Reaction of aminosulfur trifluorides with alcohols: inversion *vs.* retention

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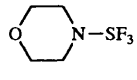
Reaction of aminosulfur trifluorides with alcohols replaces the hydroxy group with fluorine. A study with the cyclic secondary alcohols *trans*-2-bromoindan-1-ol (3), *trans*-2-methylcyclopentanol (7), *cis*-2-methylcyclopentanol (8), *trans*-[2-$^2H_1$]cyclopentanol (9), *cis*-[2-$^2H_1$]cyclopentanol (10) and *trans*-2-fluorocyclopentanol (11) gave primarily inversion of configuration *via* an S_N1-like pathway. The product stereochemistry and alkene formation in the reaction of aminosulfur trifluorides with cyclopentanols was similar to the products of solvolysis of cyclopentyl tosylates in methanol. The stereochemistry of the fluoro products was confirmed by independent synthesis or assigned by ^1H and ^{19}F NMR spectral data except for the deuteriated products 14 and 15 whose stereochemistry was assigned by their ^2H NMR data.

The development of new methods to introduce fluorine into molecules is of great interest to organic and medicinal chemists. The strong electronic contribution and negligible steric demands of fluorine present interesting and unusual properties.[1] Aminosulfur trifluoride reagents are an important class of fluorinating reagents.[2] Diethylaminosulfur trifluoride (DAST), dimethylaminosulfur trifluoride (methyl DAST) and morpholinosulfur trifluoride (morph DAST) are now commercially available. The DAST reagent has been utilized more than the other aminosulfur trifluorides. DAST reacts with aldehydes

DAST R = C_2H_5
methyl DAST R = CH_3



morph DAST

and ketones under mild conditions to give geminal difluorides[2a–c] while organic acids react with DAST to give acid fluorides.[2d] Reaction of mono alcohols with DAST replaces the hydroxy group with fluorine[2a,c] while reaction with diols gives difluorides, sulfite esters or cyclic ethers depending on the number of carbons separating the two alcohol groups.[3] In several studies, monofluorination of sugars has been accomplished by protecting some of the hydroxy groups followed by reaction with DAST.[4]

Both retention and inversion of configuration about the carbon containing the hydroxy group have been noted with DAST reactions. Reactions with sugars[4] are reported to give inversion and in some cases retention of configuration in the replacement of the hydroxy with fluorine; inversion was recorded in the reaction of DAST with steroids,[5] but retention was also observed when inversion appeared unfavourable for steric reasons.[5b] Middleton has shown that conformational effects are also a factor in hindering the S_N2 attack (leading to inversion) by fluoride ion on the reactive intermediates from *cis*- and *trans*-4-*tert*-butylcyclohexanol and morph DAST.[6] Recently we found evidence for both an S_N2 and S_N1 pathway when the fluorohydrins of cyclopentene (1 and 2) were treated with DAST.[7a] Hudlicky also reported that inversion of configuration was the major pathway in the stereospecific synthesis of all four stereoisomers of 4-fluoroglutamic acid.[7b] In this paper we report on the reaction of aminosulfur trifluorides with cyclic secondary alcohols where an S_N1 or S_N2 pathway might be expected.

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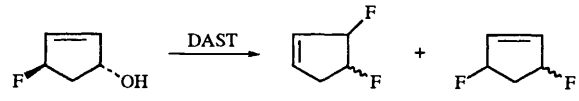
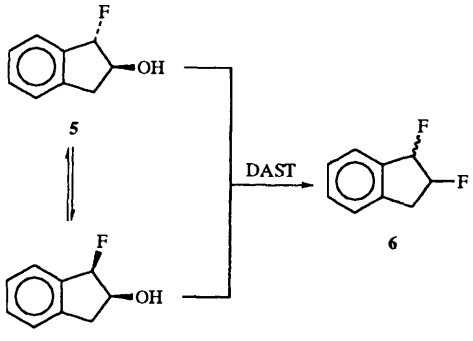


2 *cis* and *trans* isomers

3 4



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Results

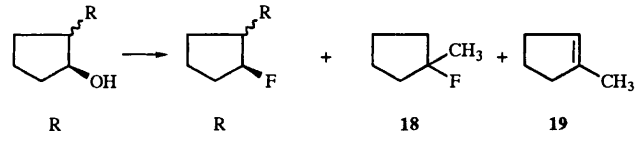
Reaction of DAST with *trans*-2-bromoindan-1-ol (3) gave only *trans*-2-bromo-1-fluorindane (4) in 88% yield. We prepared *trans*-1-fluoro-2-hydroxyindane (5)[8] in which the hydroxy group was not in the benzylic position. Unfortunately 5 rearranges to *cis*-1-fluoro-2-hydroxyindane during the reaction with DAST. Thus the difluorides (6) do not give stereochemical information for this reaction pathway.

We turned our attention to cyclic models with electron-donating (7, 8), electron-neutral (9, 10) and electron-withdrawing (11) substituents (Scheme 1). Reaction of DAST with *trans*- or *cis*-methylcyclopentanol (7 or 8) gave the rearranged

Table 1 Aminosulfur trifluorides with cyclopentanols[a]

Reagent	Alcohol	Solvent	Alkene	18	β-Fluoroproducts *trans*	*cis*	inv./ret.
DAST	**7**	$CDCl_3$	6	68	3	23	7.7
DAST	**7**	pentane	10	67	4	19	4.8
DAST[b]	**7**	CH_2Cl_2[b]	5	65	2	28	—
DAST[b]	**7**	pentane	6	57	2	35	—
DAST	**8**	$CDCl_3$	24	71	5	0.5	10.0
methyl DAST	**7**	$CDCl_3$	5	68	4	21	6.0
methyl DAST	**7**	pentane	6	68	5	21	4.2
methyl DAST	**8**	CH_2Cl_2	25	72	2.7	0.3	9.0
morph DAST	**7**	$CDCl_3$	9	66	5	20	4.0
morph DAST	**7**	pentane	9	71	5	15	3.0
morph DAST	**8**	$CDCl_3$	22	74	3.7	0.3	12.3
DAST	**9**	CH_2Cl_2	25	—	5	70[c]	14[c]
DAST	**9**	pentane	12	—	82		—[d]
DAST[b]	**9**	CH_2Cl_2[b]	14	—	86		—[d]
DAST[b]	**9**	pentane[b]	16	—	84		—[d]
DAST	**10**	CH_2Cl_2	25	—	70	5[c]	14[c]
DAST	**10**	pentane	20	—		80	—[d]
DAST	**11**	CH_2Cl_2	31	—	6	63	10.5
DAST	**11**	pentane	36	—	6	58	9.7
methyl DAST	**11**	CH_2Cl_2	33	—	8	59	7.4
methyl DAST	**11**	pentane	32	—	10	58	5.8
morph DAST	**11**	CH_2Cl_2	31	—	10	59	5.9
morph DAST	**11**	pentane	42	—	8	50	6.3

[a] Product ratios by GLC unless noted. Yields were obtained by NMR spectroscopy with toluene or 1,2-dichloroethane as internal standard. Yields in CH_2Cl_2 were 70–85%. The yields in pentane ranged from 40–60%. Reactions run at 0 °C unless noted. [b] Reactions run at −78 °C. [c] Product ratios by ^2H NMR. [d] Ratios not determined.



7 *trans* CH_3
8 *cis* CH_3
9 *trans* D
10 *cis* D
11 *trans* F

12 *trans* CH_3
13 *cis* CH_3
14 *trans* D
15 *cis* D
16 *trans* F
17 *cis* F

Scheme 1

product 1-fluoro-1-methylcyclopentane (**18**) as the major component (Table 1). Analysis of the minor products shows that inversion of configuration is preferred in the reaction of each of the three aminosulfur trifluorides with **7** and **8**. The yields and percent inversion are not greatly influenced by the solvent or by the aminosulfur trifluoride (Table 1).

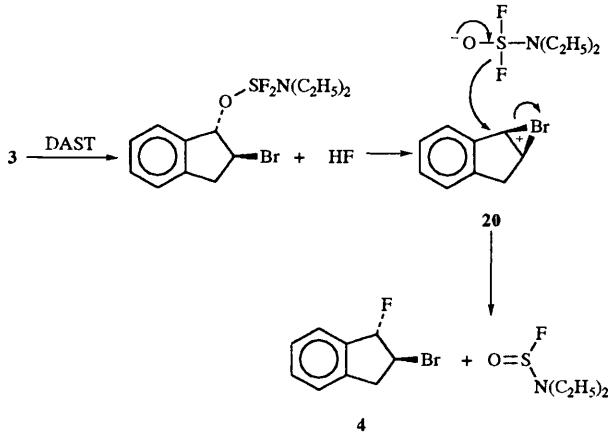
Reaction of DAST with **9** or **10** gave product yields 60–85% in either pentane or methylene chloride as solvent. The percent inversion was greater than 95% as determined by ^2H NMR (Table 1). We were unable to distinguish between the *trans* or *cis* isomers (**14** or **15**) by GLC, gas phase IR, or ^1H, ^{19}F, ^{13}C NMR. The deuterium resonances were at 1.71 and 1.91 ppm relative to $CDCl_3$ (7.24 ppm) for **14** and **15**, respectively.

Reaction of *trans*-2-fluorocyclopentanol (**11**) with either of the aminosulfur trifluorides gave mostly inversion and, in terms of stereochemistry, was similar to that found with **7** and **8** (Table 1). We were unable to prepare the *cis*-isomer of **11** for this study.

1-Methylcyclopentene (**19**) was from 5 to 25% of the product mixture for reaction of aminosulfur trifluorides with cyclopentanols **7** and **8**. [$^2H_1$]Cyclopentenes and 1-fluorocyclopentene were formed in 12–25 and 31–42%, respectively (Table 1).

Discussion

Reaction of aminosulfur trifluorides with alcohols that can form stable ions proceeds through an S_N1-like pathway. For example, Middleton reported carbocation-type rearrangements and alkene formation with alcohols like *tert*-butyl and crotyl (*trans*-but-2-enyl) alcohol;[2a] and we observed both 3,4- and 3,5-difluoro products from an allyl carbocation with DAST and cyclopentenol (**2**).[7a] Reaction of DAST with the *trans*-bromohydrin (**3**) gives *trans*-2-bromo-1-fluoroindane (**4**). Retention of configuration for this reaction is due to formation of a stable bromonium ion **20** and its reaction with the fluoride ion. A similar retention of configuration by back-side participation of a carbonyl and a sulfur was observed for reaction of DAST with nucleosides.[4b]



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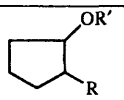
Our data suggest that a significant charge is developed along the reaction pathway for the reaction of secondary alcohols with aminosulfur trifluorides. For example, cyclopentanols **7**, **8**, **9**, **10** and **11** react with aminosulfur trifluorides to give a high degree of inversion (Table 1) which is comparable to that observed for solvolysis reactions. Solvolysis of *cis*-2-deuterocyclopentyl (*cis*-[2-$^2H_1$]cyclopentyl) brosylate,[9] and *cis*- or

Table 2 Solvolysis of *cis*- and *trans*-cyclopentyl sulfonates



R	R′	Ratio Ether:olefin	*cis*:*trans*	Yield (%) 1-Alkoxy-1-methylcyclopentane	Inversion
R = *cis*-CH_3	R′ = Ts[a]	60:40[b]	2:98	14	98
R = *trans*-CH_3	R′ = Ts[c]	72:38[d]	98:2	8	98
R = *cis*-[$^2H_1$]	R′ = Bs[e]	78:22[f]	8:92[g]	—	92[f]
R = *trans*-[$^2H_1$]	R′ = Bs[h]	80:20	—	—	—

[a] Ref. 10. [b] The olefins are 1-methylcyclopent-1-ene and 3-methylcyclopent-1-ene (92.8). [c] Our data.[12] [d] The olefin was 1-methylcyclopent-1-ene. No 3-methylcyclopent-1-ene was observed. [e] Solvolysis in 70% ethanol–water.[11] [f] The 78% was a mixture of cyclopentanol and cyclopentyl ether (44.5:34.7).[11] [g] Solvolysis in anhydrous ethanol.[9] [h] Solvolysis in 70% ethanol–water.[11] Ts = tosylate; Bs = brosylate.

trans-2-methylcyclopentyl tosylates[10] gave greater than 90% inversion (Table 2).†

A carbocation intermediate concept is also supported by the large amount of cyclopentenes from aminosulfur trifluoride reactions with cyclopentanols **9**, **10**, **11**; and the 1-methylcyclopentene plus 1-fluoro-1-methylcyclopentane (**18**) from reaction with **7** and **8**. A mixture of [1-$^2H_1$]- and [3-$^2H_1$]-cyclopentene represent 25% of the product composition of the reaction of DAST with **9** and **10** (Table 1). This is similar to the amount of [$^2H_1$]cyclopentene produced by solvolysis of *cis*- and *trans*-2-deuterocyclopentyl ([2-$^2H_1$]cyclopentyl) brosylate[11] (Table 2).

Conclusions

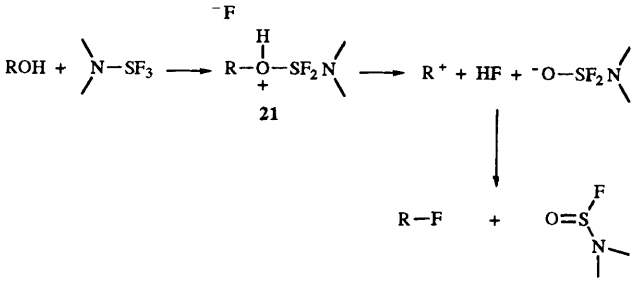
The alcohol moiety is converted to a very good leaving group **21** in these aminosulfur trifluoride reactions. A high degree of inversion is to be expected for a short-lived carbocation intermediate that reacts as an intimate ion pair. Thus we conclude that aminosulfur trifluorides react with alcohols *via* an S_N1-like process with cation intermediates that are benzylic, allylic, tertiary or even secondary. We anticipate that an S_N2 process would be involved for reaction of aminosulfur trifluorides with primary alcohols.

Experimental

General methods

cis-2-Methylcyclopentanol (**8**) was prepared by reduction of 2-methylcyclopentanone with L-Selectride.[13] *trans*-[2-$^2H_1$]-cyclopentanol (**9**) was prepared from the reaction of lithium aluminium deuteride with cyclopentene oxide.[14] The *cis*-isomer **10** was obtained by deuterioboration of cyclopentene.[15] DAST was purchased from Carbolabs, Inc. The remaining chemicals were obtained from the Aldrich Chemical Company. NMR spectra were obtained on a Varian Unity 300 (University of San Diego) and are reported relative to Me_4Si or $CFCl_3$; *J* values are given in Hz. Mass spectral analyses were obtained at 70 eV on a Hewlett-Packard 5890 GC interfaced with an HP 5970A mass selective detector. Gas chromatography analysis was accomplished on an HP 5890 (FID detector) interfaced to a 3396A integrator. The GLC and GLC–MS analyses were done with a 25 m Hewlett-Packard ultraperformance column of internal diameter 0.20 mm with a methyl silicone stationary phase of 0.33 μm film thickness. Initial temperature 40 °C for 4 min, then ramped at 10 °C min^{-1} to 180 °C. Infrared spectra were recorded neat with a Nicolet 610 Fourier Transform spectrometer. Gas phase IR spectra were obtained on the Nicolet 610 interfaced with an HP 5890 gas chromatograph. The 25 m column for GLC–FTIR analysis was identical to that used for GLC and GLC–MS analyses above, except for the internal diameter which was 0.3 mm.

† Brosylate = *p*-bromobenzenesulfonate; tosylate = toluene-*p*-sulfonate.



General procedure

The following reaction is representative. To 82 mm^3 (76 mg, 0.76 mmol) of *trans*-2-methylcyclopentanol and 3.0 ml of dry methylene chloride (dried over molecular sieves) at 0 °C with stirring under nitrogen, was slowly added 100 mm^3 (0.12 g, 1.0 mmol) of DAST. The mixture was stirred for 30 min at 0 °C and then added to aqueous 5% sodium hydrogen carbonate. The organic layer was separated and the aqueous layer extracted with methylene chloride. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and analysed by GLC and GLC–MS. The yields for these reactions were 70–85% in methylene chloride or chloroform, and 40–60% in pentane as determined by NMR spectroscopy with toluene or 1,2-dichloroethane as internal standard. The product distributions are given in Table 1.

From *trans*- or *cis*-2-methylcyclopentanol (7 or 8). Gas chromatographic analysis gave the following compounds (retention times): **19** (2.8), **18** (3.1), **12** (3.4) and **13** (3.6). 1-Methylcyclopentene (**19**) was identified by comparison of the GLC–MS of **19** with a commercial sample. Compound **13**, *cis*-2-fluoro-1-methylcyclopentane, was isolated by preparative GLC and found to be >90% pure by GLC with the following data: δ_H($CDCl_3$, TMS) 1.10 (dd, *J* 7.0 and 1.2, 3 H), 1.35–2.00 (m, 7 H), 4.84 (dtd, *J* 54.6, 4.0 and 1.5, 1 H); δ_F($CDCl_3$, $CFCl_3$) −190.5 (m); *m*/*z* (GLC–MS) (rel. intensity) 102 (M^+, 8%), 82 (3), 74 (19), 73 (6), 69 (3), 67 (12), 61 (5), 60 (7), 59 (22), 57 (7), 56 (100), 55 (19), 54 (5), 53 (6), 42 (11), 41 (49), 39 (23), 27 (20). Attempts to isolate pure *trans*-2-fluoro-1-methylcyclopentane **12** were unsuccessful. The following data were obtained on a crude reaction mixture: δ_H($CDCl_3$, TMS) 0.97 (dd, *J* 7.8 and 2.0), 4.57 (dm, *J* 49); δ_F($CDCl_3$, $CFCl_3$) −173.7 (m); *m*/*z* (GLC–MS) (rel. intensity) 102 (M^+, 6%), 82 (3), 74 (16), 73 (5), 69 (3), 67 (12), 61 (5), 60 (7), 59 (20), 57 (7), 56 (100), 55 (20), 54 (4), 53 (6), 42 (12), 41 (52), 39 (24), 27 (21). Compound **18** decomposed and eliminated hydrogen fluoride to give **19** during preparative gas chromatography.

Independent synthesis of 1-fluoro-1-methylcyclopentane (18). To 170 mg (1.70 mmol) of 1-methylcyclopentanol in 0.925 cm^3 of $CDCl_3$ at 0 °C was added 190 mm^3 (230 mg, 1.44 mmol) of DAST. After 15 min the solution was concentrated at reduced pressure. The remaining solvent and **18** were bulb-to-bulb distilled at room temperature and collected in a dry ice–acetone

bath. Analysis by NMR spectroscopy showed **18** to be >90% pure. The GLC–MS data were identical with **18** obtained from reaction of **7** or **8** with aminosulfur trifluorides. The following data were obtained: δ_H(300 MHz, $CDCl_3$) 1.47 (d, *J* 21.0, 3 H), 1.59–1.74 (m, 4 H), 1.75–2.40 (m, 4 H); δ_F(282 MHz, $CDCl_3$) −134.9. The ^{13}C NMR data were identical to that reported in the literature.[16] *m/z* (GLC–MS) (rel. intensity) 102 (M^+, 4%), 82 (6), 74 (57), 73 (100), 67 (36), 61 (26), 60 (40), 59 (60), 55 (20), 53 (17), 51 (8), 47 (9), 41 (43), 39 (41), 27 (34).

Synthesis of *trans*-2-fluorocyclopentanol (11). To 6.00 cm^3 (5.78 g, 0.0687 mol) of cyclopentene oxide in 70 cm^3 of 1.0 M tetrabutylammonium fluoride in a polyethylene bottle with a magnetic stirring bar, was slowly added, *via* a polypropylene syringe, 20 cm^3 pyridinium poly(hydrogen fluoride) at 0 °C. The mixture was allowed to warm to room temperature and then stirred for 3 h. Aqueous work-up, extraction with diethyl ether, washing with aqueous sodium hydrogen carbonate, drying with anhydrous magnesium sulfate and concentrating on a rotary evaporator gave an oil which was distilled (bulb-to-bulb at room temperature) to give 3.65 g (0.0351 mol) **11** in 50% yield (no attempt was made to maximize the yield). Subsequent distillation at 35–38 °C at 15 torr (lit. 55–57 °C, 17–18 torr)[17] gave **11** (95% by GLC, major impurity diethyl ether) with the following data: δ_H(300 MHz, $CDCl_3$) 1.18–2.14 (m, 6 H), 2.94 (br s, 1 H), 4.28 (dm, *J* 14, 1 H), 4.84 (ddt, *J* 52.0, 8.4 and 2.8, 1 H); δ_C(75.4 MHz, $CDCl_3$) 20.7 (d, *J* 1.7), 30.0 (d, *J* 21.54), 31.8 (d, *J* 1.7), 76.7 (d, *J* 27.2), 99.0 (d, *J* 175.7); δ_F(282 MHz, $CDCl_3$) −180.5 (m) lit. −181;[17] *m/z* (GLC–MS) (rel. intensity) 104 (5%), 86 (5), 85 (7), 75 (5), 76 (6), 58 (8), 57 (100), 55 (11), 43 (8), 42 (9), 41 (12), 39 (12), 31 (7), 30 (5), 27 (16).

Synthesis of 1,2-difluorocyclopentanes. Gas chromatographic analysis gave the following compounds (retention times): 1-fluorocyclopentene (3.4), **16** (5.0) and **17** (5.3). The GLC–MS for these data are identical to those obtained from independent synthesis.[18,19]

Synthesis of 1-fluoro[2-$^2H_1$]cyclopentanes. Gas chromatography analysis of reactions with **9** or **10** gave the following compounds (retention time): [2-$^2H_1$]cyclopentenes (1.9),[11] **14** and **15** (2.5). Bulb-to-bulb distillation of the crude reaction mixtures gave ^2H NMR (46 MHz, $CDCl_3$) {^1H} broad band decoupled **14** δ 1.71 (d, *J* 5.5); **15** δ 1.91 (d, *J* 3.8).[20] The following data were identical for both **14** and **15**: δ_H($CDCl_3$, TMS) 1.45–1.70 (m, 4 H), 1.70–2.05 (m, 3 H), 5.14 (dm, *J* 50, 1 H); δ_F(282 MHz, $CDCl_3$, $CFCl_3$) −170.7 (m); *m/z* (GLC–MS) (rel. intensity) 89 (0.6%), 74 (6), 70 (7), 69 (34), 68 (12), 61 (15), 60 (27), 59 (18), 57 (5), 56 (18), 47 (5), 46 (4), 44 (4), 43 (98), 42 (100), 41 (34), 40 (27), 39 (32), 27 (24); GLC–FTIR 2963 (s), 2804 (m), 2180 (w), 1440 (w), 1353 (m), 1036 (w), 978 (m) and 750 (w) cm^{-1}.

Synthesis of *trans*-2-bromo-1-fluoroindane (4). Analysis of the crude reaction mixture by NMR spectroscopy with toluene as internal standard gave **4** in 88% yield. The ^1H and ^{19}F NMR data were identical to that reported in the literature.[21]

Solvolysis. Tosylates of **7** and **8** were prepared and solvolysis carried out as described in the literature.[10] The methoxymethylcyclopentane products were independently synthesized by standard reactions from their alcohols.[22] Although these compounds are known in the literature, we present here for the first time their spectral data.

cis-2-*Methoxy*-1-*methylcyclopentane*.[10,23]—δ_H($CDCl_3$, TMS) 0.97 (d, *J* 6.8, 3 H), 1.27–1.78 (m, 6 H), 1.81–2.03 (m, 1 H), 3.29 (s, 3 H) and 3.45–3.60 (m, 1 H); δ_C(75.4 MHz, $CDCl_3$) 13.7, 14.1, 30.0, 31.4, 38.1, 57.1 and 85.4; ν(gas)/cm^{-1} 2963 (s), 2889 (s), 2831 (m), 1463 (w), 1361 (w), 1205 (w) and 1109 (s); *m/z* (GLC–MS) (rel. intensity) 114 (M^+, 32%), 99 (1), 86 (3), 85 (35), 82 (18), 72 (12), 71 (100), 67 (16), 58 (17), 55 (16), 43 (12), 41 (25) and 39 (13).

trans-2-*Methoxy*-1-*methylcyclopentane*.[10,23]—δ_H($CDCl_3$, TMS) 0.99 (d, *J*, 6.4, 3 H), 1.05–1.23 (m, 1 H), 1.50–2.00 (m, 6 H) and 3.30 (s, superimposed over a mult. from 3.20–3.38 ppm, 4 H); δ_C(75.4 MHz, $CDCl_3$) 18.7, 19.0, 30.6, 31.9, 39.5, 56.6 and 89.4; ν(gas)/cm^{-1} 2963 (s), 2885 (s), 2831 (m), 1464 (w), 1370 (w), 1202 (w) and 1117 (s); *m/z* (GLC–MS) (rel. intensity) 114 (M^+, 14%), 99 (0.5), 86 (2), 85 (25), 82 (15), 72 (11), 71 (100), 67 (21), 58 (27), 55 (21), 43 (22), 41 (49), 39 (28), 29 (38) and 27 (29).

1-*Methoxy*-1-*methylcyclopentane*.[24]—δ_H($CDCl_3$, TMS) 1.18 (s, 1 H), 1.29–1.80 (m, 8 H) and 3.11 (s, 3 H); δ_C(75.4 MHz, $CDCl_3$) 22.9, 28.3, 37.7, 50.0 and 84.5; ν(gas)/cm^{-1} 2968 (s), 2833 (w), 1460 (w), 1372 (w), 1211 (m) and 1088 (s); *m/z* (GLC–MS) (rel. intensity) 114 (M^+, 8%), 99 (13), 86 (10), 85 (100), 72 (57), 71 (17), 67 (16), 55 (53), 43 (43), 41 (36), 39 (25), 29 (17) and 27 (23).

Acknowledgements

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