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Stereo- and Regioselectivity in Dynamic Gas-Phase Thermoisomerization (DGPTI): Novel Route to α-Campholanic Acid and Derivatives

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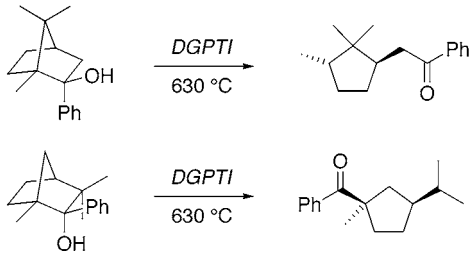
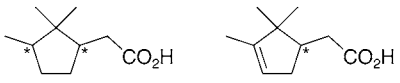
ABSTRACT



Dynamic gas-phase thermoisomerization (DGPTI) of (−)-2-phenylisoborneols effects stereo- and regioselective ring opening under formation of (+)-*trans*-α-campholanic acid derivatives. Similarly, (−)-α-2-phenylfenchol underwent under DGPTI conditions ring opening to (−)-fencholic acid derivatives. In both cases, DGPTI led to cleavage of the weakest bond in the isomeric bicyclic structures. A reaction mechanism involving a diradical intermediate is supported by a deuterium labeling study.

Alkyl esters of α-campholanic acid (**1**) are reported to reveal organoleptic properties of fruity and floral quality, which make them interesting for fragrance chemisty.[1] Although the skeleton of **1** has been prepared chemically[2] as well as photochemically,[3] the thermal chemistry of this chiral building block has apparently not yet been investigated. Among the four possible stereoisomers of **1**, mainly mixtures of cis/trans isomers were reported, predominantly obtained via hydrogenation of α-campholenic acid derivatives **2**.[4]



1 **2**

A further approach, by heating camphor imine in the presence of oxygen, is reported to deliver the amide of **1** in only one configuration but with unsatisfactory yields.[5] More recent methods involving the cleavage of the C1−C2 bond of camphor by hydrosilylation[6] or fragmentation of initially generated camphoriminyl radicals[4] lack diastereoselectivity.

As we recently discovered in our laboratory, large-ring 1-phenylcycloalkanols react under DGPTI conditions cleanly to open-chain phenones, whereas the small-ring analogues undergo only H_2O elimination.[7] Were 2-phenylisoborneol (**3**) to behave like a bicyclic small-ring 1-phenylcycloalkanol analogue, elimination of H_2O under formation of 2-phenylbornene would be expected to occur under DGPTI. In sharp contrast to this expectation, pyrolysis of (−)-2-phenylisoborneol[8] (**3**) at 630 °C afforded a monocyclic isomeric product that was easily removed from highly volatile side products, characterized, and proved to be (+)-*trans*-2-(2,2,3-trimethyl-cyclopentyl)-1-phenyl-ethanone[9] (**4**) (Scheme 1,

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(1) Rohr, M.; Flynn, C. U.S. Patent 4 547 315, 1985; *Chem. Abstr.* **1986**, *105*, 11868.
(2) Harispe, M.; Mea, D. *Bull. Soc. Chim. Fr.* **1962**, 1340.
(3) El Kaim, L.; Meyer, C. *J. Org. Chem.* **1996**, *61*, 1556.

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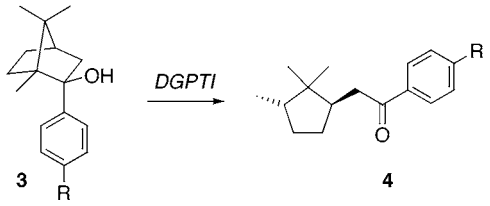
Scheme 1

Table 1). This thermal behavior might be explained by the strain incorporated in the bicyclic bornane system. The

Table 1. Effects of Para Substituents on DGPTI of 2-Phenylisoborneols **3**



R	product	*T* (°C)	yield (%)	dr (%)
H	**a**	630	73	>99
CH_3	**b**	620	45	>99
OCH_3	**c**	610	62	>99
CF_3	**d**	630	71	>99

assignment of the trans configuration is based on the observed NOE correlations as shown in Figure 1.

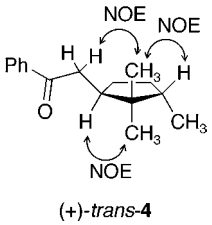
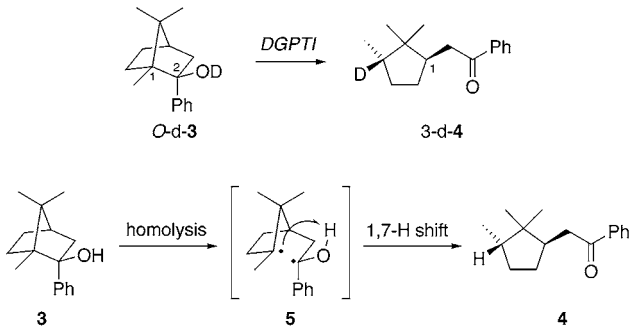


Figure 1. ^{1}H−NOE correlations of compound (+)-**4** showing its trans configuration.

We have studied the mechanism and the origin of this unique stereoselectivity in the pyrolysis of isoborneol **3** by means of deuterium labeling experiments. The thermal isomerization of O-deuterated isoborneol *O*-d-**3**[10] gave 3-d-**4**, which exhibited a broad singlet in its ^{2}H NMR spectrum at δ 1.66.

The investigation has led to the conclusion that this thermally promoted cleavage reaction proceeds via a diradical species as we found earlier for the transformation of 1-phenylcycloalkanols.[7] Moreover, the label has been proved to be transferred both stereospecifically (retention of configuration) and regiospecifically from the O-atom of *O*-d-**3** to C3 of **4** (Scheme 2). The labeling experiment reveals that

Scheme 2



initial homolysis of the C1−C2 bond of isoborneol **3** results in the formation of a monocyclic hydroxybenzyl alkyl diradical **5**, which then undergoes a disproportionation reaction via 1,7-H shift. However, cleavage of the C2−C3 bond under formation of the lower substituted alkyl radical moiety could not be detected.

Substituents at the aromatic ring affected both the yield and the required optimal temperature for the DGPTI process, but not the diastereoisomeric ratio. As summarized in Table 1, a series of readily prepared isoborneols **3a**−**d** was thermally converted to the isomeric phenones **4a**−**d** in moderate to good yields. The lower yields of 4-methyl- and

(4) (a) Lipp, P. *Ber. Dtsch. Chem. Ges.* **1922**, *55*, 1883. (b) Cason, J.; Khodair, A. I. A. *J. Org. Chem.* **1967**, *32*, 575. (c) Gream, G. E.; Wege, D.; Mular, M. *Aust. J. Chem.* **1974**, *27*, 567. (d) Treibs, W.; Mühlstädt, M.; Megges, R.; Klotz-Herdmann, I. *Justus Liebigs Ann. Chem.* **1960**, *634*, 118. (e) Ichikawa, S. *Bull. Chem. Soc. Jpn.* **1936**, *11*, 759.

(5) (a) Mahla, F.; Tiemann, F. *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 1929. (b) Blanc, G.; Desfontaines, M. *Bull. Soc. Chim. Fr.* **1903**, *29*, 608. (c) Bonnett, R.; Raleigh, J. A.; Redman, D. G. *J. Am. Chem. Soc.* **1965**, *87*, 1600.

(6) Brunner, H.; Becker, R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 703; *Angew. Chem.* **1985**, *97*, 713.

(7) Rüedi, G.; Nagel, M.; Hansen, H.-J. *Synlett* **2003**, 1210.

(8) Prepared from (+)-camphor with PhMgBr in the presence of $CeCl_3$; see: Dimitrov, V.; Brabantov, S.; Simova, S.; Kostova, K. *Tetrahedron Lett.* **1994**, *35*, 6713.

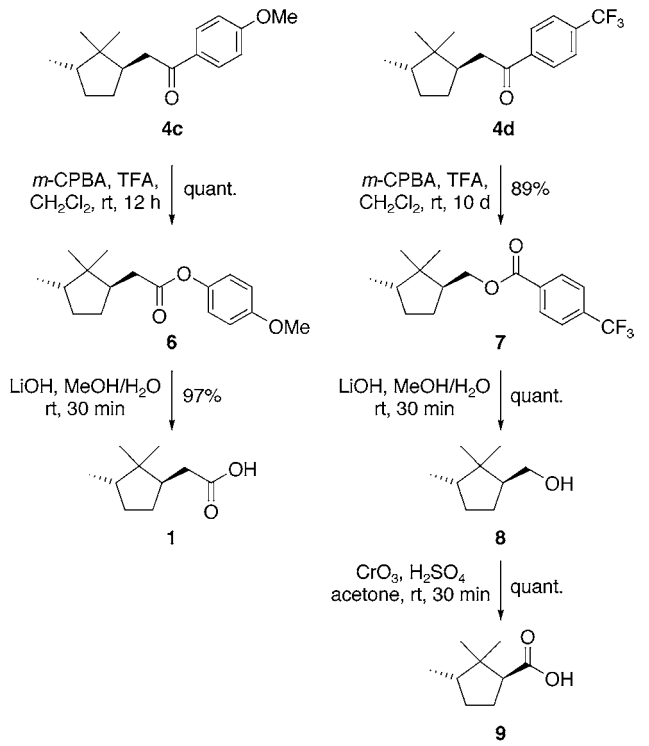
(9) (a) DGPTI process was performed in a flow reactor system using a quartz tube (110 cm length) heated in a tube furnace (100 cm lengths with six different temperature zones separately adjustable). (b) For details, see: Nagel, M.; Fráter, G.; Hansen, H.-J. *Synlett* **2002**, *275*, 280. Nagel, M.; Fráter, G.; Hansen, H.-J. *Chimia* **2003**, *57*, 196 and references therein. (c) The following procedure is illustrative. After evacuation of the apparatus with a high-vacuum oil pump, (−)-2-phenylisoborneol (**3**) (2.0 g, 8.68 mmol) was distilled slowly through the preheated reactor tube (contact time estimated at about 1−2 s). A flow of N_2 was adjusted from 1.2 L/h. At the end of the reactor unit, the isomerization products were collected in a trap cooled with liquid N_2 (90−95% recovery). Purification by flash chromatography (silica gel, 30:1 hexanes/ethyl acetate) followed by bulb-to-bulb distillation (kugelrohr) afforded (+)-*trans*-2-(2,2,3-trimethyl-cyclopentyl)-1-phenyl-ethanone (**4**) (1.46 g, 73% yield) as a colorless oil: $[a]^{23}_D$ +54.7 (*c* 0.6, MeOH); FTIR (film) 3060, 3027, 2958, 2871, 1687, 1598, 1580, 1448, 1366, 1285, 1215, 1180, 1016, 1002 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (dd, J = 8.3 and 1.4 Hz, 2H); 7.54 (tt, J = 7.4 and 1.3 Hz, 1H); 7.45 (t, J = 7.9 Hz, 2H); 3.03 (dd, J = 16.2 and 4.0 Hz, 1H); 2.73 (dd, J = 16.0 and 10.4 Hz, 1H); 2.20 (m, 1H); 1.93 (m, 1H); 1.85 (m, 1H); 1.66 (sext, J = 7.1 Hz, 1H); 1.25−1.20 (m, 2H); 0.89 (s, 3H); 0.88 (s, 3H); 0.86 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.1, 137.6, 133.0, 128.7, 128.3, 44.3, 43.7, 42.4, 40.7, 31.6, 29.7, 24.4, 23.8, 16.5 ppm; MS *m*/*z* (rel intensity) 230 (12), 221 (2), 187 (1), 173 (45), 145 (7), 120 (82), 105 (100), 95 (23), 77 (30), 69 (11).

(10) Prepared by iterative treatment of **3** with MeOD/D_2O.

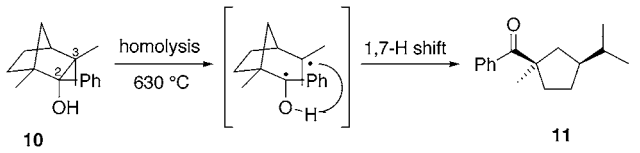
4-methoxy-substituted substrates **3b** and **3c**, respectively, are due to increased susceptibility to dehydration. The corresponding bornenes could be isolated in 20−30% yield.

The enantioselective thermoisomerization reaction summarized in Table 1 can widely be exploited in the synthesis of a broad variety of chiral monoterpenes derived from phenones of type **4**. For instance, the large difference in electronic properties between the electron-donating methoxy group (**4c**) and the electron-withdrawing trifluoromethyl group (**4d**) allows selective Baeyer−Villiger rearrangement. According to Scheme 3, treatment of **4c** with *m*-chloroperbenzoic acid and an aequimolar amount of TFA in CH_2Cl_2,[11] followed by hydrolysis of the intermediate phenyl ester **6**, afforded campholanic acid[12] (**1**) in almost quantitative yields, whereas treatment of **4d** under equivalent conditions provided cyclopentyl methyl ester **7**, which upon hydrolysis led to cyclopentyl carbinol **8** in comparable yields. Oxidation of **8** with Jones reagent[13] furnished (+)-*trans*-α-dihydrocampholytic acid (**9**). On the other hand, the Baeyer−Villiger reaction of both **4a** and **4b** gave, after hydrolysis, 3:1 mixtures of **1** and **8**, which could easily be separated.

Scheme 3



Scheme 4



It was of interest to extend our studies to (−)-fenchone, which upon treatment with PhLi in Et_2O gave (1*R*,2*R*,4*S*)-2-phenyl fenchol[14] (**10**). AM1 calculations of **10** show that the C2−C3 bond is longer than the C1−C2 bond, which is in agreement with X-ray crystallographic analyses of reported 2-arylfenchol derivatives.[15] Indeed, thermal isomerization of **10** at 630 °C provided fencholic acid derivative **11**[16] in 48% yield. In contrast to the transformation of **3** to **4**, a reaction pathway involving the cleavage of the C2−C3 bond was observed.

Further investigations on the DGPTI-induced rearrangement of fencholic derivatives of type **10** are in progress.

In conclusion, the observed stereoselective conversion of camphor and fenchone derivatives to campholanic and fencholic acid derivatives by DGPTI is novel and demonstrates the potential of pyrolytic methods.

Acknowledgment. This work was generously supported by the Swiss National Science Foundation (SNF).

Supporting Information Available: Experimental procedures and complete spectral data for all new compounds (**4a**−**d**, **6**−**9**, and **11**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Koch, S. S. C.; Chamberlin, A. R. *Synth. Commun.* **1989**, *19*, 829.

(12) -*trans*-α-Campolanic acid (**1**): $[a]^{23}_D$ +40.6 (*c* 1.0, hexane); FTIR ($CHCl_3$) 3517, 2961, 2874, 2680, 1704, 1470, 1452, 1412, 1389, 1368, 1296, 1230, 1178, 1136 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.43 (dd, J = 15.1 and 3.5 Hz, 1H); 2.12 (dd, J = 15.6 and 10.4 Hz, 1H); 2.06−1.91 (m, 2H); 1.85 (m, 1H); 1.62 (sext, J = 7.1 Hz, 1H); 1.31−1.17 (m, 2H); 0.86 (d, J = 6.9 Hz, 3H); 0.84 (s, 3H); 0.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.6, 44.5, 43.3, 42.0, 36.2, 31.1, 29.1, 23.7, 23.3, 16.0 ppm; MS *m*/*z* (rel intensity) 170 (10), 127 (11), 114 (37), 110 (26), 95 (42), 84 (67), 69 (100), 55 (23). Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.63. Found: C, 83.31; H, 9.62.

(13) Welch, J. T.; Lin, J. *Tetrahedron* **1996**, *52*, 291.

(14) Lecompte, V.; Stéphane, E.; Japuen, G. *Tetrahedron Lett.* **2002**, *43*, 3463.

(15) Allen, F. H. *Acta Crystallogr.* **2002**, *B52*, 380.

(16) Phenone **11**: $[a]^{23}_D$ −6.7 (*c* 1.0, hexane); FTIR (film) 3060, 2957, 2871, 1674, 1598, 1579, 1447, 1384, 1367, 1284, 1236, 1181, 1159, 1077, 1003, 975, 942, 797, 714, 656 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.2 and 1.4 Hz, 2H); 7.47 (tt, J = 7.4 and 1.2 Hz, 1H); 7.41 (t, J = 7.5 Hz, 2H); 2.45 (ddd, J = 13.2, 9.4, and 3.7 Hz, 1H); 1.88 (m, 1H); 1.89 (d, J = 8.9 Hz, 2H); 1.75 (sext., J = 7.9 Hz, 1H); 1.66 (ddd, J = 16.9, 8.7, and 3.7 Hz, 1H); 1.42 (s, 3H); 1.38 (sext × d, J = 6.7 and 1.7 Hz, 1H); 1.26 (m, 1H); 0.90 (d, J = 6.6 Hz, 3H); 0.89 (d, J = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 206.7, 136.9, 131.8, 129.2, 128.3, 54.7, 46.9, 43.2, 37.6, 33.6, 30.6, 28.0, 21.8, 21.7 ppm; MS *m*/*z* (rel intensity) 230 (4), 212 (1), 187 (10), 124 (25), 105 (100), 81 (63), 69 (80), 55 (28). Anal. Calcd for $C_{16}H_{22}O$ (230.35): C, 83.43; H, 9.63. Found: C, 83.39; H, 9.66.