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SKELETAL TRANSFORMATIONS OF CIS-BICYCLO[4.2.0]OCT-2-YL SYSTEM

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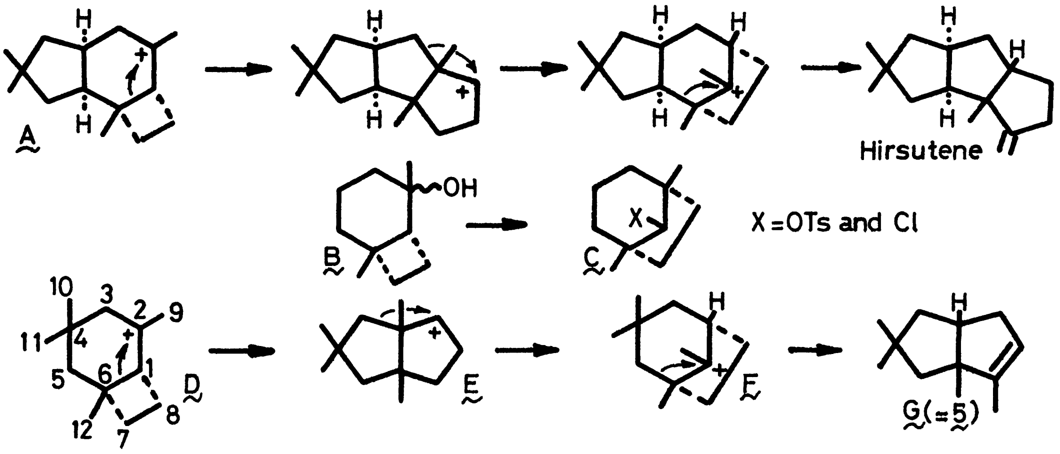
On treatment with HCO_2H at 0 °C, isomeric 2,4,4,6-tetramethyl-cis-bicyclo-[4.2.0]octan-2-ols gave rise to 1,2,7,7-tetramethyl-cis-bicyclo[3.3.0]oct-2-ene and 1,5,7,7-tetramethyl-cis,cis-1,4-cyclooctadiene, through new modes of skeletal transformation, together with a bicyclo[3.2.1]octane derivative. Mechanisms and biosynthetic significance of the new transformations are discussed.

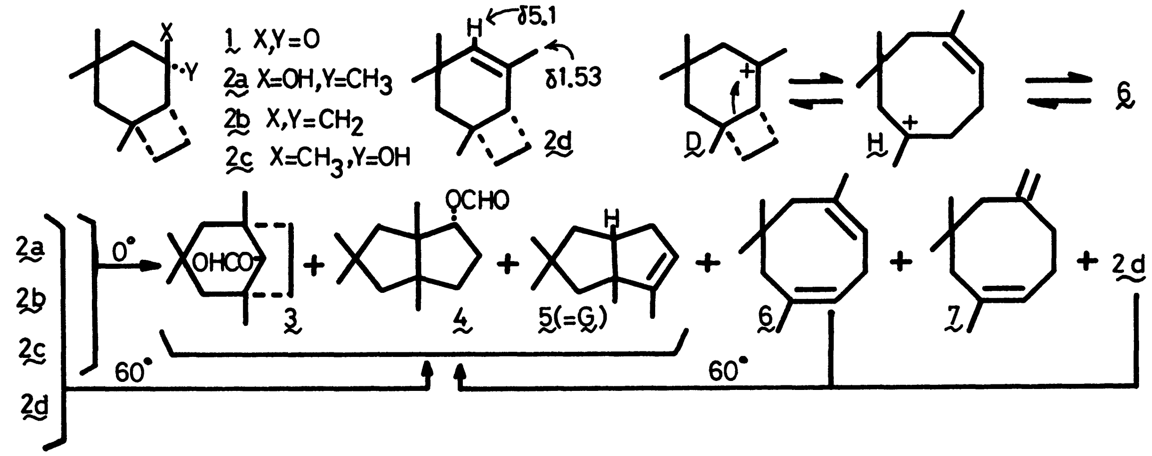
The sesquiterpene hirsutene[1] is believed to be biosynthesized from protoilludyl cation **A** through a triple 1,2 shift (Scheme I).[2] However, in vitro, such a triple rearrangement has not yet been known. Attempted rearrangements of both isomers of **B**[3] resulted in the formation of bicyclo[3.2.1]octane derivatives **C** as isolable products (Scheme I). We wish to report here a biogenetic like triple rearrangement of cis-bicyclo[4.2.0]oct-2-yl cation **D** to **G**, together with related skeletal transformations of the same cation.

Scheme I



Four bicyclic compounds **2a**,[4] **2b**,[4] **2c**,[4] and **2d**,[4] equivalent to **D** were synthesized from the known ketone **1**.[5] The Grignard reaction (CH_3MgI, 0 °C, 2 h) of **1** produced streoselectively **2a** [mp 52-54 °C, δ (CCl_4) 0.92, 0.98, 1.12, 1.20 (each 3H, s)] in 96% yield. Treatment of **1** with $Ph_3P=CH_2$ in dry PhH (rt, 2 h) afforded **2b** (78%). Epoxidation of **2b** with m-CPBA in CH_2Cl_2 at rt (1.5 h), and subsequent reduction with LAH in THF (60 °C, 1 h) produced **2c** (80% from **2b**). Isomerization of **2b** with 0.1 eq I_2 in refluxing toluene (4.5 h) gave **2d** in a quantitative yield. Stereostructure of **2a** was determined by lanthanide induced shift studies of its nmr spectrum.[6)]

Scheme II



Treatment of each of compounds 2a, 2b, and 2c in HCO_2H at 0 °C (2 h) gave a mixture of 3,[4)] 4,[4)] 5(=G),[4)] 6,[4)] 7,[4)] and 2d (Scheme II). On the other hand, at 60 °C (0.5 h), similar formolysis of 2a, 2b, 2c, and 2d afforded only the formates 3, 4, and the hydrocarbon 5(=G) (for yields, product ratios and reaction conditions, see Table I). Although exo-olefinic hydrocarbon 7 remained unchanged at 60 °C under the above conditions, endo-olefinic hydrocarbon 6 afforded the formates 3, 4, and the hydrocarbon 5(=G) (see Table I).

Table I

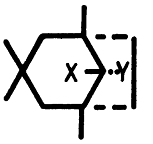
S.M.[a)]	Conditions	Y[b)]	Products, product ratios[c)]						Conditions	Y	Products, product ratios		
			3	4	2d	5(=G)	6	7			3	4	5(=G)
2a	0 °C	85%	4.4	4.4	3	1	0.25	0.15	60 °C	88%	1.8	1.8	1
2b	2 h	81%	1.6	1.6	2.1	1	0.6	0.4	0.5 h	87%	1.4	1.4	1
2c		91%	1.8	1.8	1.9	1	0.52	0.38		89%	1.1	1.1	1
2d		0%	No reaction							66%	1.1	1.1	1
6		—	—							80%	2	2	1
7		—	—							0%	No reaction		

a) Starting material b) Total yield of the products c) The product ratios were obtained by nmr or vpc

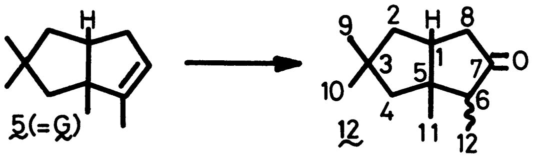
The products listed in Table I were separated by chromatography on silica gel. Their structures were determined as follows.

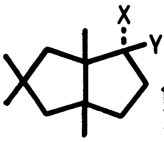
1β,3,3,5β-Tetramethyl-8β-formyloxybicyclo[3.2.1]octane (3): δ (CCl_4) 0.98, 1.13 (each 6H, s), 4.53 (1H, broad s), 8.08 (1H, s), ν (neat) 1737cm^{-1}, m/e 210 (M^+). Treatment of 3 with K_2CO_3 in aq MeOH (25 °C, 3 h) afforded 8[4)] (67%) [δ (CCl_4) 0.90 (12H, s), 1.08 (4H, s), 2.97 (1H, s)]. Jones oxidation of 8 gave ketone 9[4)] [ν (neat) 1753cm^{-1}] (82%). Reduction of 9 with $NaBH_4$ in EtOH (25 °C, 0.5 h) regenerated 8 (86%). Therefore the β-configuration of the formyloxyl group of 3 was indicated.[7)]

1β,3,3,5β-Tetramethyl-8α-formyloxybicyclo[3.3.0]octane (4): δ (CCl_4) 1.03(3H, s), 1.07 (6H, s), 1.10 (3H, s), 4.65 (1H, broad t, J=7 Hz), 7.89 (1H, s), ν (neat) 1737cm^{-1}, m/e 210 (M$^+$). Hydrolysis of **4** (K$_2$CO$_3$ aq MeOH, 25 °C, 3 h) gave alcohol **10**[4,8] (67%) [δ (CCl$_4$) 1.00, 1.04 (each 3H, s), 1.08 (6H, s), 3.51 (1H, q, J=7, 9 Hz)]. The nmr spectrum in the presence of Eu(fod)$_3$ [Eu(fod)$_3$/**10**=0.51, CCl$_4$] showed signals at δ 1.69 (3H, s, 5β-Me), 1.76 (6H, s, 3α,β-Me), 2.30 (1H, dd, J=14, 1 Hz, 4β-H), 2.52 (1H, d, J=14 Hz, 4α-H), 2.80 (3H, s, 1β-Me), 3.36 (1H, dd, J=14, 1 Hz, 2β-H), 4.37 (1H, d-quint, $J_{7\alpha-7\beta}$=14 Hz, $J_{7\beta-6\beta}$=7 Hz, $J_{7\beta-8\beta}$=7 Hz, $J_{7\beta-6\alpha}$=2 Hz, 7β-H), 4.80 (1H, m, 7α-H), 4.82 (1H, d, J=14 Hz, 2α-H), 8.05 (1H, q, J=7, 9 Hz, 8β-H). These data are accounted for by a time averaged conformation **10'**. A 1β, 5α (trans) structure will not show the observed W letter coupling between 2β-H and 4β-H. Jones oxidation of **10** afforded **11**[4] (96%) [δ (CCl$_4$) 0.85, 0.93 (each 3H, s), 1.08 (6H, s), 1.38 (1H, d, J=13 Hz), 2.02 (1H, d, J=13 Hz), ν (neat) 1745cm^{-1}]. Reduction of **11** (NaBH$_4$, EtOH, 0.5 h) regenerated selectively **10** (98%).

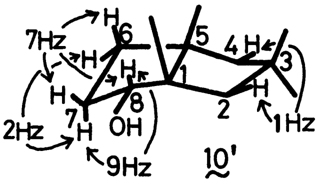


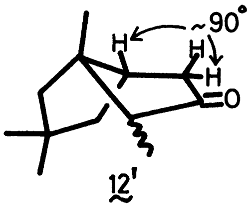
3 X=OCHO, Y=H
8 X=OH, Y=H
9 X,Y=O





4 X=OCHO, Y=H
10 X=OH, Y=H
11 X,Y=O





1,2,7,7-Tetramethyl-cis-bicyclo[3.3.0]oct-2-ene (**5**=**6**): δ (CCl$_4$) 0.98, 1.01 (each 3H, s), 1.61 (3H, broad s), 4.92 (1H, broad s), ν (neat) 800cm^{-1}, m/e 164 (M$^+$); The structure of **5** was cofirmed by lanthanide induced shift studies of the nmr spectrum of the major C·6 isomer **12** of cyclopentanones [ν (neat) 1745cm^{-1}], obtained from **5** by successive hydroboration-oxidation (aq NaOH, H$_2$O$_2$), Jones oxidation (62% from **5**) and equilibration (MeOH, MeONa). The spectrum in the presence of Eu^{3+} [Eu(fod)$_3$/**12**=0.22, CCl$_4$] of **12** exhibited peaks at δ 1.72 (3H, s, 3-Me), 1.76 (3H, s, 3-Me), 2.66 (3H, s, 5β-Me), 4.21 (S[9]=15.8, 3H, d, $J_{12-6\beta}$ or $_{6\alpha}$=7 Hz, 6α or 6β-Me), 6.91 (S=18.6, q, $J_{6\beta}$ or $_{6\alpha-12}$= 7 Hz, 6β or 6α-H), 7.34 (S=28.9, 1H, d, $J_{8\alpha-8\beta}$=18.5 Hz, $J_{8\alpha-1\beta}$=0 Hz, 8α-H), 7.76 (S=30.8, 1H, q, $J_{8\alpha-8\beta}$=18.5 Hz, $J_{8\beta-1\beta}$=8 Hz, 8β-H). These spectral data indicates a 1β, 5β (cis) structure for **12** (see approximate conformation **12'**). The 1α, 5β isomer of **12** is expected to show large $J_{8\alpha-1\alpha}$ and $J_{8\beta-1\alpha}$.

1,5,7,7-Tetramethyl-cis,cis-1,4-cyclooctadiene (**6**): δ (CCl$_4$) 0.98 (6H, s), 1.69 (6H, broad s), 2.07 (4H, s), 2.67 (2H, broad t, J=6 Hz), 5.37 (2H, broad t, J=6 Hz), m/e 164 (M$^+$). The nmr spectrum indicated a symmetrical flexible structure. Therefore the cis-cis structure was assigned.[10]

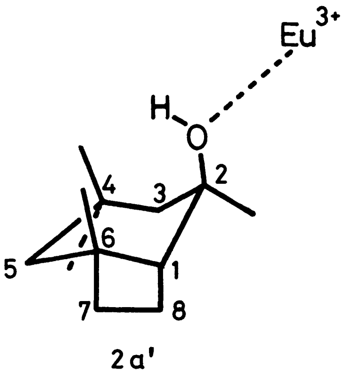
3,3,5-Trimethyl-cis-5-cycloocten-1-ylidene (**7**): δ (CCl$_4$) 0.98 (6H, s), 1.72 (3H, s), 1.89 (2H, s), 1.92 (2H, s), 4.64 (2H, m), 5.37 (1H, broad t, J=6 Hz), m/e

164 (M^+). Stereochemistry of the double bond in 7 also was deduced to be cis on the basis of the above nmr data, which show conformational mobility of the ring.

As can be seen in Table I, the hirsutene like hydrocarbon 5(=G) is formed not only through the triple rearrangement (D→E→F→G, Scheme I), but also through a series of skeletal transformations involving cyclooctenyl cation H as an intermediate ($D \rightleftarrows H \rightarrow E \rightarrow F \rightarrow G$, Scheme II). It should be noted that 4 and 7 survive the solvolytic conditions even at 60 °C and recovered unchanged. Therefore the hydrocarbon 5(=G) is formed through the cations E and H, but not via 4 and 7. Another noteworthy point is the different behavior of the cationic species from B and the dimethyl analog D. In the latter case, probably because of the steric crowdedness of the transition state leading to 3, the reaction was diverted to give other observed products.

References and Footnotes

1) S. Nozoe, J. Furukawa, U. Sankawa, and S. Shibata, Tetrahedron Lett., 1976, 195.
2) M. Tanabe, K. T. Suzuki, and W. C. Jankowski, Tetrahedron Lett., 1974, 2271.
3) Y. Yamada, Dissertation, Tohoku Univ., 1966. See also A. C. Cope, R. W. Gleason, S. Moon, and C. H. Park, J. Org. Chem., 32, 942 (1967).
4) Satisfactory analytical and spectral data were obtained for this compound.
5) D. C. Owsley and J. J. Bloomfield, J. Chem. Soc. (C), 1971, 3445.
6) The spectrum [Eu(fod)$_3$/2a=0.6, CCl_4] of 2a exhibited peaks at δ 2.90 ($S^{9)}$=3.80, 3H, s, 4α-Me), 3.56 [2H, dd, $(J_{7\alpha-8\alpha}+J_{7\beta-8\alpha})/2$=10 Hz, $(J_{7\alpha-8\beta}+J_{7\beta-8\beta})/2$=5 Hz, 7α,β-H], 3.79 (S=4.47, 3H, s, 4β-Me), 4.40 (1H, d, $J_{5\alpha-5\beta}$=13.5 Hz, 5-H), 4.76 (1H, m, 8-H), 4.91 (1H, d, $J_{5\alpha-5\beta}$=13.5 Hz, 5-H), 5.38 (1H, m, 8-H), 5.82 (1H, d, $J_{3\alpha-3\beta}$=14 Hz, 3α-H), 5.84 (S=7.79, 3H, s, 6β-Me), 8.53 (S=14.08, 3H, s, 2α-Me), 9.6 (S=15.37, 1H, d, $J_{3\alpha-3\beta}$=14 Hz, 3β-H), 11.3 (S=17.54, 1H, t, $J_{1\beta-8\alpha}$=10 Hz, $J_{1\beta-8\beta}$=10 Hz, 1β-H). These data are interpreted by a time averaged conformation 2a' with a quasi-chair, flattened six-membered ring.



2a'

7) C. S. Foote and R. B. Woodward, Tetrahedron, 20, 687 (1964).
8) Treatment of 10 with HCO_2H at 60 °C afforded the formate 4, giving no rearrangement products.
9) A. F. Cockerill and D. M. Rackham, Tetrahedron Lett., 1970, 5164.
10) trans-Cyclooctenes are rigid and their olefinic protons generally couple to the vicinal methylene protons with J=11 and 5 Hz [for examples see E. Vedejs, K. A. J. Snoble and P. L. Fuchs, J. Org. Chem., 38, 1178 (1973); A. J. Bridges and G. H. Whitham, J. Chem. Soc., Perkin Trans.I, 1975, 2264].

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