Stereoselective Addition of Methylcuprates to a 2-Formyl-cyclohexa-2,5-dienone System. A Stereoselective Total Synthesis of Racemic β-Vetivone

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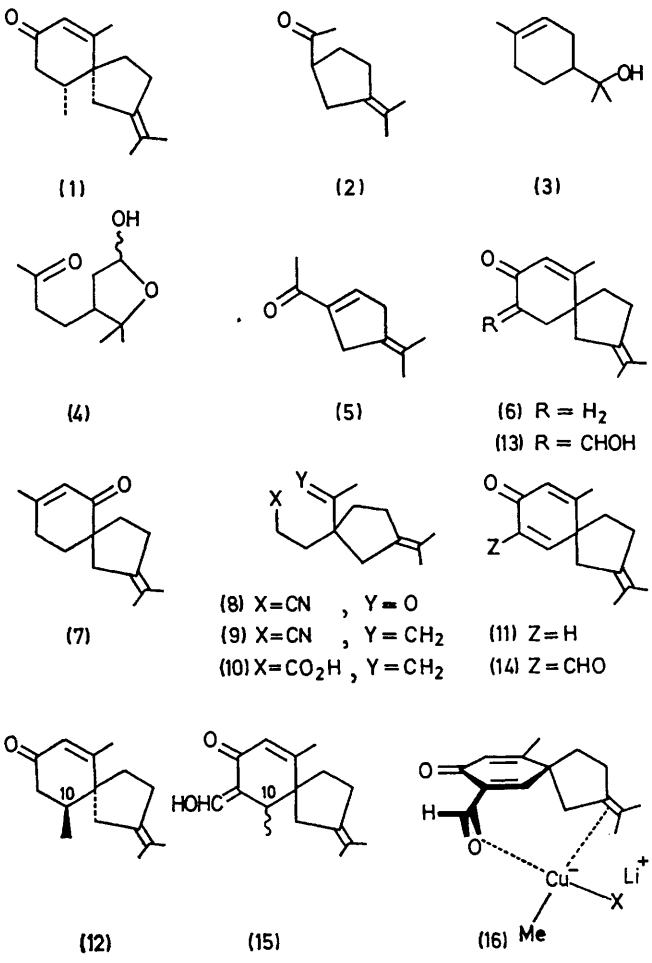
Summary The ketone (**2**), obtained from racemic α-terpineol (**3**), was converted by a six-step sequence into the 2-formyl-cyclohexadienone (**14**) which reacted stereoselectively with several methylcuprates, possibly by formation of an intermediate of type (**16**); *e.g.* with the lithium methylbromocuprate-di-isobutylamine complex a **5**:**1** mixture of racemic β-vetivone (**1**) and 10-epi-β-vetivone (**12**) was obtained, after deformylation.

WE describe a new total synthesis[1] of racemic β-vetivone, a fragrant component of vetiver oil having the structure (**1**).[1a,2] We planned to construct the spiro[4,5]decane system of β-vetivone by spiroanellation of a suitable functionalized cyclopentane derivative such as (**2**).

Ozonization of racemic α-terpineol (**3**) in methanol gave the hemiacetal (**4**) (84% yield), which was converted by treatment with dilute phosphoric acid and steam distillation to the dienone (**5**) (m.p. 47—48°; 44% yield). This compound was hydrogenated preferentially at the conjugated double bond (EtOH–H_2O, Raney Ni) yielding the desired ketone (**2**) (b.p. 93—94°, 8 mmHg; 40% yield). Preliminary experiments showed, however, that the base-catalysed Robinson anellation of ketone (**2**) with methyl vinyl ketone affords the spiroketones (**6**) (m.p. 89—90°) and (**7**) (b.p. 80—85°, 0·03 mmHg) in the unfavourable ratio of 3:7.[3]

Ketone (**6**) was eventually synthesized by the following route. Cyanoethylation of ketone (**2**) (triton B, Bu^tOH) gave the cyanoketone (**8**) (m.p. 44—45°; 85% yield) which was transformed by Wittig reaction ($Ph_3P{=}CH_2$, Me_2SO) into the olefinic nitrile (**9**) (b.p. 80—85°, 0·04 mmHg; 86% yield). Basic hydrolysis of this compound gave the acid (**10**) (b.p. 111—113°, 0·03 mmHg; 84% yield) which was con-

verted into ketone (**6**) (60—70% yield) by intramolecular acylation[4] of the corresponding acid chloride [$(COCl)_2$; $SnCl_4$, CS_2, $-25°$].



The DDQ-dehydrogenation of ketone (**6**) led to dienone (**11**) (m.p. 82—83°; 15% yield) which by reaction with lithium dimethylcuprate in ether gave a mixture of two isomeric compounds (92% yield) in a ratio of approximately 1:1, separable by silica gel chromatography. The first substance eluated is 10-epi-β-vetivone[5] (**12**) (m.p. 55—56°) and the second is racemic β-vetivone (**1**) (m.p. 47—48°), which was identified by comparison with natural (−)-β-vetivone (u.v., i.r., n.m.r. and mass spectra as well as identical retention time on a g.l.c. glass capillary column).

To circumvent the DDQ-dehydrogenation step (**6**)—(**11**), which could only be accomplished with very low yields, ketone (**6**) was converted in the usual manner into the hydroxymethylene derivative (**13**) (m.p. 56—58°) which readily dehydrogenated[6] with DDQ giving the expected dienone (**14**) (m.p. 95—96°; 80% yield from (**6**)). Lithium dimethylcuprate reacted (Et_2O, 0°) with the dienone (**14**) to give a mixture of hydroxymethylene-β-vetivones (**15**), isomeric in position 10, in a ratio of approximately 2:1, as determined by g.l.c. Deformylation of compounds (**15**) (MeOH–H_2O; 195°) gave a 2:1 mixture of racemic β-vetivone (**1**) and 10-epi-β-vetivone (**12**) [69% yield from (**14**)].

The unexpected stereoselective addition of lithium dimethylcuprate to (**14**) led us to look for reaction conditions and reagents inducing a higher share of β-vetivone. The following representative results were obtained [Et_2O, −75—0°; MeOH-H_2O, 195°; ratios of (**1**) to (**12**) in parentheses]: Me_2Cu^- Li^+ $(Bu^n{}_2S)_2$ + LiI[7], (1:1); $Me_2Cu^-Li^+$-$(Bu^i{}_2NH)_2$ + LiBr,[8] (1:1); [MeCuI]$^-$ $Li^+(Bu^n{}_2S)_2$,[9] (2·6:1); [MeCuI]$^-Li^+(Bu^i{}_2NH)_2$,[10] (3·2:1). The species [MeCuBr]$^-$-$Li^+(Bu^i{}_2NH)_2$[11] gave a most favourable, reproducible 5:1 mixture of (**1**) and (**12**) [75% yield from (**14**)], from which β-vetivone (**1**) can be isolated directly by crystallization.

The stereoselective behaviour of most cuprates can be explained by the assumption that they preferentially form an intermediate complex of type (**16**) involving the formyl group and the tetrasubstituted double bond of dienone (**14**) as ligands. The methyl ligand would then be transferred to the formyldienone system from that side of the cyclohexadienone plane where the isopropylidene group lies. The presence of the formyl group seems to be essential for the stereoselectivity of the reaction, because practically no stereoselectivity was observed if this group was missing.

(*Received*, 30*th September* 1974; *Com.* 1225.)

[1] For previous total syntheses of this sesquiterpene *cf.* (a) J. A. Marshall and P. C. Johnson, *J. Org. Chem.*, 1970, **35**, 192; (b) G. Stork, R. L. Danheiser, and B. Ganem, *J. Amer. Chem. Soc.*, 1973, **95**, 3414; (c) P. M. McCurry, jr. and R. K. Singh, *Tetrahedron Letters*, 1973, 3325; (d) K. Yamada, H. Nagase, Y. Hayakawa, K. Aoki, and Y. Hirata, *Tetrahedron Letters*, 1973, 4963.

[2] A. S. Pfau and P. A. Plattner, *Helv. Chim. Acta*, 1939, **22**, 640; J. A. Marshall and P. C. Johnson, *J. Amer. Chem. Soc.*, 1967, **89**, 2750.

[3] B. E. Ratcliffe and C. H. Heathcock, *Synthetic Comm.*, 1972, **2**, 157, obtained similar results in the Robinson anellation of acetylcyclopentane with methyl vinyl ketone.

[4] R. R. Sobti and Sukh Dev, *Tetrahedron*, 1970, **26**, 649.

[5] P. M. McCurry, jr., R. K. Singh, and S. Link, *Tetrahedron Letters*, 1973, 1155.

[6] J. A. Edwards, M. C. Calzada, L. C. Jbanez, M. E. Cabezas Rivera, R. Urquiza, L. Cardona, J. C. Orr, and A. Bowers, *J. Org. Chem.* 1964, **29**, 3481.

[7] Prepared by reaction of 2 equiv. of MeLi with 1 equiv. of $(Bu^n{}_2S)_2CuI$ (see G. M. Whitesides, W. F. Fischer, jr., J. San Filippo, jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, 1969, **91**, 4871).

[8] Prepared as in ref. 7 using $(Bu^i{}_2NH)_2CuBr$.

[9] Prepared by adding 1 equiv. of MeLi to an ethereal solution containing 1·1 equiv. of $(Bu^n{}_2S)_2CuI$ (see H. O. House and W. F. Fischer, jr., *J. Org. Chem.*, 1968, **33**, 949).

[10] Prepared as in ref. 9 using $(Bu^i{}_2NH)_2CuI$.

[11] Prepared as in ref. 9 using $(Bu^i{}_2NH)_2CuBr$.