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CHIRAL DIALKYL CYCLOHEPTANONES FROM R-(+)-CITRONELLAL

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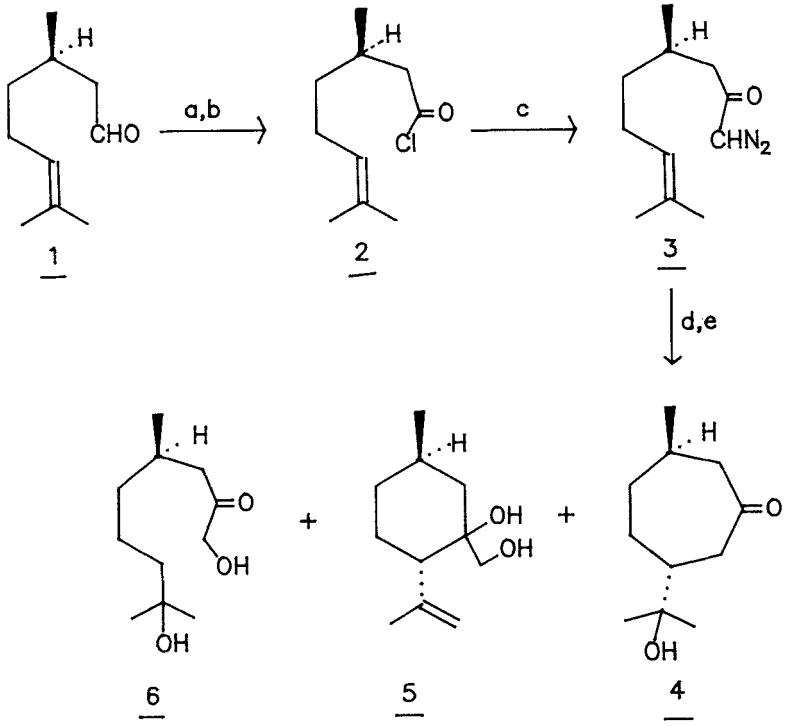
Abstract: A diastereoselective preparation of chiral cycloheptanones, having a methyl and an isopropyl group in 1,4-relationship, from R-(+)-citronellal is described.

Cycloheptanones bearing a methyl and an isopropyl group in stereochemically well defined 1,4-relationship are eminently serviceable building-blocks for the construction of various terpenes e.g., guainolides and pseudoguainolides.[1] However, access to such cycloheptanones in their chiral form is very limited despite their potential utility.[2] Herein we describe a convenient diastereoselective access to chiral cycloheptanones from the cheap, commercially available R-



Scheme 1

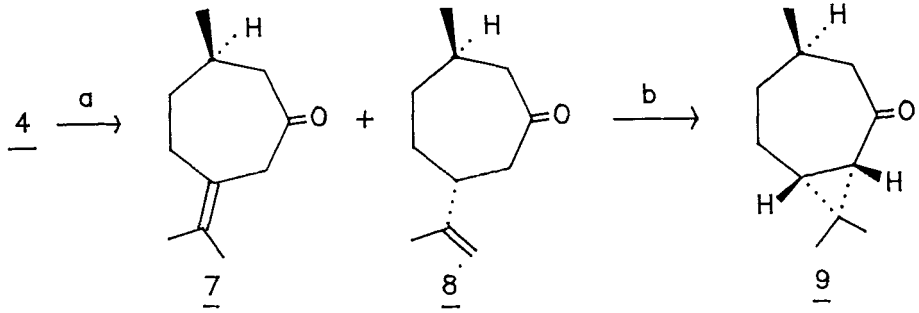
Reagents & Yield: (a) Jone's oxidation, 0°C, 1h, 80%; (b) $(COCl)_2$-Py, CH_2Cl_2, 0°C-RT, 3-4; (c) CH_2N_2-ether, 0-50°C, over night, 60% from acid; (d) CF_3COOH-CH_2Cl_2, -20°C, 30 min; (e) 10% KOH-CH_3OH, 70% from 3.

(+)-citronellal 1, employing an acid catalysed α-diazoketone cyclisation[3] as the key step.

R-(+)-Citronellal 1 was routinely transformed to the acid chloride 2 via Jone's oxidation followed by treatment with oxalyl chloride. Reaction of 2 with

ethereal diazomethane furnished the diazoketone 3 in 60% yield after purification. Several reagent systems (BF_3-ethereate in CH_2Cl_2 and CH_3NO_2, aq.$HClO_4$, $TiCl_4$, aq.HBF_4, etc.)[2c] were tried to effect the cyclisation of 3 but only very complex mixture of products was formed. However, trifluoroacetic acid in CH_2Cl_2 proved to be a reasonable medium[3a,b] and a readily separable mixture of 4, 5 & 6 (2 : 1 : 2) was obtained in 70% yield, after hydrolysis with methanolic alkali, Scheme 1. While the gross structures of 4-6 followed from their spectral data (vide experimental), the stereochemistry of 4 and 5 was deduced through simple chemical correlation. The interesting 1,2-diol 5 was catalytically hydrogenated and oxidatively cleaved with sodiummetaperiodate to furnish menthone. Dehydration of 4 with methanesulphonylchloride in the presence of triethylamine and DMAP furnished a mixture of two enones 7 and 8 (~ 1 : 1), the latter being identical (^1H & ^{13}C NMR) to the compound recently reported in literature.[2c] The enone 8 has already been transformed to the bicyclo[5.1.0]octanone 9, an important sesquiterpene synthon, in two high yielding steps,[2c] Scheme 2.

It may be noted that while the acid catalysed olefin-α-diazomethylketone cyclisation has found



Scheme 2

Reagents & Yield: CH_3SO_2Cl-$N(C_2H_5)_3$, DMAP, CH_2Cl_2, RT, 3h, 45%; (b) Ref. 2c.

extensive applications for the construction of five- and six-membered rings, the present study records one of the few examples of the formation of a seven membered ring.[3c] Earlier attempts[3c] to construct 9 directly from 3 through an intramolecular carbenoid [2+1]-cycloaddition to form a seven-membered ring have not been successful. Formation of α-hydroxyketones from α-diazoketones has been observed previously[2c] and the formation of 5 and 6 alongwith 4 is unexceptional.

Experimental Section[4]

Acid catalysed cyclisation of (4R)-1-Diazo-4,8-dimethyl-non-7-en-2-one 3: R-(+)-Citronellal (9g, 58

mmol, obtained from Fluka, $[\alpha]_D$ + 2.1°, $CHCl_3$, of low optical purity, was used as such) was oxidised with Jone's reagent at 0°C for 1h. Usual work-up furnished citronellic acid (8g, 80%). The crude acid was reacted with oxalyl chloride (3 eq.) in CH_2Cl_2 (200ml), containing pyridine (1 eq.). After stirring for 3-4 hours (0°C ——> RT), solvent was removed, the residue diluted with benzene (200ml) and filtered through a celite pad. Removal of solvent gave the acid chloride (8g, 90%), IR (neat): 1800 cm^{-1}. To the acid chloride 2 (3g, 16 mmol) in dry ether (5ml) was added excess of diazomethane with gentle swirling and the mixture was left overnight at 0-5°C. Ether was removed under vacuo and the residue was filtered through a SiO_2-gel column to furnish α-diazoketone 3 (1.8g, 60%), IR (neat): 2100, 1630, 1350 cm^{-1}. A solution of 3 (2.0g, 10 mmol) in CH_2Cl_2 (2ml) was added dropwise to a stirred solution of CF_3COOH (4ml) in CH_2Cl_2 (2ml) at -20°C under N_2. After 30 min. the reaction mixture was diluted with CH_2Cl_2 (25ml), washed with brine and dried. The residue obtained after the removal of solvent was dissolved in 10% methanolic KOH and stirred for 30 min. Methanol was removed under vacuo and the residue dissolved in ethyl acetate (50ml) and washed and dried. Removal of solvent gave an oily residue (1.4g,

~ 70%) which consisted mainly of a 2 : 1 : 2 mixture of 4, 5 and 6, respectively. Chromatography on SiO_2-gel column and elution with 20% ethyl acetate-hexane furnished 4: $[\alpha]_D^{20}$ + 4.7°C ($CHCl_3$), IR (neat): 3430, 1690 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 2.80-1.50 (11H, m) 1.18 (3H, s), 1.15 (3H, s), 0.97 (3H, d, J=7Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$): δ 211.3, 72.8, 51.3, 47.4, 45.8, 38.5, 32.5, 31.5, 26.8, 26.1, 23.9; Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.84; H, 10.93. Further elution of the coloumn gave 5: $[\alpha]_D^{20}$ + 3.9°C, IR (neat): 3400, 3050, 1635, 890 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 4.79 (2H, m), 3.39 (2H, ABq, J=11Hz), 2.2 (2H, br s), 2.10-0.90 (8H, m), 1.79 (3H, s), 0.86 (3H, d, J=7Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$): δ 145.0, 112.5, 73.4, 70.2, 50.7, 43.5, 34.8, 27.4, 27.3, 23.0, 22.4; Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.58; H, 10.86. Continued elution with the same solvent gave 6: IR (neat): 3350, 1710 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 4.16 (2H, s), 2.7 (2H, br s), 2.45-0.96 (9H, m), 1.17 (6H, s), 0.88 (3H, d, J=7Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$): δ 209.9, 70.8, 68.6, 45.6, 43.7, 37.2, 29.4, 29.2, 29.1, 21.5, 19.8; Anal. Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.25; H, 10.93.

Dehydration of 4: To a solution of the hydroxyketone 4 (90mg, 0.5 mmol) in CH_2Cl_2 (5ml) containing 4,4-dimethylaminopyridine (DMAP, 61mg), and triethylamine (2 eq.) was added methane-sulfonyl chloride (1.2 eq.) at 0°C under N_2. After 3h, the reaction mixture was diluted with water and extracted with dichloromethane (15ml). The residue (42mg, 45%) obtaining after the removal of solvent consisted of ~ 1 : 1 mixture of 7 and 8 and was charged on a SiO_2-gel coloumn. Elution with 3% ethyl acetate-hexane furnished 7: $[\alpha]_D^{20}$ + 6°C, IR (neat): 2950, 2920, 1705 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 3.13 (2H, ABq, J=16Hz), 2.78-1.48 (7H, m), 1.72 (3H, s), 1.68 (3H, s), 0.98 (3H, d, J=7Hz). Further elution gave 8: $[\alpha]_D^{20}$ + 12.4°C, IR (neat): 1690, 1440, 890 cm^{-1}; ^1H NMR (100 MHz, $CDCl_3$): δ 4.69 (2H, br s), 2.69-2.25 (5H, m), 2.06-1.17 (5H, m), 1.73 (3H, s), 1.02 (3H, d, J=7Hz); ^{13}C NMR (25.0 MHz, $CDCl_3$): δ 213.4, 149.7, 109.5, 52.1, 49.3, 43.9, 39.4, 35.3, 31.2, 24.1, 20.0. This compound was found to be spectroscopically identical with the compound recently reported in the literature.[2c]

Acknowledgements

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References

1. J.S. Glasby, Encyclopedia of the Terpenoids, John-Wiley & Sons, New York, **1982**; J.W. ApSimon (Ed.). The Total Synthesis of Natural Products, Vol. 6, John-Wiley & Sons, New York, **1983**.

2. (a) C.H. Heathcock, T.C. Germroth and S.L. Graham, J. Org. Chem., **1979**, 44, 4481. (b) M.D. Taylor, G. Minaskion, K.N. Winzenberg, P. Santone and A.B. Smith, ibid, **1982**, 47, 3960. (c) R. Baudouy, J. Gore and L. Ruest, Tetrahedron, **1987**, 43, 1099. (d) R.L. Funk, T.A. Olmstead and M. Parvez, J. Am. Chem. Soc., **1988**, 110, 3298.

3. (a) D.J. Beames, T.R. Klose and L.N. Mander, J. Chem. Soc. Chem. Commun., **1971**, 773. (b) D.J. Beames and L.N. Mander, Aust. J. Chem., **1971**, 24, 343. (c) For a review see: A.B. Smith III and R.K. Dieter, Tetrahedron, **1981**, 37, 2407.

4. For a general write-up on the experimental see: G. Mehta and H.S.P. Rao, Syn. Commun., **1985**, 15, 991.

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