and subsequent alkaline hydrolysis; the overall yield was 60% from (**4**). Reaction of (**6a**) with 1-chloro-*N*,*N*,2-trimethylprop-1-enylamine (**8**) in methylene chloride[13] gave the acid chloride (**9**), which was converted without isolation to the *N*-methoxy-*N*-methylamide (**10**) by the procedure of Weinreb *et al.*[14] The reaction of (**10**) with methylcyclopropenyl-lithium (**11**)[15] in ether was followed by a spontaneous intramolecular Diels–Alder reaction, which gave the pentacyclic ketone (**13**) as the only isolable product in a yield of 65%. Consequently, the cyclisation occurs in the *exo*-fashion with the cyclopropenyl group approaching the diene from the α face, and compound (**13**) has the same ring stereostructure as dialdehyde (**19**), a diastereoisomer of isovelleral (**2**).

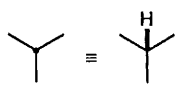
Hydroboration of (**13**) gave diol (**14**), which on partial acetylation gave monoacetate (**15**) in 86% yield together with a small amount (8%) of diacetate (**16**). Controlled acid hydrolysis of (**15**), after 92% conversion, afforded triol (**17**) in 81% yield [calc. on unrecovered (**15**)] and a small amount (13%) of diol (**14**). Subsequent periodate oxidation of (**17**) gave the unstable acetoxydialdehyde (**18**), which was directly subjected to elimination of acetic acid in refluxing pyridine, to give the diastereoisomer (**19**) of isovelleral (**2**) in a yield of 55% from triol (**17**).

It has been shown earlier[16] that isovelleral (**2**) (neat) can be thermally rearranged to the optically active pyrovellerofuran (**21**). However, when attempting to subject (**19**) to an analogous rearrangement, we found that it is possible to attain a clean thermal equilibrium between isovelleral (**2**) and its



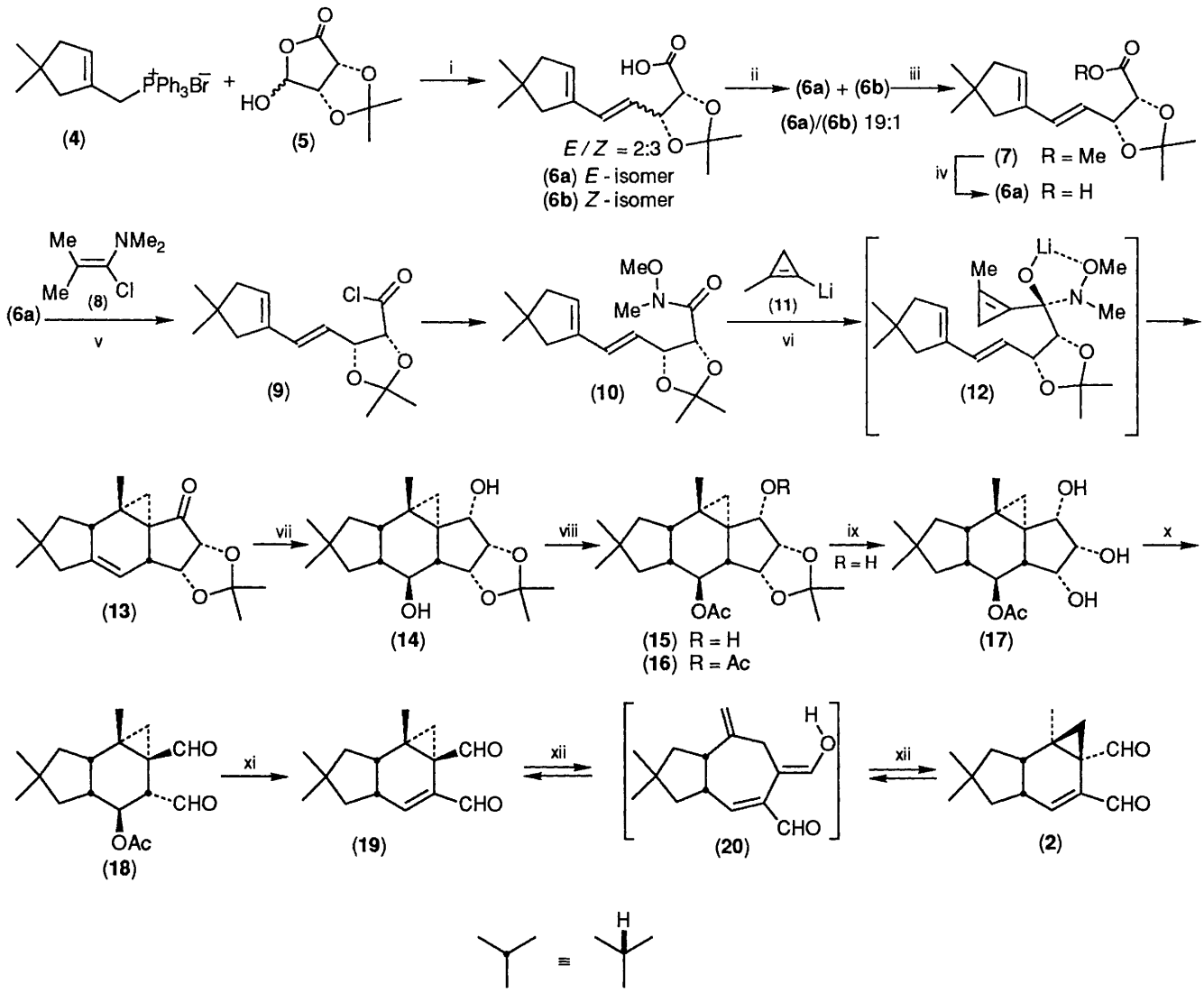
(1)

(2) R=Me
(3) R=CO_2H



† New compounds were chromatographically homogenous and gave analytical and spectroscopic data in accordance with their assigned structures.

‡ The phosphonium bromide (**4**) was prepared from 1-bromomethyl-4,4-dimethylcyclopentene[11] and triphenylphosphine.



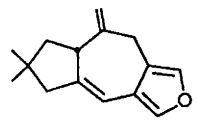
Scheme 1. *Reagents and conditions*: i, (**4**), tetrahydrofuran (THF), Bu^{n}Li (2 mol equiv.), 2 °C, then −70 °C, (**5**) (1 mol equiv.), 15 min, reflux, 2 h; ii, $Hg(OAc)_2$ (3 mol%), MeOH, 22 °C, 60 h, then zinc dust (10 mol%), 10 min; iii, diazomethane, ether, then LC, silica gel, CH_2Cl_2, 60% from (**4**); iv, NaOH, MeOH–H_2O, 97%; v, CH_2Cl_2, 2 min, 22 °C, then MeONHMe·HCl, 2 °C, Et_3N, → 22 °C, 0.5 h, 85%; vi, Et_2O, −70 °C, then (0.5 h) → 22 °C, 68%; vii BH_3·THF, THF, 22 °C, 6 h, then NaOH in H_2O, H_2O_2, 22 °C, 0.5 h, 77%; viii, pyridine, dimethylaminopyridine (DMAP), CH_2Cl_2, Ac_2O, −70 → 22 °C, 1 h, 86%; ix, H_2SO_4 (0.2 M) in MeOH–H_2O (4:1), 22 °C, 20 h, 75%, and (**15**), 8%; x, $NaIO_4$, EtOH, 22 °C, 0.5 h; xi, pyridine, reflux, 0.5 h, 55% from (**17**); xii, mesitylene, reflux, 0.5 h [ratio (**19**):(**2**) *ca.* 3:2], LC, silica gel, EtOAc–hexane, then (**19**) is recycled, 71% after five cycles.

diastereoisomer (**19**) (ratio 1:1).§ Heating of (**19**) in refluxing mesitylene for 0.5 h [40% conversion to (**2**)], chromatographic separation, and recycling of unchanged (**19**) afforded isovelleral (**2**) in a good yield.¶

Reaction of acid chloride (**9**) with methylcyclopropenyllithium in ether gave a mixture of both the *exo*-products (**22**) and (**13**) in a ratio of *ca.* 10:1 (combined yield: 9%). Our interpretation of the different stereochemical behaviour of (**9**) and (**10**) is that the former gives a ketone before the cyclisation step, while the latter gives the Diels–Alder product *via* sp^3 complex (**12**). Cyclopropenes were early recognised as reactive dienophiles,[19] and this property is further enhanced in cyclopropenyl ketones, which are also very reactive Michael acceptors. The delicate balance between cyclisation and Michael addition is illustrated by the analogous reaction between 2-methylcycloprop-1-enyl-lithium and *E*-*N*-methoxy-*N*-methylhepta-4,6-dieneamide which gave mainly the product (**25**) from Michael addition of liberated MeONHMe to an intermediate cyclopropenyl ketone, but only traces of Diels–Alder product. The conformational restraint imposed on (**12**) by the ketal ring should favour its cyclisation. A comparable

§ The electrocyclic nature of this isomerisation and intermediacy of (**20**) has been verified, *inter alia*, by interception of the intermediate (**20**).[17]

¶ (+)-Isovelleral (**2**): synthetic, m.p. 99—101 °C, $[\alpha]_D^{25}$ +278° (*c* 0.4, $CHCl_3$); isolated (from *Lactarius vellereus*), m.p. 101—103 °C, $[\alpha]_D^{25}$ +251° (*c* 1.0, $CHCl_3$); lit.[18] m.p. 105—106 °C, $[\alpha]_D^{19}$ +293° (*c* 0.4, $CHCl_3$); spectra of synthetic and isolated samples were identical. Diastereoisomer (**19**): synthetic, m.p. 72.5—74.5 °C, $[\alpha]_D^{25}$ −67° (*c* 0.7, CH_2Cl_2); sample from isomerisation of isolated (**2**), m.p. 68—70 °C, $[\alpha]_D^{25}$ −79° (*c* 1.0, CH_2Cl_2); the spectra of these samples were identical.



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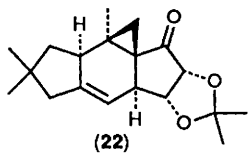

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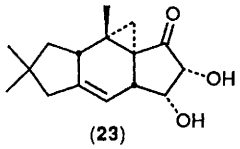

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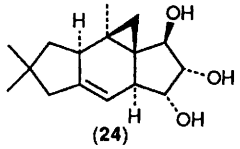

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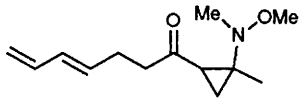

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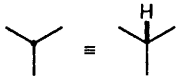

diastereoselectivity was recently demonstrated in a model study of intramolecular Diels–Alder cyclisations of carbohydrate-derived chiral nonatrienes.[20]

The stereochemical assignments were corroborated by *X*-ray crystallography of (**23**) {m.p. 173—178 °C (decomp.); $[\alpha]_D^{25}$ −222° (*c* 5, $CDCl_3$)} obtained by hydrolysis of (**13**), and of (**24**) {m.p. 190—192 °C; $[\alpha]_D^{25}$ +90.6° (*c* 2.5, MeOH)}, obtained from (**22**) *via* acid hydrolysis and borohydride reduction.[21]

The total synthesis of (+)-isovelleral also constitutes a formal total synthesis of (+)-velutinal.[5] Furthermore, it establishes that the absolute configuration of the Russulaceae sesquiterpenes derived from velutinal is in accordance with that suggested for marasmic acid.[7,8,22] ‖

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‖ *Note added in proof.* A total synthesis of racemic isovelleral has been published (S. K. Thompson and C. H. Heathcock, *J. Org. Chem.*, 1990, **55**, 3004).

References

1 For a review, see W. A. Ayer and L. M. Browne, *Tetrahedron*, 1981, **37**, 2199.
2 H. Anke, E. Hillen-Maske, and W. Steglich, *Z. Naturforsch., Teil C*, 1989, **44**, 1.
3 K. Gluchoff-Fiasson and K. Kuhner, *C. R. Acad. Sci. Ser. III*, 1982, **294**, 1067; J. Favre-Bonvin, K. Gluchoff-Fiasson, and J. Bernillon, *Tetrahedron Lett.*, 1982, **23**, 1907; O. Sterner, R. Bergman, E. Kesler, L. Nilsson, J. Oluwadiya, and B. Wickberg, *ibid.*, 1983, **24**, 1415; O. Sterner, R. Bergman, J. Kihlberg, J. Oluwadiya, B. Wickberg, G. Vidari, M. De Bernardi, F. De Marchi, G. Fronza, and P. Vita Finzi, *J. Org. Chem.*, 1985, **50**, 950.
4 S. M. Camazine, J. F. Resch, T. Eisner, and J. Meinwald, *J. Chem. Ecol.*, 1983, **9**, 1439; O. Sterner, R. Bergman, J. Kihlberg, and B. Wickberg, *J. Nat. Prod.*, 1985, **48**, 279; O. Sterner, R. Bergman, C. Franzen, and B. Wickberg, *Tetrahedron Lett.*, 1985, **26**, 3163.
5 O. Sterner, R. Bergman, and B. Wickberg, *Finn. Chem. Lett.*, 1985, 116.
6 J. Kihlberg, R. Bergman, L. Nilsson, O. Sterner, and B. Wickberg, *Tetrahedron Lett.*, 1983, **24**, 4631.
7 S. Thoren, Dissertation, University of Lund, 1974; M. De Bernardi, G. Fronza, G. Mellerio, V. Valla, G. Vidari, and P. Vita Finzi, *Gazz. Chim. Ital.*, 1984, **114**, 163.
8 P. D. Cradwick and G. A. Sim, *Chem. Commun.*, 1971, 431.
9 (a) W. J. Greenlee and R. B. Woodward, *J. Am. Chem. Soc.*, 1976, **98**, 6075; *Tetrahedron*, 1980, **36**, 3367; (b) R. K. Boeckman, Jr., and S. S. Ko, *J. Am. Chem. Soc.*, 1980, **102**, 7146; (c) Y. Tobe, D. Yamashita, T. Takahashi, M. Inata, J.-I. Sato, K. Kakiuchi, K. Kobiro, and Y. Odaira, *ibid.*, 1990, **112**, 775.
10 D. Beer, R. Meuvly, and A. Vasella, *Helv. Chim. Acta*, 1982, **65**, 2570.
11 J. S. H. Kueh, M. Mellor, and G. Pattenden, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1052.
12 J. S. Mills, *J. Chem. Soc.*, 1967, 2514.
13 A. Devos, J. Remion, A. M. Frisque-Hesbain, A. Cotens, and L. Ghosez, *J. Chem. Soc., Chem. Commun.*, 1979, 1180.
14 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.
15 R. Köster, S. Aurora, and P. Binger, *Liebigs Ann. Chem.*, 1973, 1219.
16 J. Froborg and G. Magnusson, *Tetrahedron*, 1978, **34**, 2027.
17 T. Hansson, R. Bergman, O. Sterner, and B. Wickberg, to be published.
18 G. Magnusson, S. Thorén, and B. Wickberg, *Tetrahedron Lett.*, 1972, 1105.
19 K. B. Wiberg and W. J. Bartley, *J. Am. Chem. Soc.*, 1960, **82**, 6375.
20 P. Herczegh, M. Zsély, L. Szilágyi, G. Batta, I. Bajza, and R. Bognár, *Tetrahedron*, 1989, **45**, 2793.
21 C. Stålhandske, R. Bergman, and B. Wickberg, to be published.
22 A preliminary account of this work was given at The First Princess Chulabhorn Sci. Congr. 1987, Int. Congr. on Nat. Prod., Proc. Vol. III, pp. 136—144, Mahidol University, Bangkok, 1989.