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Nucleophilic displacement of homoallylic tosylates: influence of steric hindrance and conformational rigidity

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Abstract—A comparative study on the nucleophilic displacement of homoallylic tosylates with different degrees of hindrance and rigidity is reported. π Bond participation is favoured by hindrance and rigidity, and also by weak nucleophiles such as water or dimethylformamide.

The neighboring group participation by π bonds in aliphatic nucleophilic substitution has been demonstrated for norbornyl systems in kinetic and spectroscopic studies.[1] We have recently reported that tosylate **1** undergoes nucleophilic displacement with participation of the π bond when it reacts with malonate and hydroxyl anions, while other nucleophiles give a normal S_N2 displacement.[2]

Among the plethora of factors that may affect the displacement of homoallylic tosylates, here we have tested two that to our knowledge have not been studied previously: the influence of steric hindrance in the homoallylic system and the conformational rigidity of the system.

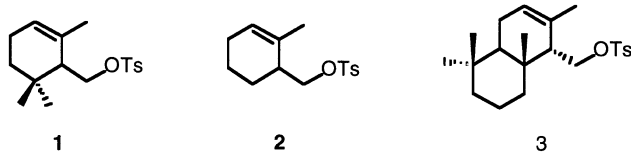
For the comparative displacement study we chose three tosylates, a hindered and flexible one **1**, an unhindered and flexible one **2**, and a hindered and rigid one **3** (Fig. 1). The simplest compound **2**, among the selected tosylates, was obtained from Hagemann's ester by selective deoxygenation by the Srikrishna method,[3] followed by reduction and tosylation. The sterically hindered tosylate **1** was obtained from α-cyclogeraniol[4] and the rigid tosylate **3** from *epi*-drimenol.[5]

We began the study with the hindered and flexible tosylate **1** for which preliminary results obtained by reaction of **1** with several nucleophiles have been reported elsewhere.[2] Here, the nucleophilic displacement study was extended to weak nucleophiles such as pivalate salts. We were interested also for the influence of the size of the counterion in the nucleophilic displacement of tosylate **1** by the pivalate anion, in relation with the reported effect of the cation associates to pivalate anion on the product distribution from the nucleophilic displacement of allylic substrates.[6]

The reactions were approached with two solvents and refer to Eq. (1) and Table 1. Both solvents have a common feature; the reaction rate increases as the size of the counterion increased. The order of reactivity based on the size of the cation is attributed to a decrease in ion pairing as the size of the cation increases, taking into account that coulombic attraction dominates over the counterion solvation.[7]

Significant differences in the reaction products were observed for each solvent. In DMPU, only the normal displacement product **5** (X=OPiv) was obtained. However, in DMF, besides the S_N2 product **5** (X=OPiv) the bicyclic formate **4** (X=OCOH) was obtained, corresponding to the homoallylic displacement of tosylate **1** by the solvent DMF. The very low reactivity of lithium pivalate makes DMF a good competitor (Eq. (2)).

Tosylate **2** was selected for its functional and structural characteristics, very similar to those of tosylate **1**. The main structural difference of tosylate **2** with respect to its analogue **1** is the absence of the *gem*-dimethyl in the environment of the homoallylic system, which is expected to facilitate normal S_N2 nucleophilic displacement. The reaction of **2** with a basic aqueous solution in DMF at 50°C gave exclusively the alcohol **6** (X=OH). All the reactions



1 2 3

Figure 1.

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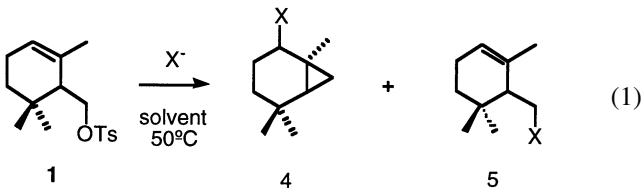


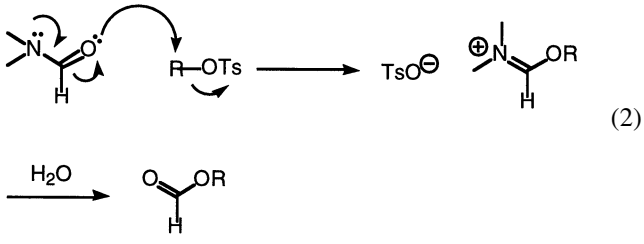
(1)

The reaction of tosylate **2** with other nucleophiles, in a parallel way to that described for tosylate **1** by us previously,[2] gave exclusively the products of normal displacement (Eq. (4)). Differences in the behaviour of tosylates **1** and **2** were only found for the reaction with sodium malonate. The hindered tosylate **1** gave homoallylic displacement, whereas the unhindered tosylate **2** gave normal S_N2 displacement.

Table 1.

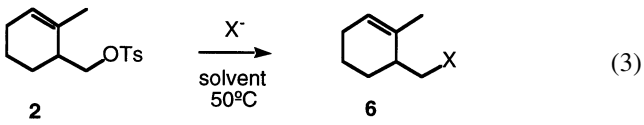
Nucleophile	Counterion	DMF		DMPU	
		Time 48 h conversion (%)	Product ratio **5** (X=OPiv): **4** (X=OCOH)	Time 48 h conversion (%)	Product ratio **5** (X=OPiv): **4** (X=OCOH)
$PivO^-$	Li^+	56	50:50	10	100:0
$PivO^-$	Na^+	86	60:40	60	100:0
$PivO^-$	K^+	93	80:20	80	100:0

described in Eq. (3) and Table 2 with DMF as solvent were slower than the correspondent was for tosylate **1** (Eq. (1), Table 1). Likewise, all the products obtained arise from normal S_N2 nucleophilic displacement. These results contrast with those obtained for the hindered tosylate **1** (Table 1) for which homoallylic displacement in the reaction with the very weak nucleophile DMF was found. This, together with the faster displacement reaction of tosylate **1**, is evidence of the neighboring group participation or the existence of a homoallylic carbocation. It is thought that in the case of tosylate **1** the hindered environment (i.e. *gem*-dimethyl) is responsible for this behaviour.

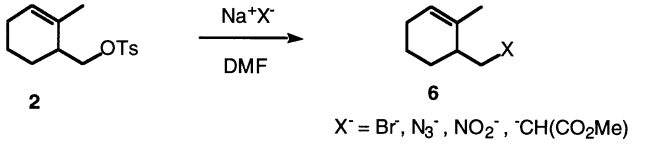


(2)

The influence of counterion size in the displacement of tosylate **2** by pivalate anion in two solvents, DMF and DMPU (Table 2) was similar to that of the hindered tosylate **1**. A small but significant difference was found in DMPU when tosylates **1** and **2** were compared. The normal S_N2 displacement was faster for the less hindered tosylate **2** as would be expected (Tables 1 and 2).



(3)



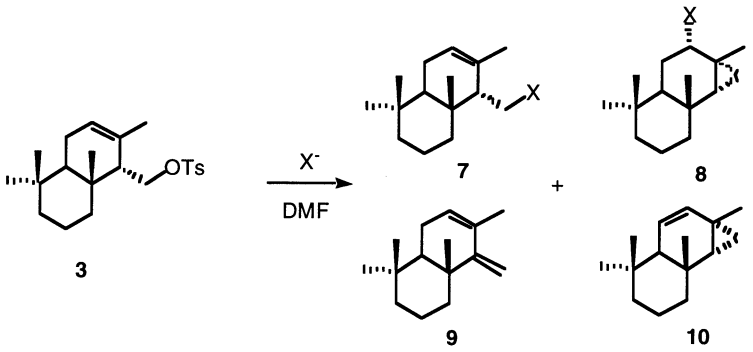
(4)

The third substrate selected for the displacement study was the bicyclic tosylate **3**, which has both the steric hindrance factor, found in tosylate **1**, and a new factor: the conformational rigidity. The results found for the reactions of tosylate **3** with several different nucleophiles are described in Eq. (5) and Table 3.

Table 3 shows those weak nucleophiles such as water and ethanol (entries **1** and **2**) gave homoallylic displacement exclusively, while pivalate and acetate anions (entries 3 and 4) gave products from normal and homoallylic displacement in equal amounts. This result contrasts with that found for tosylate **1**, for which no homoallylic displacement was observed in the reaction with the pivalate anion. The hydroxide anion is a stronger nucleophile than carboxylates, but at the same time is a stronger base; these properties are reflected in the reaction with tosylate **3**, which afforded equal amounts of normal **7** and homoallylic **8** displacement and the elimination product **9** (entry 5). Nothing new was observed for the reaction of **3** with respect to **1** with the malonate anion (homoallylic displacement) and the phenyl sulfide anion (normal displacement), (entries 6 and 12). The results were completely new for the reaction with the bromide or iodide anions, which afforded the elimination product **9**, and the tricyclic unsaturated hydrocarbon **10**, presumably formed by homoallylic displacement

Table 2.

Nucleophile	Counterion	DMF		DMPU	
		Time 48 h conversion (%)	Product	Time 48 h conversion (%)	Product
$PivO^-$	Li^+	30	**6** (X=OPiv)	50	**6** (X=OPiv)
$PivO^-$	Na^+	50	**6** (X=OPiv)	100	**6** (X=OPiv)
$PivO^-$	K^+	70	**6** (X=OPiv)	100	**6** (X=OPiv)



(5)

Table 3.

Entry	Nucleophile	T(°C)	t (h)	% Yield			
				7	**8**	**9**	**10**
1	EtOH[a]	50	16		(X=OEt) 100		
2	5N H_2O/NaOH[b]	50	16		(X=OH) 95		
3	NaOPiv	50	6	(X=OPiv) 46	(X=OPiv) 53		
4	KOAc	50	6	(X=OAc) 50	(X=OAc) 48		
5	NaOH[c]	70	16	(X=OH) 36	(X=OH) 32	27	
6	$NaCH(CO_2Me)_2$	100	6		$(X=CH(CO_2Me)_2)$ 86		
7	NaCN	50	30	(X=CN) 73	(X=CN) 19		
8	NaBr	50	16			37	61
9	NaI	50	16			32	61
10	$NaNO_2$	60	6	(X=ONO) 56	(X=ONO) 40		
11	Me_2CuLi	25	12	(X=OH) 97			
12	NaSPh/Bu_4NBr	25	24	(X=SPh) 93			

[a] No DMF.
[b] Solvent DMF.
[c] No H_2O.

followed by dehydrohalogenation (entries 8 and 9). The cyanide anion (entry 7) gave mainly the normal displacement product **7** (X=CN) and some homoallylic displacement **8** (X=CN)[8] as occurred for the nitrite anion (entry 10). In the reaction of **3** with nitrite anion the respective alkyl nitrites **10** and **11** (X=ONO) was obtained, which were hydrolysed in the isolation procedure to alcohols **10** and **11** (X=OH), respectively. It is interesting to note that the last two nucleophiles gave the normal displacement product (i.e. the cyano and nitro compounds) in the reaction with tosylate **1**. Moreover, the ambidentate anion nitrite attacks the tosylate **3** with the oxygen atom and the tosylate **1** with the nitrogen atom.

Finally, the reaction of **3** with the dimethyl lithium cuprate reagent (entry 11) afforded the alcohol **7** (X=OH) which must arise from the attack on the sulphur atom of the tosyl group by the 'methyl anion'. This result is also different to that found for tosylate **1** which afforded the normal displacement product **5** (X=Me) (Eq. (1)).

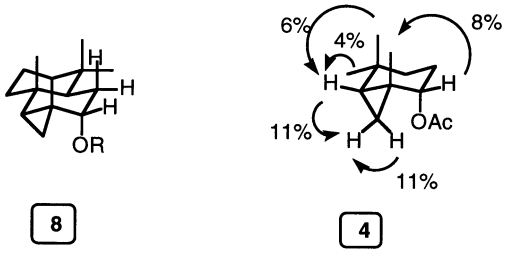


Figure 2.

1. Stereochemical outcome of nucleophilic displacements

The sterochemistry of the tricyclic alcohol **8** (X=OH) (Fig. 2), which arose from the homoallylic displacement of the tosylate **3**, was assigned according to its ^{1}H NMR spectrum, which among others shows a doublet signal centred at 4.18 ppm with a coupling constant of J=5.5 Hz attributed to the hydrogen geminal to the axial hydroxyl group (Fig. 2). The analogous signal of the corresponding acetate **8** (X=OAc) (Fig. 2) appears as a double doublet at 5.18 ppm with J=6 Hz and J'=2 Hz. The same tricyclic alcohol was obtained by hydrolysis of the acetate 8 (X=OAc), pivalate 8 (X=OPiv) and nitrite 8 (X=ONO). From these data it is clear that the entering nucleophile has the α orientation, which is *cis* with respect to the cyclopropanic methylene. The situation must be similar for the cyano[8] and malonate derivatives.

The relative *cis* orientations of the hydroxyl group and the cyclopropanic methylene in the bicyclic alcohols **4** (X=OH) are the same, as has been shown for the tricyclic alcohol **8**. These structures were elucidated through their ^{1}H NMR spectra, H–C correlations and NOE experiments. For the trimethyl acetate **4**, the signal triplet centred at 5.08 ppm and J=J'=6 Hz indicate an axial orientation for the acetate group, which can be accommodated in two isomers; only the isomer in which the cyclopropanic methylene and the acetate group are *cis* can justify the NOE between the cyclopropanic hydrogen and the *gem*-dimethyl system.

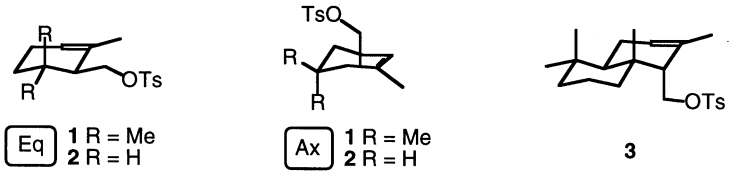


Figure 3.

2. Discussion

From the data it is observed that while tosylate **2** only afforded S_N2 displacement products with all kind of nucleophiles assayed, the tosylate **3** gave mixtures of homoallylic and normal displacements products, exception made of thiolate and 'methyl' nucleophiles. In the middle is the tosylate **1**, which gave homoallylic displacement only with poor nucleophiles (H_2O, DMF), and malonate anion. It seems to be clear that nucleophile nature exclusively does not control the regioselectivity observed. For example, pivalate anion gave normal S_N2 displacement with tosylates **1** and **2**, and homoallylic with **3**; malonate anion gave normal displacement with **2** and homoallylic with **1** and **3**, We have not found a general criterion to explain the reactivity pattern of nucleophiles, for example, with tosylate **3**, the anions iodide and thiolate, which are both good nucleophiles and soft bases shown different behaviour. Likewise, iodide (good nucleophile and soft base) and pivalate (poor nucleophile and hard base) anions show behaviour affinities.

The conformational rigidity and the good orientation of the leaving group are the factors, which govern the π participation to give homoallylic displacement. In the bicyclic tosylate **3** the double bond is in a geometric favourable position for backward attack on the carbon bearing the leaving group.

The tosylates **1** and **2** can adopt two main conformations (Fig. 3) which differ in 0.3 kcal/mol, approximately;[9] while for the trimethyl tosylate **1** the axial conformation is favourite, the equatorial one is the main for the monomethyl tosylate **2**. The little energy difference between axial and equatorial conformation will not justify the reactivity differences between **1** and **2**, but it do if is added the steric hindrance factor. In conclusion, when the leaving group is in a correct orientation hindrance, rigidity, and poor nucleophilicity favour the π bond participation.

3. Experimental

3.1. General methods

Commercial reagents were used as received. Diethyl ether was distilled from sodium. Dimethylformamide was distilled under nitrogen from BaO. Hexane and ethyl acetate were distilled before use. Melting points were determined on a hot-stage apparatus and are not corrected. IR spectra were obtained on a Bomem FT MB-100 as thin films. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker WP 200 SY (200 and 50 MHz, respectively) or on a Bruker Advance DRX 400 (400 and 100 MHz, respectively). Mass spectra were obtained on a Shimadzu 17A GC/QP 5000 MS at 70 eV (EI). Elemental analyses were obtained on a LECO CHNS-932 instrument. All reactions were carried out under an argon atmosphere in glassware dried overnight and cooled under argon. Reactions were monitored by TLC. Flash column chromatographies were carried out using silica gel 60 (0.040–0.063 mm Merck). Organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure with the aid of a rotary evaporator.

3.1.1. Reaction of tosylate 1 with pivalates salts—General procedure. To a stirred solution of tosylate **1** (308 mg, 1 mmol) in DMF or DMPU (4 ml) was added pivalate salt (1.5 mmol). The reaction mixture was stirred at 50°C under argon atmosphere for 48 h. Diethyl ether was added and the organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether.

3.1.2. 1,5,5-Trimethyl-bicyclo[4.1.0]heptan-2-yl formate 4 (X=OCOH). Colourless oil: IR ν 2955, 1724 cm^{-1}; ^1H NMR δ 0.25 (1H, dd, J=4 Hz, J'=8 Hz), 0.60 (2H, m), 0.92 (3H, s), 1.06 (3H, s), 1.12 (3H, s), 5.21 (1H, t, J=6 Hz), 8.10 (1H, s) ppm; MS *m/z* (relative intensity) 182 (1, M^+), 154 (5), 136 (40), 121 (79), 107 (48), 93 (100), 81 (55), 67 (50), 55 (62); HRMS (EI) calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1336.

3.1.3. α-Cyclogeranyl pivalate 5 (X=OCOPiv). Colourless oil: IR ν 2967, 1728 cm^{-1}; ^1H NMR δ 0.91 (3H, s), 0.94 (3H, s), 1.18 (9H, s), 1.71 (3H, s), 4.04 (1H, dd, J= 3 Hz, J'=11 Hz), 4.14 (1H, dd, J=5.5 Hz, J'=11 Hz), 5.45 (1H, m) ppm; MS *m/z* (relative intensity) 238 (1, M^+), 181 (12), 154 (20), 136 (22), 121 (73), 107 (25), 93 (78), 81 (40), 57 (100), 41 (25); HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.2001.

3.1.4. Reaction of tosylate 2 with H_2O/NaOH. To a stirred solution of tosylate **2** (280 mg, 1 mmol) in DMF (4 ml) was added 5N aqueous solution of NaOH (1 ml). The reaction mixture was stirred at 50°C under argon atmosphere for 48 h, and diluted with diethyl ether. The organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether to yield (2-methyl-cyclohex-2-enyl)-methanol **6** (X=OH) as a colorless oil (38 mg, 30%): IR ν 3349, 1022 cm^{-1}; ^1H NMR δ 1.63 (3H, s), 1.89 (3H, m), 3.60 (2H, m), 5.47 (1H, m) ppm; MS *m/z* (relative intensity) 126 (42, M^+), 108 (78), 93 (100), 79 (68), 67 (92), 41 (70).

3.1.5. Reaction of tosylate 2 with pivalates salts—General procedure. To a stirred solution of tosylate **2** (280 mg, 1 mmol) in DMF or DMPU (4 ml) was added

pivalate salt (1.5 mmol). The reaction mixture was stirred at 50°C under argon atmosphere for 48 h. Diethyl ether was added and the organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether.

3.1.6. 2-Methyl-cyclohex-2-enyl-methyl pivalate 6 (X=OCOPiv). Colorless oil: IR ν 2930, 1732 cm^{-1}; ^1H NMR δ 1.20 (9H, s), 1.70 (3H, s), 1.97 (3H, m), 4.01 (1H, dd, J=7 Hz, J'=11 Hz), 4.15 (1H, dd, J=5 Hz, J'=11 Hz), 5.50 (1H, m) ppm; MS *m/z* (relative intensity) 210 (1, M^+), 108 (88), 93 (100), 79 (45), 67 (21), 57 (95); HRMS (EI) calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1653.

3.1.7. 6-Bromomethyl-1-methyl-cyclohexene 6 (X=Br). A solution of tosylate **2** (200 mg, 0.7 mmol) in DMF (6 ml) was added NaBr (216 mg, 2.1 mmol), and the reaction mixture was stirred under argon at 80°C for 48 h. Water was added and the mixture was extracted with diethyl ether. The organic layer was washed with aqueous $NaHSO_3$ (5%), brine, dried and evaporated to yield a yellow oil (119 mg, 88%) identified as the bromo derivative 6 (X=Br): IR ν 2930, 1449, 648 cm^{-1}, ^1H NMR δ 1.70 (3H, s), 1.95 (3H, m), 3.40 (1H, dd, J=9 Hz, J'=10 Hz), 3.60 (1H, dd, J=4 Hz, J'=10 Hz), 5.55 (1H, m) ppm; HRMS (EI) calcd for $C_8H_{13}Br$ 188.0201, found 188.0197.

3.1.8. 2-Methyl-cyclohex-2-enylmethyl-azide 6 (X=N_3). A solution of tosylate **2** (200 mg, 0.7 mmol) in DMF (3 ml) was added NaN_3 (247 mg, 3.4 mmol), and the reaction mixture was stirred under argon at 80°C for 4 h. Diethyl ether was added and the organic layer was washed with water, brine, dried and evaporated to yield a colorless oil (105 mg, 97%) identified as the methyl azide **6** (X=N_3): IR ν 2930, 2097 cm^{-1}, ^1H NMR δ 1.69 (3H, s), 1.98 (3H, m), 3.25 (1H, dd, J=7, 12 Hz), 3.45 (1H, dd, J=4.5 Hz, J'=12 Hz), 5.55 (1H, m) ppm, HRMS (EI) calcd for $C_8H_{13}N_3$ 151.1109, found 151.1162.

3.1.9. 1-Methyl-6-nitromethyl-cyclohexene 6 (X=NO_2). A solution of tosylate **2** (200 mg, 0.7 mmol) in DMF (3 ml) was added $NaNO_2$ (192 mg, 2.8 mmol), and the reaction mixture was stirred under argon at 80°C for 12 h. Diethyl ether was added and the organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated to yield a colorless oil (102 mg, 92%) identified as the nitro compound **6** (X=NO_2): IR ν 2928, 1553, 1451, 1020 cm^{-1}, ^1H NMR δ 1.70 (3H, s), 1.95 (3H, m), 3.69 (2H, m), 5.60 (1H, m) ppm; MS *m/z* (relative intensity) 155 (4, M^+), 140 (28), 125 (4), 111 (13), 95 (100), 79 (46), 67 (70), 40 (58); HRMS (EI) calcd for $C_8H_{13}NO_2$ 155.0946, found 155.0976.

3.1.10. Dimethyl 2-(2-methyl-cyclohex-2-enylmethyl) malonate 6 (X=$CH(CO_2CH_3)_2$). To a mixture of dimethyl malonate (309 mg, 2.3 mmol) and NaH (75 mg, 1.6 mmol) in DMF (2 ml) was stirred at room temperature under argon for 1 h. To this clear solution was added tosylate **2** (420 mg, 1.5 mmol) in DMF (0.5 ml), and the mixture was heated at reflux for 23 h. Then, was cooled, diluted with diethyl ether and water was added dropwise. The organic layer was separated, and the aqueous phase was extracted with ether. The combined extract were washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. Evaporation of the solvent left the unsaturated ester **6** (X=$CH(CO_2CH_3)_2$) as a colorless oil (306 mg, 85%): IR ν 2980, 1750 cm^{-1}; ^1H NMR δ 1.63 (3H, s), 3.46 (1H, m), 3.69 (3H, s), 3.71 (3H, s), 5.40 (1H, s) ppm; ^{13}C NMR δ 21.7 (2), 25.2, 26.9, 31.7, 36.5, 49.9, 52.3 (2), 123.2, 135.6, 169.7, 170.0 ppm; MS *m/z* (relative intensity) 240 (5, M^+), 206 (22), 149 (100), 132 (13), 123 (160, 105 (15), 91 (660, 71 (14), 57 (30), 40 (96); HRMS (EI) calcd for $C_{13}H_{26}O_4$ 240.1362, found 240.1357.

3.1.11. Reaction of tosylate 3 with CH_3CH_2OH. To a solution of tosylate **3** (150 mg, 0.4 mmol) in ethanol (2 ml) was heated at 50°C under argon for 16 h. The solvent was evaporated under reduced pressure to afford a residue, which was dissolved in water and extracted with diethyl ether. The extracts were washed with brine, dried and evaporated to afford a colorless oil (100 mg, 100%) identified as 2-ethoxy-1a,4,4,7a-tetramethyl-decahydro-cyclopropa[*a*]naphthalene **8** (X=OCH_2CH_3): IR ν 2940, 1125 cm^{-1}; ^1H NMR δ 0.13 (1H, dd, J=5 Hz, J'=9 Hz), 0.45 (1H, dd, J=6 Hz, J'=9 Hz), 0.80 (3H, s), 0.82 (3H, s), 1.04 (3H, s), 1.14 (3H, s), 1.18 (3H, t, J=7 Hz), 3.51 (3H, m) ppm; ^{13}C NMR δ 11.7, 15.6, 19.0, 20.0, 21.5, 23.1, 25.6, 28.0, 32.4, 33.0, 33.4, 38.1, 40.0 (2), 42.3, 63.2, 77.7 ppm; HRMS (EI) calcd for $C_{17}H_{30}O$ 250.2297, found 250.2288.

3.1.12. Displacement of tosylate 3 with H_2O/NaOH. To a stirred solution of tosylate **3** (200 mg, 0.53 mmol) in DMF (2 ml) was added 5N aqueous solution of NaOH (0.5 ml). The reaction mixture was stirred at 50°C under argon atmosphere for 16 h and then diluted with diethyl ether. The organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether (80:20) to yield 1a,4,4,7a-tetramethyl-decahydro-cyclopropa[*a*]-naftalen-2-ol 8 (X=OH) as a colorless solid (112 mg, 95%): mp 70°C, IR ν 3374, 2924 cm^{-1}; ^1H NMR δ 0.08 (1H, dd, J=4 Hz, J'=8 Hz), 0.6 (2H, m), 0.82 (3H, s), 0.84 (3H, s), 1.05 (3H, s), 1.18 (3H, s), 4.13 (1H, d, J=5.5 Hz) ppm; ^{13}C NMR δ 10.7, 18.8, 21.3, 22.8, 22.9, 26.7, 28.4, 32.3, 32.4, 33.4, 38.7, 39.6, 39.8, 42.1, 70.7 ppm; MS *m/z* (relative intensity) 204 (98, $M^+ - H_2O$), 189 (51), 161 (87), 148 (38), 133 (80), 119 (100), 105 (92), 91 (79), 77 (60), 55 (71), 41 (81); Anal. calcd for $C_{15}H_{26}0$: C, 81.02, H, 11.79, found: C, 81.13, H, 11.91.

3.1.13. Reaction of tosylate 3 with sodium pivalate. To a stirred solution of tosylate **3** (151 mg, 0.40 mmol) in DMF (1.6 ml) was added sodium pivalate (74 mg, 0.6 mmol). The reaction mixture was stirred at 50°C under argon atmosphere for 6 h. Diethyl ether was added and the organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue (120 mg) was heated at 50°C for 1 h in a mixture of ethanol (1 ml) and water (0.2 ml) containing potassium hydroxide (4.6 mg, 0.83 mmol). After cooling and solvent removal, the residue solid was dissolved in water and the solution was extracted with diethyl ether. The extract was washed with brine, dried, filtered and evaporated. Chromatography of the residue (hexane–diethyl ether, 70:30) gave (2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-naftalen-1-yl)-methanol **7** (X=OH) as an oily compound (41 mg, 46%): IR ν 3675,

1045 cm^{-1}; ^1H NMR δ 0.84 (3H, s), 0.88 (3H, s), 0.90 (3H, s), 1.72 (3H, s), 3.71 (2H, m), 5.55 (1H, br s) ppm; ^{13}C NMR δ 18.8, 21.7, 22.1, 23.0, 24.0, 33.0, 33.2, 36.1, 36.8, 42.7, 43.4, 57.8, 61.3, 124.4, 131.5 ppm; HRMS (EI) calcd for $C_{15}H_{26}O$ 222.1984, found 222.1979.

The second fraction (47 mg, 53%) as identified with alcohol **8** (X=OH).

3.1.14. Reaction of tosylate 3 with potassium acetate. To a stirred solution of tosylate **3** (56 mg, 0.15 mmol) in DMF (1 ml) was added potassium acetate (44 mg, 0.45 mmol). The reaction mixture was stirred at 50°C under argon atmosphere for 6 h. Diethyl ether was added and the organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. Chromatography of the residue (hexane–diethyl ether, 90:10) gave 1a,4,4,7a-tetramethyl-decahydro-cyclopropa[*a*]naphthalen-2-yl acetate **8** (X=$OCOCH_3$) as a colorless oil (19 mg, 48%): IR ν 2940, 1748 cm^{-1}; ^1H NMR δ 0.13 (1H, dd, J=5 Hz, J'=4 Hz), 0.54 (1H, dd, J=6 Hz, J'=8 Hz), 0.77 (3H, s), 0.78 (3H, s), 0.79 (1H, m), 1.04 (3H, s), 1.12 (3H, s), 2.04 (3H, s), 5.18 (1H, dd, J=2 Hz, J'=6 Hz) ppm, MS *m/z* (relative intensity) 264 (10, M^+), 222 (13), 204 (37), 189 (55), 161 (30), 149 (32), 133 (56), 119 (100), 105 (70), 93 (59), 69 (59), 55 (71), 43 (87); HRMS (EI) calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2091.

The second fraction (21 mg, 53%) was identified as 2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalen-1-ylmethyl acetate **7** (X=$OCOCH_3$) as a colorless oil (20 mg, 50%): IR ν 2985, 1750 cm^{-1}; ^1H NMR δ 0.78 (3H, s), 0.79 (3H, s), 0.85 (3H, s), 1.58 (3H, s), 2.04 (3H, s), 4.10 (2H, m), 5.49 (1H, br s) ppm; HRMS (EI) calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2075.

3.1.15. Reaction of tosylate 3 with NaOH. To a stirred solution of tosylate **3** (47 mg, 0.12 mmol) in DMF (3 ml) was added sodium hydroxide (15 mg, 0.37 mmol). The reaction mixture was stirred at 70°C under argon atmosphere for 16 h, and then diluted with diethyl ether. The organic layer was washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether (95:5). The first fraction (7 mg, 27%) was an oily compound identified as 1,1,4a,6-tetramethyl-5-methylene-1,2,3,4,4a, 5,8,8a-octahydro-naphthalene **9**: IR ν 3078, 1650 cm^{-1}; ^1H NMR δ 0.86 (3H, s), 0.92 (3H, s), 0.96 (3H, s), 1.80 (3H, s), 4.79 (1H, s), 4.83 (1H, s), 5.66 (1H, br s) ppm, MS *m/z* (relative intensity) 204 (16, M^+), 189 (11), 161 (15), 133 (46), 119 (100), 105 (52), 91 (37), 69 (25), 55 (41), 41 (63); HRMS (EI) calcd for $C_{15}H_{24}$ 204.1878, found 204.1890. The second fraction (9 mg, 32%) was identified as the alcohol **8** (X=OH). The third compound (10 mg, 36%) was identified as the alcohol **7** (X=OH).

3.1.16. Reaction of tosylate 3 with $NaCH(CO_2CH_3)_2$. A mixture of dimethyl malonate (31 mg, 0.23 mmol) and 50% NaH (8 mg, 0.18 mmol) in DMF (2 ml) was stirred at room temperature under argon for 1 h. To this clear solution was added tosylate **3** (56 mg, 0.15 mmol) in DMF (0.5 ml), and the mixture was heated at 100°C for 6 h. Then, was cooled, diluted with diethyl ether and water was added dropwise. The organic layer was separated, and the aqueous phase was extracted with ether. The combined extract were washed with aqueous HCl (2N), $NaHCO_3$ (5%), brine, dried and evaporated. Evaporation of the solvent left dimethyl 2-(1a,4,4,7a-tetramethyl-decahydro-cyclopropa[*a*]naphthalen-2-yl)-malonate **8** (X=$CH(CO_2CH_3)_2$) as a colorless oil (43 mg, 86%): IR ν 2985, 1738 cm^{-1}; ^1H NMR δ 0.05 (1H, dd, J=5 Hz, J'=8 Hz), 0.41 (2H, m), 0.73 (3H, s), 0.75 (3H, s), 1.01 (3H, s), 1.09 (3H, s), 3.39 (1H, d, J= 10 Hz), 3.71 (3H, s), 3.73 (3H, s) ppm; ^{13}C NMR δ 12.93, 17.42, 18.75, 21.27, 22.28, 23.16, 28.78, 32.42, 32.83, 33.36, 38.02, 38.44, 39.90, 41.16, 42.27, 52.14 (2), 55.78, 169.29, 169.51 ppm; MS *m/z* (relative intensity) 336 (3, M^+), 204 (95), 189 (59), 175 (14), 161 (39), 138 (34), 133 (79), 119 (100), 105 (67), 95 (64), 69 (67), 55 (73), 41 (73); HRMS (EI) calcd for $C_{20}H_{32}O_4$ 336.2301, found 336.2291.

3.1.17. Displacement of tosylate 3 with NaCN. To a solution of tosylate **3** (100 mg, 0.26 mmol) in DMF (2 ml) was added NaCN (73 mg, 1.5 mmol), and the reaction mixture was stirred under argon at 50°C for 30 h. Diethyl ether was added and the organic layer was washed with water, brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether (95:5). The first fraction (12 mg, 19%) was identified as 2-cyanato-1a,4,4,7-tetramethyl-decahydro-ciclopropa[*a*]naphthalene **8** (X=CN): IR ν 2965, 2250 cm^{-1}; ^1H NMR δ 0.36 (1H, m), 0.68 (2H, m), 0.83 (3H, s), 0.86 (3H, s),1.09 (3H, s), 1.16 (3H, s), 3.00 (1H, m) ppm; MS *m/z* (relative intensity) 231 (12, M^+), 216 (78), 199 (12), 191 (12), 175 (15), 160 (10), 146 (16), 124 (88), 119 (41), 109 (100), 95 (55), 81 (65), 55 (60), 41 (70); HRMS (EI) calcd for $C_{16}H_{25}N$ 231.1987, found 231.1976.

The second fraction (45 mg, 73%) was an oily compound identified as (2,5,5,8a-tetramethyl-1,4,4a,5,6,7,8,8a-octahydro-naphthalenyl)-acetonitrile **7** (X=CN): IR ν 2935, 2239 cm^{-1}; ^1H NMR δ 0.87 (3H, s), 0.89 (3H, s), 1.16 (3H, s), 1.76 (3H, s), 2.34 (2H, m), 5.47 (1H, br s) ppm, MS *m/z* (relative intensity) 231 (12, M^+), 216 (70), 188 (14), 174 (10), 160 (12), 147 (20), 135 (26), 123 (37), 107 (28), 95 (100), 69 (92), 55 (70), 41 (92); HRMS (EI) calcd for $C_{16}H_{25}N$ 231.1987, found 231.1972.

3.1.18. Displacement of tosylate 3 with NaBr. A solution of tosylate **3** (54 mg, 0.14 mmol) in DMF (2 ml) was added NaBr (44 mg, 0.4 mmol), and the reaction mixture was stirred under argon at 50°C for 16 h. Water was added and the mixture was extracted with diethyl ether. The organic layer was washed with aqueous $NaHSO_3$ (5%), brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether (99:1). The first fraction (18 mg, 61%) was identified as 1a,4,4,7a-tetramethyl-1a,3a,4,5,6,7, 7a,7b-octahydro-1H-cyclopropa[a]naphthalene **10**: IR ν 3049, 1653 cm^{-1}; ^1H NMR δ 0.41 (1H, dd, J=4 Hz, J'= 7 Hz), 0.57 (1H, dd, J=5 Hz, J'=8 Hz), 0.86 (3H, s), 0.87 (3H, s), 0.88 (3H, s), 1.16 (3H, s), 5.33 (1H, dd, J=3 Hz, J'=10 Hz), 5.80 (1H, dd, J=3 Hz, J'=10 Hz) ppm; MS *m/z* (relative intensity) 204 (65, M^+), 189 (32), 161 (62), 147 (24), 133 (65), 119 (90), 105 (85), 91 (67), 77 (45), 55 (68), 41 (100); HRMS (EI) calcd for $C_{15}H_{24}$ 204.1878, found 204.1854. The second fraction (11 mg, 37%) was identified as the alkene **9**.

3.1.19. Displacement of tosylate 3 with NaI. A solution of tosylate **3** (63 mg, 0.16 mmol) in DMF (2 ml) was added NaI (75 mg, 0.5 mmol), and the reaction mixture was stirred under argon at 50°C for 16 h. Water was added and the mixture was extracted with diethyl ether. The organic layer was washed with aqueous $NaHSO_3$ (5%), brine, dried and evaporated The residue was chromatographed using hexane–diethyl ether (99:1). The first fraction (21 mg, 61%) was identified as alkene **10**. The second fraction (11 mg, 32%) was identified as the alkene **9**.

3.1.20. Reaction of tosylate 3 with $NaNO_2$. A solution of tosylate **3** (60 mg, 0.16 mmol) in DMF (3 ml) was added $NaNO_2$ (45 mg, 0.6 mmol), and the reaction mixture was stirred under argon at 60°C for 6 h. Diethyl ether was added and the organic layer was washed with water, brine, dried and evaporated. The residue was chromatographed using hexane–diethyl ether (70:30). The first fraction (20 mg, 56%) was identified as the alcohol **7**; the second fraction (14 mg, 40%) was identified as the alcohol **8** (X=OH).

3.1.21. Reaction of tosylate 3 with CH_3CuLi. To a suspension of CuI (93 mg, 0.65 mmol) in diethyl ether (2.5 ml) was added 1 M CH_3Li (1.3 mmol, 1.3 ml) at 0°C and the reaction mixture was stirred for 30 min. To this clear solution was added dropwise tosylate **3** (113 mg, 0.3 mmol) in diethyl ether (1 ml) and the mixture was stirred at room temperature for 12 h. Then, was added dropwise a saturated NH_4Cl solution and the mixture was extracted with diethyl ether. The organic layer was washed with brine, dried and evaporated. Evaporation of the solvent afforded the unsaturated alcohol **7** (X=OH) (65 mg, 97%).

3.1.22. Reaction of tosylate 3 with NaSPh. A mixture of tosylate **3** (45 mg, 0.12 mmol), HSPh (13 mg, 0.12 mmol), NaOH (10 mg, 0.5 mmol) and Bu_4NBr (3.76 mg, 6.9×10^{-3} mmol) in a mixture of benzene/H_2O (0.5 ml, benzene–H_20: 3/4) was vigorously stirred at room temperature under argon atmosphere for 24 h. Then, was added diethyl ether and water. The organic layer was separated and the aqueous phase was extracted with diethyl ether. The combined extract were washed with brine and dried. Evaporation of the solvent left 1a,4,4,7a-tetramethyl-2-phenylsulfanyl-decahydro-cycloprop[a]naphthalene **7** (X=SPh) as a yellow oil (35 mg, 93%): IR ν 3060, 2950, 1600, 1470 cm^{-1}; ^1H NMR δ 0.88 (3H, s), 0.90 (3H, s), 0.93 (3H, s), 1.65 (3H, d, J=2 Hz), 2.80 (1H, dd, J=12 Hz, J'=2 Hz), 3.08 (1H, dd, J=6 Hz, J'=12 Hz), 5.38 (1H, br s), 7.2–7.5 (5H, m) ppm; ^{13}C NMR δ 18.61, 21.64, 21.92, 22.96, 24.06, 32.81, 33.01, 35.25, 36.58, 36.76, 42.44, 42.60, 54.36, 121.80, 127.06, 127.60, 128.64, 128.91, 129.18, 134.46, 138.21 ppm; MS *m/z* (relative intensity) 314 (3, M^+), 264 (5), 218 (98), 185 (10), 154 (15), 109 (100), 95 (20), 65 (40); HRMS (EI) calcd for $C_{21}H_{30}S$ 314.2068, found 314.2094.

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