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Double α-ketol rearrangement of (1*S*,2*R*,4*R*)-2-acetyl-1-vinyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptane

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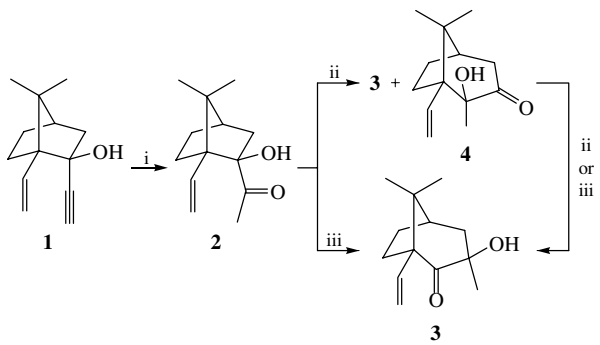
The title compound undergoes an α-ketol rearrangement in the NaH–THF and $BF_3{\cdot}Et_2O$–CH_2Cl_2 systems.

The α-ketol rearrangement[1] is an efficient method for the carbonyl 1,2-shift and reorganization of the ring system structure. This is confirmed by a number of cyclic and steroid ketols, precursors of taxoids,[2–7] *etc*. The α-ketol rearrangement is an equilibrium process, which proceeds under the effect of both Lewis acids and alkalis (for tertiary alcohols).[8]

An interesting and original domino type double α-ketol rearrangement initiated by bases (NaH, Bu^{t}OK) was observed in the transformations of camphor ketol **2** produced from acetylenic alcohol **1**.[9] The treatment of **2** with 1 equiv. of NaH in THF at 20 °C led to a mixture of **3** and **4** (Scheme 1). The increase of the duration of the reaction led to an increase in the share of **3** at an adequate decrease in the content of **4**. After 12 h, compound **2** transformed completely to a mixture of **3** + **4** with a certain prevalence of **3**. Within next 12 h, only isomer **3** was detected in the reaction mixture. The behaviour of **2** in the Bu^{t}OK–THF system is analogous. In this case, the rearrangement proceeded more quickly and within ~12 h compound **2** transformed completely to **3**. The treatment of **2** with 1 equiv. of $BF_3{\cdot}Et_2O$ in anhydrous CH_2Cl_2 at –20 °C afforded quickly and selectively tertiary alcohol **3**. TLC showed the absence of regioisomeric compound **4**. Note that the ageing of the mixture of **3** and **4** produced with BF_3 under conditions (i) leads to compound **3** only.†

Apparently, the rearrangement of **2** in the NaH–THF and Bu^{t}OK–THF systems proceeds through the formation of an isomeric mixture of **3** + **4**, and the rearrangement of **4** to **3** proceeds simultaneously. The transformation of **4** to **3** with the migration of a methyl group should also be attributed to α-ketol rearrangements. It is a suprafacial Me shift, and the Me group in the final product is α-oriented. In the ^{13}C NMR spectra of regioisomeric ketols **3** and **4**, the signals of C(1) and C(4) are characteristic. The signals of C(1) in **3** and C(4) in **4** are more downshifted because of the effect of a carbonyl group on the α-carbon atom. The C(4) methylene protons in **4** are resolved and characteristic for similar systems J_{gem} 17.7 Hz.[10] In the proof of β-stereoorientation of a hydroxyl group in **4** (and **3**) NOE-experiments were unsuccessful. Therefore, the following facts were taken into account in acceptance of the configurations of new chiral centres in compounds **3** and **4**. As is well



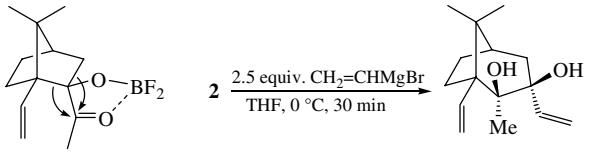
Scheme 1 *Reagents and conditions*: i, Me_2CO–aq. H_2SO_4–HgO cat., 0.5 h, 77%; ii, 1 equiv. NaH, THF, 20 °C, 12 h, 80% (**3** + **4**), or 1 equiv. Bu^{t}OK, THF, 20 °C, 4 h, (**3** + **4**), 12 h, 90% (**3**); iii, 1 equiv. $BF_3{\cdot}Et_2O$, CH_2Cl_2, –20 °C, 0.5 h, 86% (**3**).

† *(1S,2R,4R)-2-Acetyl-1-vinyl-2-hydroxy-7,7-dimethylbicyclo[2.2.1]-heptane* **2**. Colourless crystals, mp 80–82 °C, $[\alpha]_D^{20}$ –53° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.77 (s, Me), 0.90 (m, 1H), 1.18–1.25 (m, 1H), 1.20 (s, Me), 1.65–1.90 (m, 4H), 2.18 (s, 3H, Me), 2.45 (d, 1H, 3-H, *J* 13.0 Hz), 2.60 (s, 1H, OH), 5.07 (dd, 1H, *J* 17.8 and 1.7 Hz), 5.45 (dd, 1H, CH_2=, *J* 11.0 and 1.7 Hz), 6.20 (dd, 1H, =CH, *J* 11.0 and 17.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.37 (Me), 21.15 (Me), 25.11 [C(6)], 25.62 [C(5)], 26.93 (Me), 40.62 [C(3)], 45.76 [C(4)], 52.00 [C(7)], 57.50 [C(1)], 89.50 [C(2)], 117.73 and 135.09 (CH_2=CH), 209.5 (CO). Found (%): C, 75.24; H, 9.79. Calc. for $C_{13}H_{20}O_2$ (%): C, 74.96; H, 9.68.

1-Vinyl-3-hydroxy-3,8,8-trimethylbicyclo[3.2.1]octan-2-one **3**. Colourless crystals, mp 36–38 °C, $[\alpha]_D^{20}$ –13° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.80 (s, Me), 0.88 (s, 3-H), 1.36 (s, Me), 1.70 [m, 2H, C(6)H_{endo}, C(7)H_{endo}], 1.95 [m, 2H, C(4)H_α, C(5)H], 2.20 [m, 3H, C(6)H_{exo}, C(7)H_{exo}, C(4)H_α], 3.45 (s, 1H, OH), 5.10 (dd, 1H, *J* 1.2 and 17.6 Hz), 5.30 (dd, 1H, *J* 1.2 and 11.0 Hz), 6.00 (dd, 1H, CH=CH_2, *J* 11.0 and 17.6 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.58 (Me), 23.76 (Me), 26.64 [C(6)], 27.31 [C(7)], 32.06 (Me), 42.85 [C(4)], 44.78 [C(5)], 47.79 [C(8)], 64.00 [C(6)], 73.76 [C(2)], 116.27 and 135.09 (CH=CH_2), 217.96 (CO). MS (EI), *m/z* (I_{rel}, %): 208 $[M]^+$ (19), 179 $[M – Et]^+$ (13), 165 $[M – Pr]^+$ (10), 147 (16), 137 (26), 122 (63), 120 (65), 111 (25), 102 (100), 92 $[C_7H_8]^+$ (90), 79 (65), 65 (68), 43 $[Pr]^+$ (100), 29 $[Et]^+$ (66).

(1S,2S,5R)-1-Vinyl-2-hydroxy-2,8,8-trimethylbicyclo[3.2.1]octan-3-one **4**. Oil, $[\alpha]_D^{20}$ –28° (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 0.82 (s, Me), 1.20 (s, Me), 1.28 (s, Me), 1.50–2.10 (m, 5H), 2.25 [dd, 1H, C(4)H_α, *J* 1.3 and –17.7 Hz], 3.03 [ddd, 1H, C(4)H_β, *J* 1.3, 3.6 and 17.7 Hz], 5.05 [dd, 1H, *J* 1.3 and 17.7 Hz], 5.25 [dd, 1H, *J* 1.3 and 11.0 Hz], 6.10 (dd, 1H, CH=CH_2, *J* 11.0 and –17.7 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.59 (Me), 21.63 (Me), 25.32 (Me), 27.12 and 27.20 [C(6), C(7)], 44.66 [C(4)], 44.04 [C(5)], 47.79 [C(8)], 56.46 [C(1)], 79.59 [C(2)], 115.84 and 137.44 (CH=CH_2), 213.94 (CO). Found (%): C, 75.11; H, 9.53. Calc. for $C_{13}H_{20}O_2$ (%): C, 74.96; H, 9.68.

known,[5,6,11–13] rearrangements of α-ketols catalysed with BF_3 and $Al(OPr^i)_3$ proceed *via* intermediate chelate complexes with preservation of the dimensional (α or β) OH group. For example, in intermediate complex **A** generated from **2** by the effect of BF_3, the migration of any near bond should result in ketols with a β-hydroxyl group. The reactions of formylborneol and isoformylborneol with the Grignard reagent proceeded similarly.[14] RMgX started sequential processes of ring expansion (α-ketol rearrangement) and alkylation through initial chelate, and in rearranged ketol chelat-bounded with MgX catalysed by NaH the OH group was α- or β-positioned as in the parent compound.



A **5**

Scheme 2

We carried out the reaction of **2** with vinylmagnesium bromide under conditions described in ref. 14, which resulted in transformed ketol **5** in 65% yield (Scheme 2).‡ The comparison of NMR data for *syn*-Me compounds **3**, **4**, **5** and **6**[14] suggests the β-position and down-shifting influence of C^2_β-OH in ketols **4** and **5** [δ(Me) 1.20 (s) for **4** and **5**, 0.88 (s) and 0.87 for **3** and **6**] (supplementary data, Figure 1S; available free of charge *via* http://www.turpion.org/suppl/mc/2189/suppl2189.pdf).

In summary, note that in the investigated rearrangement regardless of the catalyst, the primary β-orientation of a hydroxyl group is conserved in transformed ketols. The transfer **2** → **4** → **3** catalysed by NaH can be classified as a rare example[15] of a double α-ketol rearrangement.

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References

1 (*a*) N. L. Wendler, in *Molecular Rearrangements*, ed. P. de Mayo, Wiley-Interscience, New York, 1964, p. 1019; (*b*) S. Selman and J. F. Eastham, *Quart. Rev.*, 1960, **14**, 221.
2 (*a*) N. L. Wendler, D. Taub and H. Kio, *J. Am. Chem. Soc*., 1960, **82**, 5701; (*b*) N. L. Wendler and D. Taub, *J. Am. Chem. Soc*., 1958, **80**, 3402.
3 H. Brunner, H. Kagan and G. Kreitzer, *Tetrahedron: Asymmetry*, 2003, **14**, 2177.
4 L. A. Paquette, K. D. Combrink, S. W. Elmore and M. Zhao, *Helv. Chim. Acta*, 1992, **75**, 1772.
5 J. H. Rigby, N. M. Niyaz and B. Bazin, *Tetrahedron*, 2002, **58**, 2836.
6 L. A. Paquette, F. J. Montgomery and T.-Z. Wang, *J. Org. Chem.*, 1995, **60**, 7857.
7 G. Appendino, J. Jakupovic, G. Cravotto and M. Varese, *Tetrahedron Lett*., 1994, **35**, 6547.
8 J. March, *Advanced Organic Chemistry*, 5th edn, Wiley, New York, 2001, p. 1401.
9 N. S. Vostrikov, A. V. Abutkov and M. S. Miftakhov, *Izv. Akad. Nauk, Ser. Khim*., 2001, 1181 (*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 1238).
10 B. V. Crist, S. L. Stephen and D. A. Lightner, *J. Am. Chem. Soc*., 1982, **104**, 6040.
11 N. L. Wendler, in *Molecular Rearrangements*, ed. P. de Mayo, Wiley-Interscience, New York, 1964, p. 1114ff.
12 N. L. Wendler, *Chem. Ind*., 1959, 20.
13 J. M. McIntosh and K. C. Cassidy, *Can. J. Chem.*, 1991, **69**, 1315.
14 T.-F. Yang, Zh.-N. Zhang, Ch.-H. Tseng and L.-H. Chen, *Tetrahedron Lett*., 2005, **46**, 1917.
15 A. Klásek, K. Kořistek, J. Polis and J. Košmrlj, *Tetrahedron*, 2000, **56**, 1551.

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‡ (*1*S,*2*R,*3*R,*5*R)-*1,3-Divinyl-2,3-dihydroxy-2,8,8-trimethylbicyclo[3.2.1]-octane* **5**. Colourless crystals, mp 122 °C, $[\alpha]_D^{20}$ +33° (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 0.75 (s, Me), 1.20 (s, Me), 1.30 (s, Me), 1.60–1.90 (m, 6H), 2.60 (s, 1H, OH), 5.04 (dd, 1H, *J* 2.0 and 17.2 Hz), 5.20 (dd, 1H, $=CH_2$, *J* 2.0 and 11.1 Hz), 5.14 (dd, 1H, *J* 1.3 and 10.8 Hz), 5.30 (dd, 1H, $=CH_2$, *J* 1.3 and 17.3 Hz), 6.15 (dd, 1H, =CH, *J* 11.1 and 17.3 Hz), 6.21 (dd, 1H, =CH, *J* 10.8 and 17.3 Hz). ^{13}C NMR ($CDCl_3$) δ: 20.34 (Me), 22.29 (Me), 24.45 [C(6)], 25.20 (Me), 25.79 [C(7)], 40.78 [C(4)], 45.73 [C(5)], 52.53 [C(8)], 58.89 [C(1)], 78.84 [C(3)], 85.03 [C(2)], 113.99 and 143.16 (CH_2=CH), 117.75 and 137.61 (CH_2=CH). Found (%): C, 76.11; H, 10.06. Calc. for $C_{15}H_{24}O_2$ (%): C, 76.23; H, 10.24.