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A CONVENIENT REDUCTION OF ALKYLATED TOSYLMETHYL ISOCYANIDES[1]: APPLICATIONS FOR THE SYNTHESIS OF NATURAL PRODUCTS[#]

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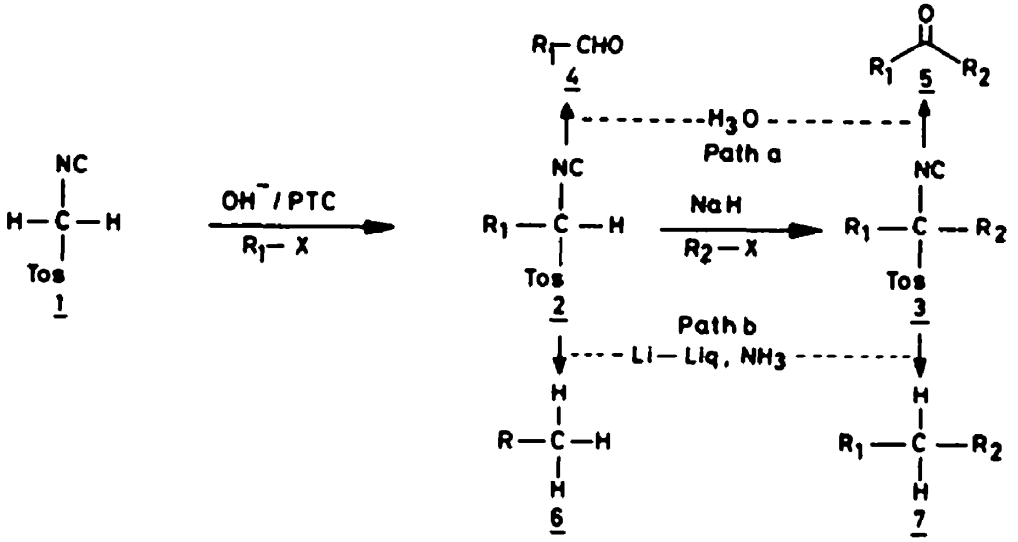
Abstract : A convenient and simple method for the reduction of mono- and dialkylated tosylmethyl isocyanides with lithium in liquid ammonia to corresponding hydrocarbons is described. The utility of this methodology adopted in the synthesis of tricos-9Z-ene (7g), a sex pheromone of common house fly, (-)-1S,5R,7S-exo-brevicomin (17), an antipode of sex pheromone of Western pine beetle and (4S,5S)-5-hydroxy-4-decanolide (L-factor, 19), a proposed autoregulator for leukaemomycin biosynthesis.

Tosylmethyl isocyanide[2] (1, TosMIC) has been shown to be a useful reagent in organic synthesis not only as a valuable synthon for heterocyclic compounds, but also in a variety of other synthetic transformations[2,3] as well. One interesting aspect of TosMIC is its potential ability to serve as carbonyl anion equivalent[4]. The presence of two anion stabilising substituents facilitate the alkylation of TosMIC with mild bases like NaOH, K_2CO_3 etc., under phase transfer catalysis. TosMIC, therefore, may be monoalkylated with alkyl halide using sodium hydroxide in the presence of phase transfer catalyst while the

SCHEME 1



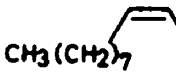
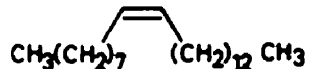
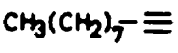
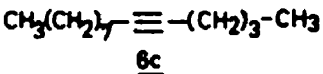
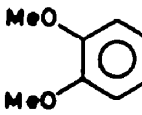
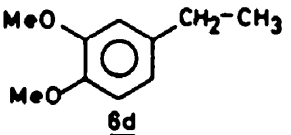
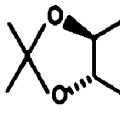
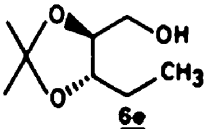
second alkylation could be performed by employing NaH as base in a suitable solvent. These alkylated TosMICs are converted to several symmetrical and unsymmetrical ketones in the presence of traces of aqueous acid (Scheme I, Path a). We have recently developed[5] a convenient methodology to reduce

the alkylated TosMIC to the corresponding hydrocarbons by using lithium in liquid ammonia (Scheme I, Path b). We wish to report its detailed account here.

Various alkylated TosMICs were prepared by employing the procedure developed by A.M. Van Leusen and coworkers[2]. For example, treatment of 1 with different alkyl halides in 40% aqueous NaOH and CH_2Cl_2 in the presence of phase transfer catalyst afforded monoalkylated TosMIC (Table 1, 2a-e) in 70-90% yield, while monoalkylated TosMIC 2 on treatment with sodium hydride and second alkyl halide afforded the dialkylated TosMIC (Table 2, 3a-h) in good yield.

TABLE 1

Li/Liq — NH_3 REDUCTION OF MONOALKYLATED Tos MIC

	MONOALKYLATED TosMIC 2 R_1	Yield %	PRODUCT 6	YIELD*%
2a		80	6a	92
2b		75	 6b	95
2c		78	 6c	92
2d		85	 6d	90
2e		85	 6e	70

* The Yields of 6 are based on 2

Initially, reduction of simple monoalkylated TosMIC, i.e., 1-tosylundecyl isocyanide 2a was performed. Accordingly, compound 2a was reacted with lithium in liquid ammonia for 2 hr to afford undecane in 92% yield. This reaction was further extended successfully for the reduction of various monoalkylated TosMICs (Table 1, 2a-e). This means that a new method is available to replace the halogen atom in primary alkyl halides by a methyl group in a two step procedure. An application of this methodology is given below in the synthesis of exo-brevicomin (17, Scheme IV).

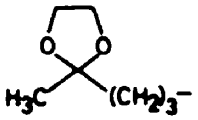
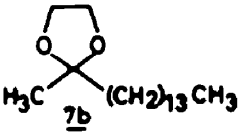
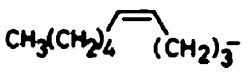
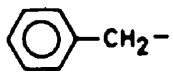
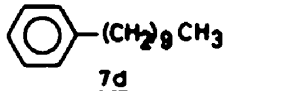
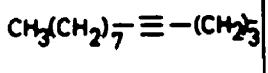
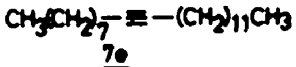
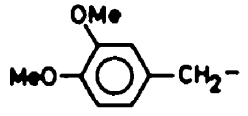
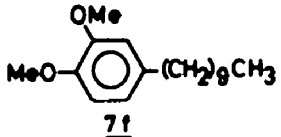
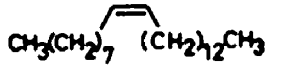
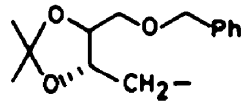
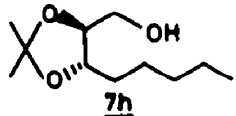
After achieving encouraging results with the reduction of monoalkylated TosMICs with lithium in liquid ammonia, this reaction was extended to dialkylated TosMICs. For this purpose, the ethereal solution of dialkylated TosMIC, 9-tosyl-9-heptadecyl isocyanide (3a) was treated with lithium in liquid ammonia for 2 hr to afford heptadecane (7a) in 93% yield. In order to illustrate the generality of this method, reduction of various dialkylated TosMICs having olefinic, acetylenic and aromatic functionalities was carried out successfully (Table 2, 3a-h).

A plausible mechanism for the reduction of TosMIC is depicted in Scheme II. Accordingly, lithium transfers an electron to the carbon atom of isocyanide, thus getting oxidised to Li^+ and creating a radical anion A[6]. The resulting radical anion A produces LiCN and radical B which ultimately, is reduced to carbanion C by another lithium atom. The carbanion C, in turn, accepts a proton from solvent to afford sulphone D. It was observed that when a limited amount of lithium was used for the reduction, the sul-

phone D was indeed isolated along with the reduced product 7. Finally, the sulphone D gets reduced[7] to corresponding hydrocarbon 7 in due course of the reaction (Scheme II).

TABLE 2

Li / Liq. NH_3 REDUCTION OF DIALKYLATED TosMIC 3

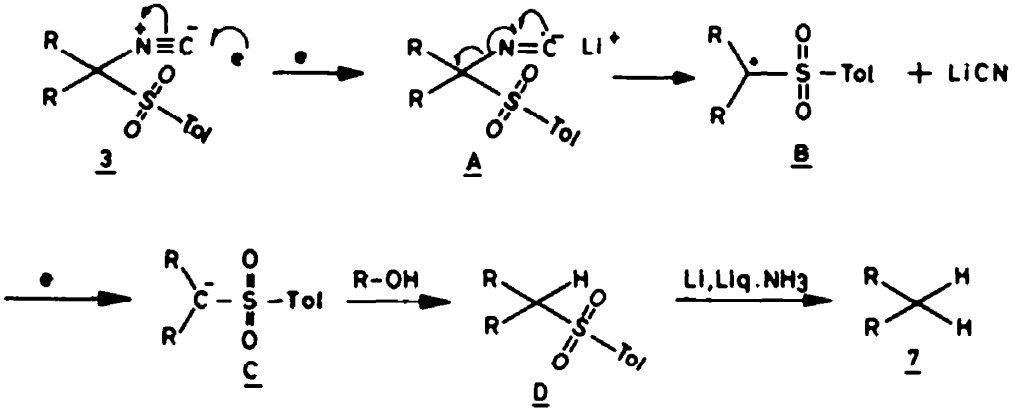
	DIALKYLATED TosMIC 3			PRODUCT 7	YIELD* %
	R_1	R_2	YIELD %		
3a	$n\text{-}C_8H_{17}-$	$n\text{-}C_8H_{17}-$	90	$n\text{-}C_{17}H_{36}$ 7a	93
3b	$n\text{-}C_{10}H_{21}-$		88	 7b	91
3c	$n\text{-}C_{10}H_{21}-$		89	 7c	90
3d	$n\text{-}C_8H_{17}-$		90	 7d	95
3e	$n\text{-}C_8H_{17}-$		91	 7e	90
3f	$n\text{-}C_8H_{17}-$		90	 7f	95
3g	$n\text{-}C_9H_{19}-$		85	 7g ≡ 6b	90
3h	$CH_3CH_2CH_3-$		50	 7h	45

* The Yields of 7 are based on 3

It is pertinent to mention here that this reduction is highly chemoselective as triple bonds, aromatic rings, double bonds etc., are unaffected under these reaction conditions. However, benzyl protection as in 3R was found to be cleaved as anticipated. In addition, this reaction is practically useful due to the fact that it offers no side products, the byproducts (LiCN, TosLi) arising from the reaction are highly soluble in water and could be removed easily.

The importance of this methodology was indeed realized by successful synthesis of (Z)-9-tricosene[8] (7g), (-)-exo-brevicomin[9] (17), (4S,5S)-5-hydroxy-4-decanolide i.e., L-factor[10] (19) which will be discussed below.

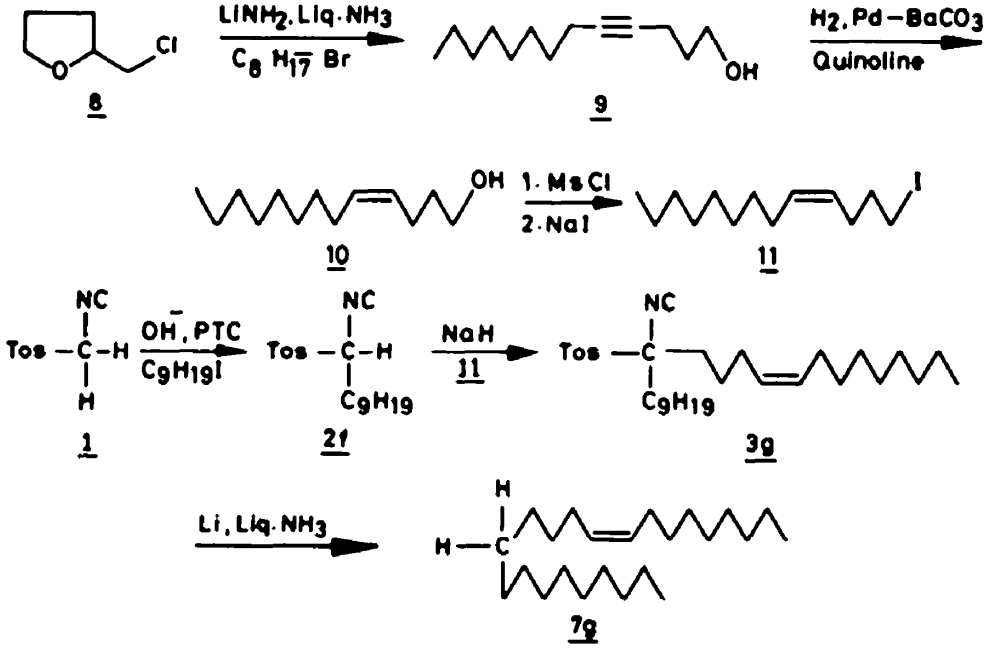
SCHEME II



Synthesis of tricos-9Z-ene (6b, ≡7g)

Tricos-9Z-ene[8] *(muscalure, 7g), a sex pheromone of common house fly, Musca domestica, has been isolated from the cuticle and feces of the female fly. This pheromone was synthesized by employing reductions of monoalkylated TosMIC (2b, Table 1) as well as by reducing the dialkylated TosMIC (3g, Table 2). Thus, in accordance with the second approach, tetrahydrofurfuryl chloride (8) on treatment with lithium amide in liquid ammonia and n-octyl bromide in THF afforded tridec-4-yn-1-ol*[11] *(9, Scheme III). 9 was partially reduced over Lindlar catalyst to afford tridec-4Z-en-1-ol (10). Alcohol 10 was con-*

SCHEME III

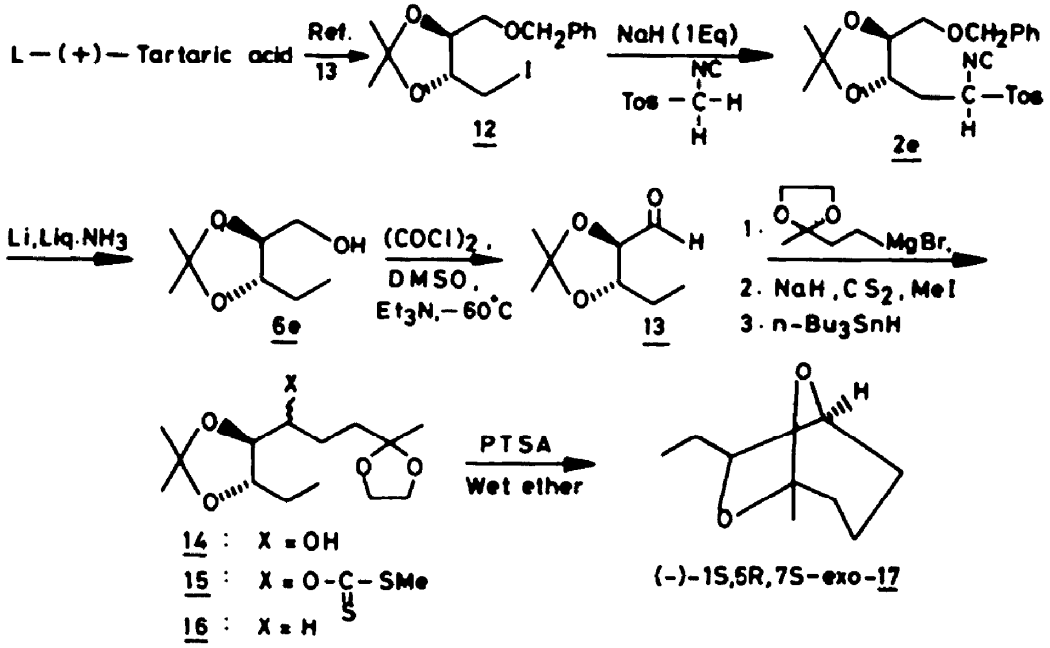


verted to 1-iodotridec-4Z-ene (11) via its corresponding mesylate. 1-Tosyldecyl isocyanide (2f) (prepared from TosMIC and n-nonyl iodide under phase transfer catalysis conditions) was alkylated with the iodide (11) using sodium hydride to afford 10-tosyl-10-tricos-14Z-enyl isocyanide (3g). 3g was reduced with lithium in liquid ammonia in the usual manner to afford tricos-9Z-ene[12] *(7g).*

Synthesis of (-)-1S,5R,7S-exo-Brevicomin (17)

(+)-1R,5S,7R-exo-Brevicomin is the active component[9] (natural pheromone) of the Western pine beetle, "Dendroctonus Brevicomis". This pheromone possesses three asymmetric carbon atoms and is highly dissymmetric molecule. In this paper, we wish to report the synthesis of (-)-1S,5R,7S-exo-brevicomin (17), the antipode of the active isomer. The main feature of the synthesis of 17 is the introduction of the methyl group by making use of the reduction of monoalkylated TosMIC (Scheme IV). For this purpose L-(+)-tartaric acid was chosen as the starting material. Tartaric acid possesses its vicinal hydroxyl

SCHEME IV



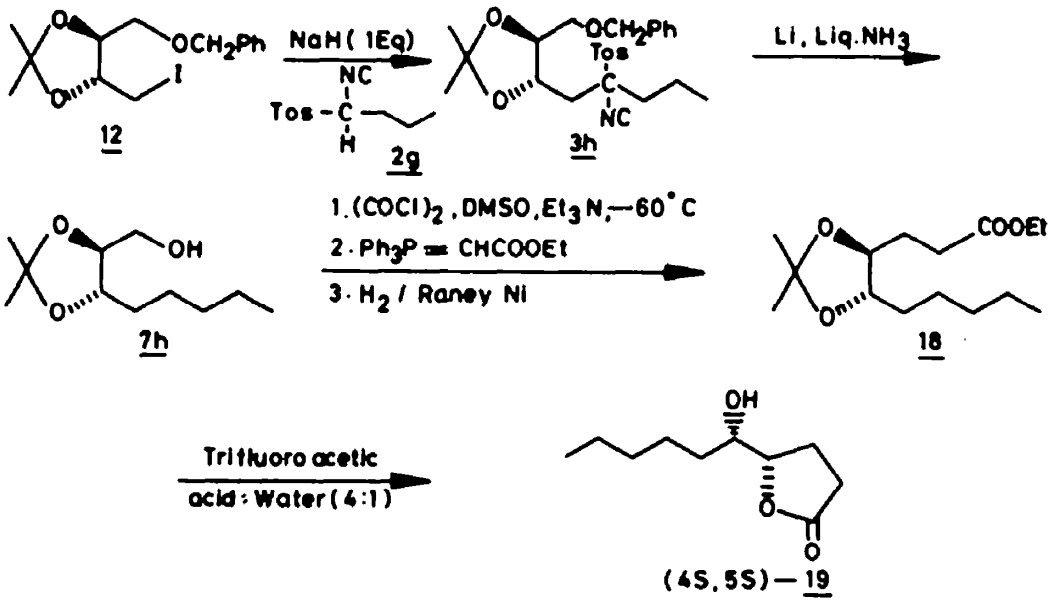
groups in threo-configuration and therefore affords exclusively the desired exo-brevicomin without any contamination of endo-brevicomin. Thus, tartaric acid was transformed to (4S,5R)-4-benzyloxymethyl-5-iodomethyl-2,2-dimethyl-1,3-dioxolane (12) by known procedure[13]. TosMIC was alkylated with 12 in DMF using 1 eq of sodium hydride to afford (4S,5S)-4-benzyloxymethyl-2,2-dimethyl-5-(2'-tosyl-2'-isocyanoethyl)-1,3-dioxolane (2e). Compound 2e was found to be very unstable and therefore, it was subjected to the next reaction without purification. Accordingly, treatment of 2e with lithium in liquid ammonia afforded (4S,5S)-4-ethyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (6e). It may be noted that the debenzylation occurred simultaneously under the reaction condition. Alcohol 6e was treated with oxalyl chloride and dimethylsulfoxide[14] in methylenechloride in the presence of triethylamine at -60° which yielded (4R,5S)-2,2-dimethyl-5-ethyl-4-formyl-1,3-dioxolane (13). This aldehyde (13) on reaction with 3,3-ethylenedioxybutyl magnesium bromide[15] in THF at 0° for 4 hr afforded (4S,5S)-4-ethyl-2,2-dimethyl-5-[3-(2-methyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]-1,3-dioxolane (14). The hydroxyl group in compound 14 was deoxygenated using Barton-McCombie[16] method (via xanthate 15) to afford (4S,5S)-4-ethyl-2,2-dimethyl-5-[3-(2-methyl-1,3-dioxolan-2-yl)-propyl]-1,3-dioxolane[17] (16). Treatment of 16 with PTSA in wet ether yielded (-)-exo-brevicomin[17] (17). $[\alpha]_D$ -66.9° (c, 2, ether), Lit.[17a] -67.5° (c, 2.15, ether). Likewise, the natural (+)-exo-brevicomin could be prepared by using (-)-(SS)-tartaric acid.

Synthesis of (4S,5S)-5-hydroxy-4-decanolide (L-factor, 19)

The proposed autoregulators for Lukaemomycin biosynthesis, L-factors (4S,5S)- and (4S,5R)-5-hydroxy-4-decanolides were first isolated from the mutant strains of Streptomyces griseus[10]. The synthesis of 19 starts with the known (4S,5R)-4-benzyloxymethyl-5-iodomethyl-2,2-dimethyl-1,3-dioxolane (12) obtained from L-(+)-tartaric acid in six steps[13].

The union of the monoalkylated TosMIC (2g) with the iodide 12 using sodium hydride/DMSO as a base afforded the dialkylated TosMIC 3h (Scheme V). This dialkylated TosMIC 3h was found to be unstable and was taken into further reactions without purification. Thus, dialkylated TosMIC 3h on treatment with lithium in liquid ammonia afforded (4S,5S)-5-pentyl-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (7h) in 45% yield. Alcohol (7h) on Swern oxidation[14] afforded the corresponding aldehyde which was

SCHEME V



immediately reacted with ethoxycarbonylmethylenetriphenylphosphorane in benzene to afford the E/Z α,β-unsaturated ester, which was hydrogenated in presence of excess of Raney nickel to yield 18. Interaction of 18 with TFA:Water (4:1) gave (4S,5S)-L-factor (19) in 70% yield. $[\alpha]_D$ +27° (c, 2, $CHCl_3$), Lit.[18e] $[\alpha]_D$ +33° (c, 1.64, $CHCl_3$). The spectroscopic analysis of 19 was in good agreement with the reported values[18e].

In conclusion the reduction method described above appears to be a novel and simple one for conversion of dialkylated and monoalkylated TosMIC to hydrocarbons. This would also help in preparation of long chain compounds, e.g., higher fatty acids and alcohols.

Experimental

IR spectra were recorded in nujol or neat on a Perkin Elmer Model 683 spectrometer with sodium chloride optics. ^{1}H-NMR spectra were obtained on Varian T-60 or Varian FT-80 or Bruker WH-90 spectrometer in $CDCl_3$ or CCl_4 solutions containing TMS as an internal standard with chemical shifts (δ) expressed in ppm down field from TMS. Mass spectra were run on AEI MS 30 or CEC 21-110 B spectrometer.

Preparation of monoalkylated TosMICs

1-Tosylundecyl isocyanide (2a)

A mixture of tosylmethyl isocyanide (TosMIC, 1, 0.975 g, 0.005 mol), n-decyl iodide (1.34 g, 0.005 mol), tetrabutylammonium bromide (0.320 g, 0.001 mol), 40% aqueous NaOH (15 ml) and dichloromethane (15 ml) was stirred at 0° for 2 hr and then at room temperature for 12 hr. The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was washed with water, brine and dried (Na_2SO_4). Removal of the solvent under reduced pressure gave a solid which was crystallised from ether–petroleum ether to afford pure 2a (1.5 g) in 80% yield. m.p. 55-57°. IR (Nujol) : 2120 cm^{-1}

(N=C), PMR ($CDCl_3$) : δ 0.9 (distorted t, 3H, CH_3), 1.33 (bs, 18H, 9 x CH_2), 2.43 (s, 3H, Ar-CH_3), 4.22-4.56 (m, 1H, -CHNC), 7.20 (d, J=8 Hz, 2H, Ar-H), 7.60 (d, J=8 Hz, 2H, Ar-H). Analysis calc for $C_{19}H_{29}NO_2S$: C, 68.86; H, 8.66; N, 4.12; S, 9.55; Found : C, 68.53; H, 8.63; N, 4.08; S, 9.48%.

Various other monoalkylated TosMICs (Table 1, 2a-e) were prepared by using the corresponding alkyl halide by adopting above procedure. The analytical data of these monoalkylated TosMICs is given below.

1-Tosyltricos-14Z-enyl isocyanide (2b)

Compound 2b was prepared by using erucyl iodide[21] and TosMIC in 75% yield. m.p. 46°. IR (Nujol): 2140 cm^{-1} (N=C), 745 cm^{-1} (cis double bond). PMR ($CDCl_3$) : δ 0.8 (distorted t, 3H, CH_3), 1.2 (bs, 34H, 17 x CH_2), 1.85-2.12 (m, 4H), 2.39 (s, 3H, Ar-CH_3), 4.28-4.58 (m, 1H, CHNC), 5.24 (t, J=5 Hz, 2H, olefinic), 7.3 (d, J=8 Hz, 2H, Ar-H), 7.73 (d, J=8 Hz, 2H, Ar-H). Analysis calc for $C_{31}H_{51}NSO_2$: C, 74.25; H, 10.2; N, 2.78; S, 6.38; Found : C, 74.16; H, 10.18; N, 2.69; S, 6.27%.

1-Tosyltetradec-5-ynyl isocyanide (2c)

Compound 2c was prepared by using 1-iodo-4-decyne and TosMIC in 78% yield which was found to be a low melting solid. IR (Neat) : 2145 cm^{-1} (N=C), 1600 cm^{-1} (aromatic, C=C), PMR ($CDCl_3$) : δ 0.88 (distorted t, 3H, CH_3), 1.3 (bs, 18H, 9 x CH_2), 1.93-2.12 (m, 4H), 2.4 (s, 3H, Ar-CH_3), 4.23-4.59 (m, 1H, CHNC), 7.3 (d, J=8 Hz, 2H, Ar-H), 7.78 (d, J=8 Hz, 2H, Ar-H). Analysis calc for $C_{22}H_{31}NSO_2$: C, 70.77; H, 8.31; N, 3.75; S, 8.58; Found : C, 70.56; H, 8.27; N, 3.69; S, 8.48%.

1-(3,4-Dimethoxybenzyl)-1-tosyl isocyanide (2d)

Compound 2d was prepared by using 3,4-dimethoxybenzyl bromide and TosMIC in 85% yield. M.P. 166°. IR (Nujol) : 2150 cm^{-1} (N=C), 1595 cm^{-1} (aromatic C=C). PMR ($CDCl_3$) : δ 2.5 (s, 3H, Ar-CH_3), 3.9 (s, 6H, 2 x OCH_3), 4.35-4.78 (m, 1H, CHNC), 6.8 (s, 3H, Ar-H), 7.37 (d, J=8 Hz, 2H, Ar-H), 7.8 (d, J=8 Hz, 2H, Ar-H). Analysis calc for $C_{18}H_{19}NSO_4$: C, 62.61; H, 5.5; N, 4.05; S, 9.27; Found : C, 62.43; H, 5.45; N, 4.13; S, 9.23%.

Preparation of dialkylated TosMICs

9-Tosyl-9-heptadecyl isocyanide (3a)

To a suspension of prewashed sodium hydride (0.528 g, 0.022 mol) in DMSO-ether (1:5, 18 ml) was added TosMIC (1, 1.95 g, 0.01 mol) in ether (15 ml) at room temperature. After 10 min. n-octyl iodide (4.8 g, 0.02 mol) in ether (15 ml) was added dropwise and stirred at room temperature for 3 hr. Reaction mixture was poured in water, organic layer was separated and aqueous layer was extracted with ether. The combined organic extract was washed with water, brine and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure afforded 3a (3.77 g) in 90% yield as gummy product. IR (Neat): 2130 cm^{-1} (N=C), 1600 cm^{-1} (aromatic C=C). PMR (CCl_4) : δ 0.9 (distorted t, 6H, 2 x CH_3), 1.3 (bs, 28H, 14 x CH_2), 2.45 (s, 3H, Ar-CH_3), 7.23 (d, J=8 Hz, 2H, Ar-H), 7.68 (d, J=8 Hz, 2H, Ar-H).

In all the experiments, the dialkylated TosMICs, thus obtained, were used as such for the next reaction. Any attempted purification always resulted in partial decomposition of the products. It was, therefore, satisfactory elemental analysis could not be obtained.

Various other dialkylated TosMICs (Table 2, 3a-3h) were prepared by alkylating monoalkylated TosMIC with the corresponding halide as described above. The physical data of these dialkylated TosMICs is given below.

2,2-Ethylenedioxy-6-tosyl-6-hexadecyl isocyanide (3b)

The monoalkylated TosMIC i.e., 1-tosylundecyl isocyanide (2a) was alkylated with 4,4-ethylenedioxypentyl bromide[19] to obtain 3b in 88% yield as described above. IR (Neat) : 2140 cm^{-1} (N=C), 1600 cm^{-1} (aromatic C=C), PMR (CCl_4) : δ 0.9 (distorted t, 3H, CH_3), 1.24 (bs, 27H), 2.42 (s, 3H, Ar-CH_3), 3.81 (s, 4H), 7.21 (d, J=8 Hz, 2H, Ar-H), 7.60 (d, J=8 Hz, 2H, Ar-H).

11-Tosyl-11-henicos-6Z-enyl isocyanide (3c)

Compound 3c was prepared by alkylating 1-tosylundecyl isocyanide (2a) with (Z)-1-iodo-4-decene in 89% yield. IR (Nujol) : 2130 cm^{-1} (N=C); 735 cm^{-1} (cis double bond). PMR ($CDCl_3$) : δ 0.9 (distorted t, 6H, 2 x CH_3), 1.33 (bs, 28H, 14 x CH_2), 1.82-1.98 (m, 4H), 2.43 (s, 3H, Ar-CH_3), 5.13-5.40 (m, 2H olefinic), 7.2 (d, J=8 Hz, 2H, Ar-H), 7.70 (d, J=8 Hz, 2H, Ar-H).

1-Phenyl-2-tosyl-2-decyl isocyanide (3d)

Compound 3d was prepared by alkylating 1-tosylnonyl isocyanide with benzylbromide in 90% yield. IR (Neat) : 2140 cm^{-1} (N=C) and 1600 (aromatic C=C). PMR ($CDCl_3$) : δ 0.85 (distorted t, 3H, CH_3), 1.21 (bs, 14H, 7 x CH_2), 2.48 (s, 3H, Ar-CH_3), 3.18 (d, J=3.5 Hz, 2H, CH_2-Ph), 7.3-7.45 (m, 7H, Ar-H), 7.82 (d, J=8 Hz, 2H, Ar-H).

9-Tosyl-9-tricos-13-ynyl isocyanide (3e)

The dialkylated TosMIC 3e was prepared by alkylating 1-tosylnonyl isocyanide with 1-bromo-4-tridecyne in 91% yield. IR (Neat) : 2140 cm^{-1} (N=C), 1600 cm^{-1} (aromatic C=C). PMR ($CDCl_3$) : δ 0.87 (distorted t, 3H, CH_3), 2.23 (bs, 30H, 15 x CH_2), 1.92-2.1 (m, 4H), 2.48 (s, 3H, Ar-CH_3), 7.38 (d, J=8 Hz, 2H, Ar-H), 7.86 (d, J=8 Hz, 2H, Ar-H).

3',4'-Dimethoxyphenyl-2-tosyl-2-decyl isocyanide (3f)

The dialkylated TosMIC 3f was prepared by alkylating 1-tosylnonyl isocyanide with 3,4-dimethoxy benzyl bromide in 90% yield. IR (Neat) : 2145 cm^{-1} (N=C). PMR ($CDCl_3$) : δ 0.82 (distorted t, 3H, CH_3), 1.2 (bs, 14H, 7 x CH_2), 2.49 (s, 3H, Ar-CH_3), 3.3 (d, J=3.5 Hz, 2H, CH_2-Ar), 3.75 (s, 6H, 2 x OCH_3), 6.82 (s, 3H, Ar-H), 7.34 (d, J=8 Hz, 2H, Ar-H), 7.82 (d, J=8 Hz, 2H, Ar-H).

Reduction of mono- and dialkylated TosMICs

A typical procedure for reduction is as follows.

To a freshly distilled liquid ammonia (50 ml) at -33° was added lithium (50 mg, 0.007 mol) in one portion, followed by dialkylated TosMIC 3a (294 mg, 0.0007 mol) in ether (3 ml) and ethanol (0.12 ml). After 2 hr, ammonia was allowed to evaporate by bringing it to room temperature. Then, water was added and extracted with ether (5 x 10 ml). The organic layer was washed with water (20 ml), brine (20 ml), dried (Na_2SO_4) and concentrated. Distillation of the residue (pot temperature 125-135° at 1 mm) afforded heptadecane 7a (156 mg, 93%) as a colourless liquid. PMR (CCl_4) : δ 0.9 (distorted t, 6H, 2 x CH_3), 1.27 (bs, 30H, 15 x CH_2).

The physical data of the reduced products are given below.

n-Undecane[20] (6a)

B.P. 92-95°/20 mm. PMR (CCl_4) : δ 0.95 (t, 6H, 2 x CH_3), 1.3 (bs, 18H, 9 x CH_2).

Tricos-9Z-ene (6b)

B.P. 180°/1 mm (Lit. 158°/0.1 mm). IR (Neat) : 735 cm^{-1} (cis double bond). PMR ($CDCl_3$) : δ 0.87 (distorted t, 6H, 2 x CH_3), 1.23 (bs, 34H, 17 x CH_2), 1.87-2.16 (m, 4H), 5.29 (t, J=5.5 Hz, 2H, olefinic).

Tetradec-5-yne (6c)

B.P. 120°/1 mm (bath temp.). PMR (CCl_4) : δ 0.9 (distorted t, 6H, 2 x CH_3), 1.3 (bs, 16H, 8 x CH_2), 1.94-2.12 (m, 4H). Mass : 194 (M^+), 137, 109, 96, 81 (100%).

3,4-Dimethoxyethylbenzene (6d)

B.P. 112°/1 mm. PMR ($CDCl_3$) : δ 1.2 (t, J=7.5 Hz, 3H, CH_3), 2.6 (q, J=7.5 Hz, 2H, CH_2CH_3), 3.8 (s, 6H, 2 x OCH_3), 6.73 (bs, 3H, Ar-H). Mass : 166 (M^+), 151 (100%), 135, 123, 108. Analysis calc for $C_{10}H_{14}O_2$: C, 72.3; H, 8.43; Found : C, 72.18; H, 8.39%.

2-Methyl-2-tetradecyl-1,3-dioxolan (7b)

B.P. 150°/1 mm (pot temperature). PMR (CCl_4) : δ 0.88 (distorted t, 3H, CH_3), 1.24 (bs, 24H), 3.82 (s, 4H). Mass : 284 (M^+), 269 (100%), 197, 99, 87. Analysis calc for $C_{18}H_{36}O_2$: C, 76.05; H, 12.67; Found : C, 75.92; H, 12.58%.

Henelcos-6Z-ene (7c)

B.P. 151-153°/1 mm. IR (Neat) : 735 cm^{-1} (cis double bond). PMR (CCl_4) : δ 0.87 (distorted t, 6H, 2 x CH_3), 1.2 (bs, 30H, 15 x CH_2), 1.43-1.96 (m, 4H), 5.15-5.39 (m, 2H, olefinic).

n-Decylbenzene (7d)

B.P. 103°/1 mm (bath temperature). PMR (CCl_4) : δ 0.88 (distorted t, 3H, CH_3), 3.23 (bs, 16H, 8 x CH_2), 2.18-2.58 (m, 2H, CH_2-Ph), 6.81 (bs, 5H, Ar-H). Mass : 218 (M^+), 182, 133, 117, 104, 91 (100%).

Docosan-9-yne (7e)

PMR (CCl_4) : δ 0.88 (distorted t, 6H, 2 x CH_3), 1.27 (bs, 32H, 16 x CH_2), 1.92-2.14 (m, 4H). Mass: 306 (M^+), 193, 137, 113.

3,4-Dimethoxydecylbenzene (7f)

PMR (CCl_4) : δ 0.88 (distorted t, 3H, CH_3), 1.23 (bs, 16H, 8 x CH_2), 2.2-2.6 (m, 2H, CH_2-Ph), 3.68 (s, 6H, 2 x OCH_3), 6.48 (s, 3H, Ar-H). Mass : 278 (M^+), 263, 164, 151 (100%).

Synthesis of Muscalure (6b, ≡ 7g)

Tridec-4Z-en-1-ol (10)

Tridec-4-yn-1-ol[11] (9, 19.6 g, 0.1 mol) in hexane (100 ml) containing two drops of quinoline was hydrogenated over Lindlar catalyst (Pd-$BaCO_3$, 500 mg) at atmospheric pressure till the required amount of hydrogen was absorbed. Catalyst was filtered and the filtrate washed with 2% HCl, water, brine and dried (Na_2SO_4). Solvent removed and the crude was distilled to afford 10 (18.810 g) in 95% yield, b.p. 120°/1 mm. IR (Neat) : 3350 cm^{-1} (OH), 745 cm^{-1} (cis double bond). PMR (CCl_4) : δ 0.88 (distorted t, 3H, CH_3), 1.23 (bs, 14H, 7 x CH_2), 1.91-2.32 (m, 4H), 2.18 (bs, 1H, OH, exchanges with D_2O), 3.40 (t, J=6 Hz, 2H, CH_2OH), 5.1 (t, J=5 Hz, 2H, olefinic). Analysis calc for $C_{13}H_{26}O$: C, 78.79; H, 13.12; Found : C, 78.52; H, 13.1%.

1-Iododec-4Z-ene (11)

Treatment of 10 (15.84 g, 0.08 mol) with methanesulfonyl chloride (10.34 g, 0.09 mol) in dichloromethane (100 ml) containing triethylamine (20.2 g, 0.2 mol) at 0° gave the mesylate (20.824 g) in 95% yield. The crude mesylate was treated with NaI (24 g, 0.16 mol) in boiling acetone (300 ml) for 5 hr. Acetone was removed and the residue was treated with ether and water. Ether was separated and washed with sodium thiosulphate solution, water, brine and dried (Na_2SO_4). Solvent was removed and the residue was distilled to afford pure 11 (22.16 g) in 90% yield, b.p. 150°/1 mm. IR (Neat) : 750 cm^{-1} (cis double bond). PMR (CCl_4) : δ 0.9 distorted t, 3H, CH_3), 1.28 (bs, 14H, 7 x CH_2), 1.86-2.12 (m, 4H), 3.10 (t, J=6 Hz, 2H), 5.08-5.35 (m, 2H, olefinic). Analysis calc for $C_{13}H_{25}I$: C, 50.65; H, 8.11; I, 41.23; Found: C, 50.51; H, 8.9; I, 41.12%.

1-Tosyldecyl isocyanide (2f)

Compound 2f was prepared in the usual manner as discussed earlier under PTC conditions using n-nonyl iodide and TosMIC. M.P. 61°. IR (Nujol) : 2140 cm^{-1} (N=C). PMR ($CDCl_3$) : δ 0.9 (distorted t, 3H, CH_3), 1.3 (bs, 16H, 8 x CH_2), 2.5 (s, 3H, Ar-CH_3), 4.31-4.53 (m, 1H, CHNC), 7.4 (d, J=8 Hz, 2H, Ar-H), 7.89 (d, J=8 Hz, 2H, Ar-H). Analysis calc for $C_{18}H_{27}NSO_2$: C, 67.2; H, 8.4; N, 4.3; S, 9.96; Found : C, 67.12; H, 8.35; N, 4.15; S, 9.81%.

10-Tosyl-10-tricos-14Z-enyl isocyanide (3g)

The dialkylated TosMIC 3g was prepared from 2f and the iodide 11 in the usual manner. IR (Nujol): 2140 cm^{-1} (N=C), 740 cm^{-1} (cis double bond). PMR ($CDCl_3$) : δ 0.87 (distorted t, 6H, 2 x CH_3), 1.25 (bs, 32H, 16 x CH_2), 1.73-2.18 (m, 4H), 2.47 (s, 3H, Ar-CH_3), 5.25-5.5 (m, 2H, olefinic), 7.4 (d, J=8 Hz, 2H, Ar-H), 7.78 (d, J=8 Hz, 2H, Ar-H).

(Z)-9-Tricosene (7g, Muscalure)

The dialkylated TosMIC 3g was subjected to lithium/liquid ammonia reduction in the usual manner to afford (Z)-9-tricosene (7g). B.P. 180°/1 mm. IR (Neat) : 735 cm^{-1} (cis double bond). PMR (CCl_4) : δ0.87 (distorted t, 6H, 2 x CH_3), 1.23 (bs, 34H, 17 x CH_2), 1.87-2.18 (m, 4H), 5.29 (t, J=5 Hz, 2H, olefinic). Mass : 322 (M^+), 294.

Synthesis of (-)-exo-Brevicomin (17)

(4S,5S)-4-Ethyl-5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (6e)

To a prewashed NaH (1.68 g, 0.07 mol) in DMF (20 ml) was added TosMIC (13.65 g, 0.07 mol) in DMF (50 ml) at 0° in 20 min. After 10 min, iodide 12 (25.34 g, 0.07 mol) in DMF (40 ml) was added dropwise at 0°C. After 3 hr ether (100 ml) and water (300 ml) was added to the reaction mixture. Ether was separated and the aqueous layer extracted with ether. The combined ether layer was washed with water, brine, dried (Na_2SO_4). Solvent removed at room temperature to afford 2e (25.5 g) in 85% yield. IR (Neat) : 2120 cm^{-1} (N=C). This compound was found to be unstable and taken into further reactions without purification.

Accordingly, to a freshly distilled liquid ammonia (500 ml) was added 2e (21.45 g, 0.05 mol) in THF. Simultaneously, lithium (3.5 g, 0.5 mol) was added in portions. After 90 min. the reaction mixture was quenched with ammonium chloride. Ammonia was evaporated and the residue treated with ether and water. Ether layer was separated and washed with brine and dried (Na_2SO_4). Solvent removed and the crude was distilled to afford 6e (5.6 g) in 70% yield, b.p. 70°/2 mm (Lit.[17] 75°/3.5 mm). IR (Neat): 3420 cm^{-1} (OH). PMR ($CDCl_3$) : δ 0.95 (t, J=6 Hz, 3H, CH_3), 1.31 (s, 6H, 2 x CH_3), 1.4-1.6 (m, 2H), 1.9 (bs, 1H, OH, exchanges with D_2O), 3.6-3.8 (m, 2H). $[\alpha]_D$ -21.2° (c, 5, $CHCl_3$) [Lit.[17] -23.3° (c, 7.85, MeOH)].

(4R,5S)-2,2-Dimethyl-5-ethyl-4-formyl-1,3-dioxolane (13)

To a cooled (-60°) solution of oxalyl chloride (2 ml, 0.02 mol) in CH_2Cl_2 (50 ml) was added dropwise DMSO (3.5 ml, 0.045 mol) in CH_2Cl_2 (10 ml). After 5 min. alcohol 6e (3.2 g, 0.002 mol) was added dropwise and stirred for 20 min. Afterwards, triethylamine (10.1 ml, 0.1 mol) was added dropwise and stirred for 10 min. Reaction mixture was poured in water, organic layer separated and the aqueous layer extracted with CH_2Cl_2. All the combined extracts were washed with 1% HCl, water, brine and dried (Na_2SO_4). Solvent removed and the crude was purified through column chromatography to afford 13 (2.212 g) in 70% yield. IR (Neat) : 1720 cm^{-1} (carbonyl), 2850 cm^{-1} (-CHO). PMR ($CDCl_3$) : δ 1.0 (t, J=6 Hz, 3H, CH_3), 1.3 (s, 6H, 2 x CH_3), 1.52-1.82 (m, 2H, 1 x CH_2), 3.8-4.0 (m, 2H), 9.88 (d, J=2.5 Hz, 1H, -CHO). Analysis calc for $C_{18}H_{24}O_3$: C, 60.76; H, 8.86; Found : C, 60.62; H, 8.7%.

(4S,5S)-4-Ethyl-2,2-dimethyl-5-[3-(2-methyl-1,3-dioxolan-2-yl)-1-hydroxypropyl]-1,3-dioxolane (14)

A solution of 3,3-ethylenedioxybutyl bromide (3.9 g, 0.02 mol) in THF (10 ml) was added dropwise to magnesium (1.44 g, 0.06 mol) in THF (5 ml) at 15°. After stirring for 1 hr at room temperature, olive brown solution was obtained. This Grignard reagent[15] was cooled to 0° and aldehyde 13 (1.58 g, 0.01 mol) in THF (5 ml) was added dropwise. After 4 hr, saturated ammonium chloride solution was added and stirred for 15 min. Aqueous layer was extracted with ether and the combined ether extract washed with brine, dried (Na_2SO_4). Solvent was removed and the crude was purified through column chromatography to afford 14 (1.972 g) in 72% yield. IR (Neat) : 3420 cm^{-1} (OH). PMR ($CDCl_3$) : δ 1.0 (t, J=6 Hz, 3H, CH_3), 1.3 (s, 3H, CH_3), 1.38 (s, 6H, 2 x CH_3), 1.52-1.88 (m, 6H, 3 x CH_2), 2.78 (bs, 1H, OH, exchanges with D_2O), 3.52-3.88 (m, 3H), 3.93 (s, 4H). Analysis calc for $C_{14}H_{26}O_5$: C, 61.3; H, 9.49; Found : C, 61.23; H, 9.41%.

(4S,5S)-4-Ethyl-2,2-dimethyl-5-[3-(2-methyl-1,3-dioxolan-2-yl)-1-xanthyl propyl]-1,3-dioxolane (15)

To a suspension of prewashed NaH (0.144 g, 0.006 mol) in THF (3 ml) was added alcohol 14 (1.37 g, 0.005 mol) in THF (8 ml). After 1 hr, reaction mixture was cooled to 0° and CS_2 (0.76 g, 0.01 mol) was added dropwise to the reaction mixture and stirred at room temperature for 30 min. Again the reaction mixture was cooled to 0° and methyl iodide (1.42 g, 0.01 mol) was added dropwise. After 4 hr, THF was removed from the reaction mixture and the residue was taken in ether. The organic layer was washed with water, brine and dried (Na_2SO_4). Solvent was removed and the crude was purified through column chromatography to afford pure 15 (1.73 g) in 95% yield. PMR ($CDCl_3$) : δ 1.0 (t, J=6 Hz, 3H, CH_3), 1.32 (s, 3H, CH_3), 1.4 (s, 6H, 2 x CH_3), 1.44-1.9 (m, 6H, 3 x CH_2), 2.57 (s, 3H, SCH_3), 3.72-3.88 (m, 2H), 3.92 (s, 4H), 5.76-6.0 (m, 1H, $C\underline{H}OCSSCH_3$).

(4S,5S)-4-Ethyl-2,2-dimethyl-5-[3-(2-methyl-1,3-dioxolan-2-yl)-propyl]-1,3-dioxolane (16)

A mixture of 15 (1.45 g, 0.004 mol), azobis-isobutyronitrile (AIBN) (50 mg) and toluene (15 ml) was heated at 100° under nitrogen. To this hot reaction mixture, freshly prepared tributyltin hydride[16] [1.46 g (1.5 ml), 0.005 mol] was added dropwise and refluxed for 5 hr. Reaction mixture was cooled to room temperature and directly purified on silica gel column to afford pure 16[17] (1.0 g) in 97% yield. PMR ($CDCl_3$) : δ 0.97 (t, J=6 Hz, 3H, CH_3), 1.27 (s, 3H, CH_3), 1.33 (s, 6H, 2 x CH_3), 1.4-1.7 (m, 4H, 2 x CH_2), 3.45-3.65 (m, 2H), 3.9 (s, 4H). $[\alpha]_D$ -22.93° (c, 3, $CHCl_3$). [Lit.[17] -23.2° (c, 2.74, $CHCl_3$)].

(1S,7S)-(-)-Exo-7-ethyl-5-methyl-6,8-dioxabicyclo [3.2.1] octane (-)-exo-Brevicomine (17)

To a mixture of compound 16 (0.77 g, 0.003 mol) and wet ether (10 ml) was added PTSA (20 mg) at room temperature. After 12 hr, the reaction mixture was diluted with ether. Ether was separated and washed with water, brine and dried (Na_2SO_4). Solvent was removed and crude was distilled to afford 17 (0.42 g) in 90% yield, b.p. 69-72°/20 mm (Lit.[17] 100°/105 mm). PMR ($CDCl_3$) : δ 0.9 (t, J=7 Hz, 3H, CH_3), 1.4 (s, 3H, CH_3), 1.2-1.85 (m, 8H, 4 x CH_2), 3.9 (t, J=6 Hz, 1H), 4.13 (bs, 1H). Mass : 156 (M^+),

114, 98, 85, 68. Analysis calc for $C_9H_{18}O_2$: C, 69.23; H, 10.25; Found : C, 69.16; H, 10.2%. $[\alpha]_D$ -66.9° (c, 2, ether) [Lit.[17] -67.5°, (c, 2.15, ether)].

Synthesis of L-factor (19)

(4S,5S)-5-Pentyl-4-hydroxymethyl-2,2-dimethyl-1,3-dioxolane (7h)

To a prewashed sodium hydride (0.24 g, 0.01 mol) in DMSO (5 ml) was added 1-tosylbutyl isocyanide[22] (2g, 2.3 g) in ether (10 ml) at 0°C for 20 min. After 30 min. iodide (12) (3.62 g, 0.01 mol) in ether (10 ml) was added dropwise at 0°C. After 2 hr, ether (50 ml) and water (25 ml) were added to the reaction mixture. Ether layer was separated and the aqueous layer was extracted with ether. The combined ether layer was washed with water, brine and dried (Na_2SO_4). Solvent removed under reduced pressure afforded the dialkylated TosMIC (3h) (2.3 g) in 50% yield. This compound was found to be unstable and was immediately reduced by using lithium in liquid ammonia in usual fashion to afford 7h in 45% yield. $[\alpha]_D$ -30° (c, 2, CH_2Cl_2). IR (Neat) : 3450 cm^{-1}; PMR ($CDCl_3$) : δ 0.95 (t, 3H), 1.0-1.60 (m, 14H), 1.7 (s, 1H, D_2O exchangeable), 3.41-4.00 (m, 4H). Analysis calc for $C_{11}H_{22}O_3$: C, 65.3; H, 10.9; Found: C, 65.4; H, 10.8%.

(4S,5S)-5-Pentyl-4-n-propionate-2,2-dimethyl-1,3-dioxolane (18)

To a solution of oxalylchloride[14] (0.25 g, 0.002 mol) in dichloromethane (5 ml) was added DMSO (1 ml) at -50°C and stirred for 10 min. Alcohol 7h (0.202 g, 0.001 mol) in dichloromethane (2 ml) was added dropwise to the above solution and stirred for another 15 min. The reaction mixture was decomposed by adding triethylamine (1 ml) and was allowed to come to room temperature. The reaction mixture was extracted with ether, washed with cold 5% HCl followed by water and dried to afford the unstable aldehyde which was immediately interacted with ethoxycarbonylmethylenetriphenylphosphorane (0.338 g, 0.001 mol) in benzene (2 ml) and stirred for 1 hr. Benzene was removed and the resulting α,β-unsaturated ester was reduced with Raney Nickel (2 g) in ethanol (5 ml) under normal temperature and pressure. After 6 hr, the catalyst was collected on celite, washed with ethanol and the combined filtrate was concentrated. Column chromatography (ethyl acetate-light petroleum, 1:10) of the residue gave 18 (0.1 g) in 50% yield. $[\alpha]_D$ -18.66 (c, 0.9, CH_2Cl_2); IR (Neat) : 1740 cm^{-1}. PMR ($CDCl_3$) : δ 0.95 (t, 3H), 1.0-2.1 (m, 19H), 2.1-2.4 (m, 2H), 3.6 (m, 2H), 4.05 (q, 2H).

(4S,5S)-5-Hydroxy-4-decanolide (L-factor, 19)

To a mixture of trifluoroacetic acid (4 ml) and water (1 ml) was added the ester 18 (0.054 g, 0.002 mol) and stirred for 4 hr. The reaction mixture was diluted with water and extracted with ether, dried (Na_2SO_4) and concentrated. The final purification was effected by performing the column chromatography (benzene) to afford (4S,5S)-L-factor (19, 0.032 g) in 95% yield. $[\alpha]_D$ +27.0° (c, 1. $CHCl_3$); Lit.[18e] +33.1° (c, 1.64, $CHCl_3$). IR (Neat) : 1770, 3470 cm^{-1}. PMR ($CDCl_3$) : δ 0.9 (t, 3H, CH_3), 1.2-2.7 (m, 13H), 3.6 (m, 1H, H-5), 4.45 (m, 1H, H-4). Analysis calc for $C_{10}H_{18}O_3$: C, 64.5; H, 9.7; Found : C, 64.3; H, 9.6%.

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