SYNTHESIS AND NOE AND 2D-NOESY SPECTROSCOPIC STUDIES OF TWO *N*-PROPIONYL DERIVATIVES OF TERPENE-DERIVED CHIRAL AUXILIARIES

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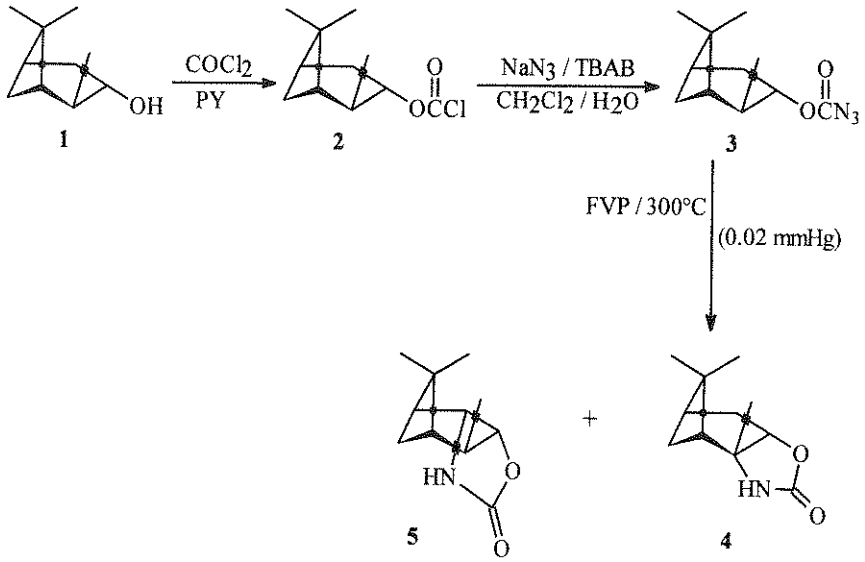
تحضير مشتقين N–بروبيونايل من المركبات الكيرالية المساعدة المشتقة من التربينات (أحدهما مشتق من (-)-٣-بينانول، والآخر مشتق من أيزومنثول) تم إنجازها بواسطة استعمال بيوتايل ليثيوم عادي كقاعدة و بروبيونايل كلورايد ككاشف للأسيلة. من أجل زيادة محصلة النواتج لكلٍ من مشتقي N–بروبيونايل خاصةً المشتق من أيزومنثول، تم استخدام كاشف أسيلة آخر لهذا الغرض. استخدام كاشف الأسيلة (الرخيص والمتوفر تجارياً) بروبيونيك أنهيدريد أعطى تقريباً نفس الحصيلة لمشتق N–بروبيونايل المشتق من (-)-٣-بينانول، لكن لسوء الحظ هذه الطريقة لم ترفع الحصيلة لمشتق N–بروبيونايل المشتق من أيزومنثول كثيراً على الرغم من ارتفاعها قليلاً. المحاولات للتمييز بين بروتوني البروكيرال ميثيلين في مجموعة N–بروبيونايل وجميع البروتونات ومجموعات الميثايل الدياستيريوميرية الأخرى في مشتقي N–بروبيونايل للمركبات الكيرالية المساعدة قد تم أداؤها باستخدام أطياف nOe المطروحة لرنين البروتون النووي المغناطيسي وكذلك باستخدام دراسات 2D-NOESY الطيفية.

The synthesis of two *N*-propionyl derivatives of terpene-derived chiral auxiliaries (one is derived from (-)-3-pinanol, and the other from isomenthol) has been achieved *via* the use of *n*-butyllithium as a base and propionyl chloride as an acylation reagent. In order to increase the yield of both *N*-propionyl derivatives, particularly *N*-propionyl derivative of chiral auxiliary derived from isomenthol, the alternative acylation reagent was employed for this purpose. Using, cheap and readily available acylation reagent, propionic anhydride gave almost the same yield of *N*-propionyl derivative of chiral auxiliary derived from (-)-3-pinanol, but unfortunately, this procedure did not increase the yield of the *N*-propionyl derivative of chiral auxiliary derived from isomenthol much, although it was slightly better. Attempts to distinguish between the prochiral methylene protons in the *N*-propionyl group, and all other diastereotopic protons and methyl groups in these two *N*-propionyl derivatives of chiral auxiliaries were carried out by using ^{1}H NMR nOe difference spectra and 2D-NOESY spectroscopic studies.

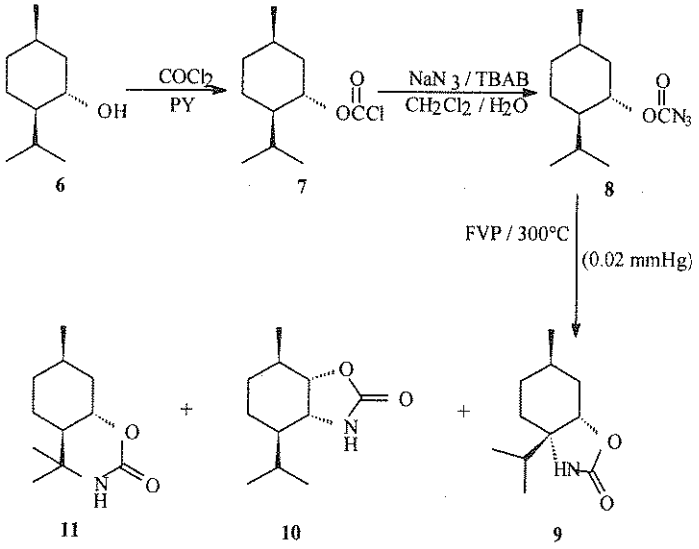
INTRODUCTION

The synthetic route chosen for the synthesis of the chiral oxazolidinone auxiliaries used as starting materials, cheap readily available chiral alcohol and involved a stereospecific intra-molecular nitrene insertion process [1]. This nitrene insertion route to chiral oxazolidinones has been used previously by Paryzek [2] and Alewood [3] in the field of steroid chemistry. The chiral substrates selected for investigation were terpene alcohols which are available from the chiral pool. The first one to be investigated was (-)-3-pinanol **1** which was chosen and used by Cadogan *et al* [4,5] as the starting material for the synthesis of the chiral oxazolidinone auxiliary **4** (Scheme 1). Azidoformate **3** was synthesized from **1** according to the sequence shown in Scheme 1. This azidoformate **3**, which was an oil, was thermally decomposed using flash vacuum pyrolysis (300°C, 0.02mmHg). This produced a mixture consisting of the oxazolidinones **4** and **5** in the ratio of 3:1 respectively. The major product **4** was easily isolated by flash column chromatography in a yield of 65% [4,5].



Scheme 1

The second terpene alcohol to be studied was inexpensive isomenthol **6** [4,5]. This starting material was chosen and employed by Cadogan *et al* [4,5] for the synthesis of the chiral oxazolidinone auxiliary **9** (Scheme 2). Flash vacuum pyrolysis of azidoformate **8** (300°C, 0.02 mmHg), which was prepared from chloroformate **7**, gave rise to a mixture consisting of the two oxazolidinones **9** and **10**, and also the six-membered oxazinone **11**, these were formed in the ratio of 7:1:2 respectively. The chiral oxazolidinone **9** was isolated as a thick syrup (51%) [4,5] by subjecting the crude pyrolysis mixture to column chromatography.



Scheme 2

EXPERIMENTAL

Preparation of (2*R*,6*S*) - 3 -aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]decan-4-one (4) and (1*S*,4*R*,6*S*)-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0]nonane-8-one (9).

Literature methods were used to prepare (2*R*,6*S*)-3-aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]-decan-4-one (**4**) [4,5] and (1*S*,4*R*,6*S*)-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0]nonane-8-one (**9**) [4,5].

Preparation of (2*R*,6*S*)-*N*-propionyl-3-aza-2,9,9-trimethyl-5-oxatricyclo[6.1.1.0^{2,6}]decan-4-one (12).

To a solution of *auxiliary* **4** (0.50 g, 2.56 mmol) in dry THF (20ml), at –78 °C under argon, was added *n*-butyllithium (1.76ml of 1.6M solution, 2.82 mmol, 1.1 eq) *via* syringe. After stirring for 30 minutes a solution of freshly distilled propionic anhydride (0.521g, 4.00mmol, 1.56 eq) in THF (5ml) was added dropwise *via* syringe. The resulting solution was stirred at –78 °C for 5 minutes before being allowed to warm to room temperature and then stirred at this temperature for 30 minutes. TLC analysis revealed that the reaction was complete and quenching was effected with sodium carbonate solution. After stirring for 10 minutes at room temperature, the layers were separated and the aqueous layer extracted with dichloromethane (3x20ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over ($MgSO_4$), filtered and evaporated to yield a pale yellow oil which was purified by flash chromatography (50g silica) using *n*-hexane:ether (4:1) as elution solvent to give **(12)** as a colourless solid which was recrystallised from hexane to give the pure compound as a colourless crystals (0.527g, 82%); mp 101-102°C (from hexane); FTIR (nujol) ν_{max} 1770(oxazolidinone C=O), 1700(C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.45 (1H, dd, *J*=8.9, 2.6 Hz, CH_NO), 2.95 (1H, dq, *J*=17.9, 7.23 Hz, CH_MH_KC=O), 2.90 (1H, dq, *J*=17.9, 7.23 Hz, CH_MH_KC=O), 2.92 (1H, dd, *J*= 4.7 Hz, H_L), 2.52-2.40 (1H, m, CH_J), 2.33-2.23 (1H, m, H_H), 2.01-1.99 (1H, m, CH_G), 1.98-1.92 (1H, m, H_F), 1.66 (3H ,s ,$CH_{3\ (E)}$), 1.31 (3H ,s ,$CH_{3\ (D)}$), 1.11 (3H, t, *J*=7.3 Hz, $CH_{3(C)}CH_2$), 1.02 (1H, d, *J*=11.2 Hz, H_B), 0.93 (3H, s, $CH_{3\ (A)}$) ppm; ^{13}C NMR (100.2 MHz, CDCl3) δ 174.69 (C=O), 153.90 (C=0), 76.46(CHO), 67.56(quatC), 46.16(CH_L), 38.84 (CH_G), 37.97(quatC), 34.79(CH_JH_F), 30.61 (CH_MH_K), 27.35(CH_HH_B, $CH_{3\ (D)}$), 25.58 ($CH_{3\ (E)}$), 24.26($CH_{3\ (A)}$), 8.43($CH_{3\ (C)}$) ppm; MS (EI) m/z 32(63%), 41(34), 57(base), 109(38), 251(71,M^+); Accurate mass (EI); Found: 251.15213 (85%); $C_{14}H_{21}NO_3$ (M^+) requires 251.15213.

Preparation of (1*S*,4*R*,6*S*)-*N*-propionyl-9-aza-1-isopropyl-4-methyl-7-oxabicyclo[4.3.0] nonane-8-one 13.

A similar procedure to that for the preparation of **12** was adopted for the *N*-propionyl derivative of *auxiliary* **9** although the combined organic extracts were washed with water (20ml), dried ($MgSO_4$), filtered and evaporated to yield a slightly pale yellow viscous oil. The residue was subjected to flash column chromatography (50g silica) using hexane:ether (1:1) elution to give **13** as clear oil which crystallized on standing (0.322g, 50%); mp 51.9-53.2 °C; FTIR (nujol) ν_{max} 1762(oxazolidinone C=O), 1712(C=O) cm^{-1}; ^{1}H NMR (400 MHz , $CDCl_3$) δ 4.44 (1H, t, *J*=2.8 Hz, CH_QO), 2.98 (1H, dq, *J*=17.7, 7.3 Hz, $CH_PH_NCH_3$), 2.92 (1H, dq, *J*=17.7, 7.3 Hz, $CH_PH_NCH_3$), 2.72 (1H, septet, *J*=6.9 Hz, CH_M),

2.24 (1H, m, H_L), 1.95-1.92 (1H, m, H_K), 1.86-1.80 (1H, m, H_J), 1.78-1.73 (1H, m, CH_H), 1.65-1.58 (1H, m, H_G), 1.33-1.25 (1H, m, H_F), 1.22-1.17 (1H, m, H_E), 1.14 (3H, t, J=7.3 Hz, $CH_{3(D)}CH_2$), 0.96 (3H, d, J=6.6 Hz, $CH_{3(C)}$), 0.90 (3H, d, J=6.9 Hz, $CH_{3(B)}$), 0.87 (3H, d, J=6.9 Hz, $CH_{3(A)}$) ppm; ^{13}C NMR (100.2 MHz, $CDCl_3$) δ 175.48(C=O), 154.88(C=O), 73.67(CHO), 67.43 (quat C), 34.34(CH_KH_F), 31.82(CH_M), 30.55 (CH_PH_N), 26.27(CH_GH_E), 25.16(CH_LH_J), 22.71 ($CH_{3\ (C)}$), 20.84 (CH_H), 16.89($CH_{3\ (B)}$), 16.55($CH_{3\ (A)}$), 8.70($CH_{3\ (D)}$) ppm; MS (FAB) m/z 57(22%), 95(17), 137(23), 154(18), 198(32), 254(base M+H); Accurate mass (FAB); Found : 254.17480; $C_{14}H_{24}NO_3$ requires 254.17562.

RESULTS AND DISCUSSION

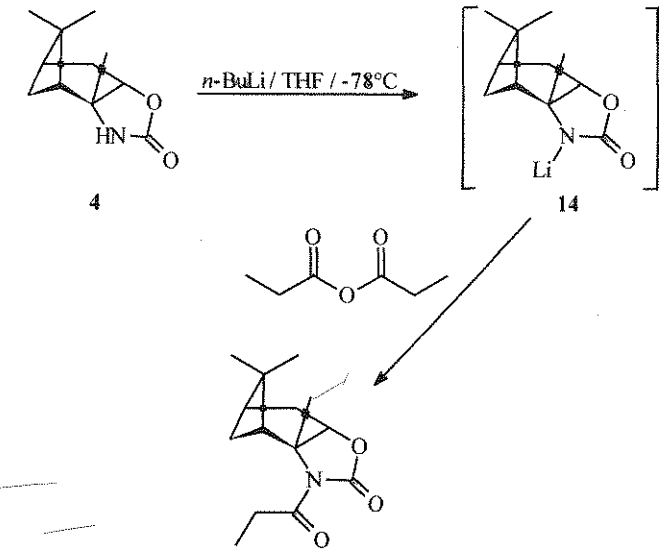
Further applications of chiral auxiliary **9** were not pursued when attempts to functionalize it resulted in the formation of thick gums, which proved extremely difficult to purify [4, 5]. Nonetheless, method used by Evans *et al* [6] was employed for the preparation of the *N*-propionyl derivatives **(12)** and **(13)** of chiral auxiliaries **(4)** and **(9)** respectively. In essence, solutions of chiral auxiliaries **(4)** and **(9)** in anhydrous THF (tetrahydrofuran) were treated individually with *n*-butyllithium at –78 °C, followed by acylation of the resulting anions with freshly distilled propionyl chloride. Thus, use of this procedure with the chiral auxiliaries **(4)** and **(9)** gave an 84% yield of the *N*-propionyl derivative **(12)** and a 42% yield of the desired *N*-propionyl derivative **(13)**.

In order to increase the yield of both *N*-propionyl derivatives **(12)** and **(13)**, particularly **(13)**, the alternative acylation reagent was employed for this purpose. Thus, anions **(14)** and **(15)** (which resulted *via* treatment of solutions of the chiral auxiliaries **(4)** and **(9)** in anhydrous THF, individually, with *n*-butyllithium at –78 °C) were acylated with, cheap and readily available acylation reagent, freshly distilled propionic anhydride (Schemes 3 and 4).

Unfortunately, this procedure led to a reasonable yield (50%) of *N*-propionyl derivative **(13)**, although it was slightly better. This procedure afforded almost the same yield (82%) of the *N*-propionyl derivative **(12)**.

Attempts to distinguish between the prochiral methylene protons H_K and H_M in the *N*-propionyl derivative **(12)** and H_N and H_P in the *N*-propionyl derivative **(13)**, and the other diastereotopic protons and methyl groups were carried out by using nuclear Overhauser effect (nOe) and NOESY spectroscopic studies of **(12)** and **(13)**. ^{1}H NMR nOe difference spectra of the *N*-propionyl derivatives **(12)** and **(13)** are accumulated in Tables 1 and 2, respectively.

Table 1 shows that irradiation of three protons of methyl A caused a 19.4% enhancement of the signal due to H_N, 5.8% due to H_L, 14.0% due to H_J, 14.5% due to H_D and 18.6% due to H_E. That proves methyl A protons are close close position to methyl E protons. Irradiation of methyl D protons gave 11.6% enhancement of H_A, but did not give any enhancement for H_E. Whilst, irradiation of methyl E protons gave no enhancement of signal for H_D, but gave 18.6% enhancement of signal for H_A. These results confirm H_A and H_E protons are close to each other in space and then two methyl groups H_A and H_D are distinguishable.



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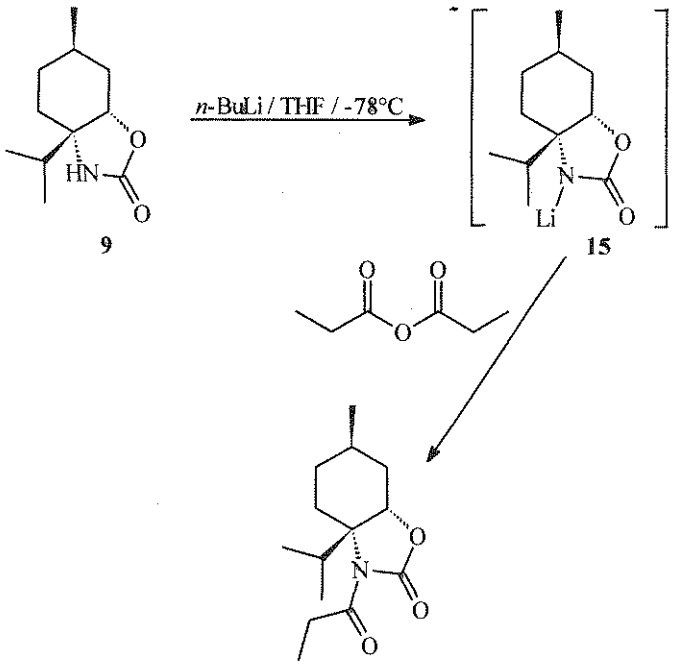

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Sceheme 4

Table 1: ^{1}H NMR steady state nOe data for the *N*-propionyl derivative (12).

Irradiation Site	Signal enhancement (%)										
	H_A	H_B	H_D	H_E	H_G	H_H	H_J	H_K	H_L	H_M	H_N
H_A	-	-	14.5	18.6	-	-	14.0	-	5.8	-	19.4
H_B	-	-	-	-	5.0	21.1	3.3	2.9	4.5	-	-
H_C	-	-	-	-	-	4.1	3.7	7.4	5.8	7.4	-
H_D	11.6	-	-	-	6.4	14.5	2.5	13.6	3.7	-	-
H_E	18.6	-	-	-	-	-	2.9	8.3	2.5	-	10.7
H_F	-	-	-	-	-	1.7	20.7	-	5.3	-	-
H_G	-	6.2	-	-	-	2.3	20.1	-	-	-	2.1
H_H	-	20.2	-	-	4.1	-	1.7	1.7	2.5	-	2.5
H_J	-	-	-	-	20.7	-	-	-	4.5	2.9	5.0
H_K	-	-	-	-	-	19.0	16.1	-	-	-	-
H_L	-	-	-	-	-	20.2	14.4	-	-	-	-
H_M	-	-	-	-	-	-	20.7	-	-	-	-
H_N	-	-	-	-	-	-	20.2	-	-	-	-

Table 2. ^{1}H NMR steady state nOe data for the *N*-propionyl derivative (13).

Irradiation Site	Signal enhancement (%)														
	H_A	H_B	H_C	H_D	H_E	H_F	H_G	H_H	H_J	H_K	H_L	H_M	H_N	H_P	H_Q
H_A	-	-	-	-	-	1.2	-	3.7	-	1.6	21.0	7.0	1.6	1.6	11.2
H_B	-	-	-	-	-	-	-	-	-	1.2	20.7	-	-	-	12.0
H_C	-	-	-	-	-	4.1	-	-	-	2.5	21.1	-	-	-	9.9
H_D	-	-	-	-	-	-	6.6	-	-	-	20.7	3.3	1.6	6.3	1.7
H_E	-	-	-	-	-	-	21.1	-	-	-	18.2	3.7	3.7	3.7	1.7
H_F	-	-	-	-	-	-	5.4	-	-	21.5	17.8	-	-	-	4.1
H_G	4.5	6.2	5.4	14.5	5.8	12.4	-	-	-	-	12.0	-	-	-	-
H_H	-	4.6	4.1	6.6	2.1	3.3	-	-	-	-	21.1	-	-	-	-
H_J	-	-	-	-	-	-	20.7	-	-	3.7	2.9	-	1.6	1.6	-
H_K	-	-	-	-	-	3.3	13.2	7.4	-	-	0.7	-	-	-	2.1
H_L	-	-	-	-	-	-	20.7	-	2.9	1.0	-	-	-	-	1.7
H_M	-	-	-	-	-	-	20.7	-	-	0.5	1.2	-	1.7	1.7	0.5
H_N	-	-	-	-	-	-	18.2	4.1	-	-	-	1.3	-	-	0.5
H_P	-	-	-	-	-	-	20.7	2.5	-	2.9	-	1.4	-	-	0.7
H_Q	3.7	2.1	-	2.5	-	-	24.8	6.6	2.9	2.9	-	-	4.2	4.5	-

Irradiation of H_G gave 2.1% enhancement of signal for H_N, 20.1% for H_J, 2.3% for H_H and 6.2% for H_B. That proves H_B is closer than H_H to H_G in space. Whereas, irradiation of H_D gave 14.5% enhancement of signal for H_H, confirming that H_D is in close position to H_H. These results prove that discrimination between the diastereotopic protons H_B and H_H was achieved by irradiation of H_D and H_G, individually.

Irradiation of protons H_B, H_D and H_H, individually, caused enhancement of signal due to H_G slightly more than enhancement of signal caused due to H_J. Whereas, irradiation of H_A, H_F and H_N, individually, gave 14.0%, 20.7% and 20.2% enhancement of signal, respectively, for H_J, but did not affect H_G. These results confirm that diastereotopic protons H_G and H_J are distinguishable.

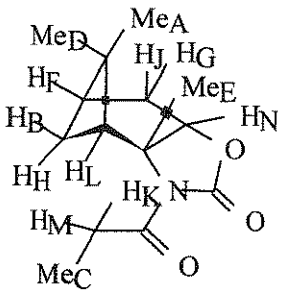
Irradiation of H_J gave 2.9% enhancement of signal for H_M, but did not give any for H_K. That proves H_M is in close position to H_J. Irradiation of protons H_B and H_H, individually, gave small enhancement of signal for H_K. Whereas, irradiation of protons H_D and H_E, individually, caused

13.6% and 8.3 % enhancement of signal, respectively, due to H_K, but did not cause enhancement of signal for H_M. All of these results prove that discrimination between the diastereotopic protons H_K and H_M was achieved by irradiation of H_J, H_D and H_E, individually.

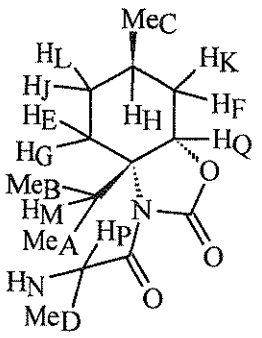
Fig. 1 illustrates a portion of the 2D-NOESY spectrum of the *N*-propionyl derivative **12**. The one-dimensional spectrum, as with COSY, is found along the diagonal, and cross peaks occur when two protons are close in space. Thus, methyl D protons and methyl E protons show two cross peaks with proton H_K at δ 2.90 and 1.31 and at 2.90 and 1.66 ppm, respectively. That proves H_K is in close in space to two methyl protons H_D and H_E. There is another cross peak at δ 2.92 and 2.29 ppm, confirming that H_K and the bridgehead proton H_L are both close in space to H_H. All of these results determined by NOESY spectrum confirm all results determined by nOe difference spectra and all of them confirm that H_K and H_M are distinguishable.

Table 2 shows that irradiation of methyl A protons, methyl B protons, methyl C protons, methyl D protons, H_E, H_F, H_G and H_H, individually, gave 21%, 20.7%, 21.1%, 20.7%, 18.2%, 17.8%, 12.0% and 21.1% enhancement of signal, respectively, for H_L, whereas, all of these irradiations did not affect H_J. Irradiation of H_Q only gave 2.9% enhancement of signal for H_J. These results confirm that H_L is close in space to H_A, H_B, H_C, H_D, H_E, H_F, H_G and H_H, whilst, H_J is close in space to H_Q. These results prove that discrimination between the diastereotopic protons H_J and H_L was achieved by irradiation of protons H_A to H_H or irradiation of H_Q.

Irradiation of H_G and H_H, individually caused 12.4% and 3.3% enhancement of the signal, respectively, due to H_F, whereas, irradiation of these protons did not affect H_K. That proves H_F is close in position to H_G and H_H. Irradiation of H_J, H_p and H_Q, individually, caused 3.7%, 2.9% and 2.9% enhancement of the signal, respectively, due to H_K, but did not affect HF. That proves H_K is close in position to H_J, H_p and H_Q. These results confirm that diastereotopic methylene protons H_F and H_K are distinguishable.



12



13

Irradiation of methyl D protons, H_F, H_J, H_K, H_L, H_M, H_N, H_P and H_Q, individually, gave 6.6%, 5.4%, 20.7%, 13.2%, 20.7%, 20.7%, 18.2%, 20.7% and 24.8% of enhancement of signal, respectively, for H_G, whilst, did not affect on H_E. That proves H_G is close in space to all of these protons. Irradiation of H_H gave 2.1% enhancement of signal for H_E, but did not affect H_G. These results prove that discrimination between the diastereotopic protons H_E and H_G was achieved by irradiation of H_D, H_F, H_J, H_K, H_L, H_M, H_N, H_P and H_Q, individually, or irradiation of H_H.

Discrimination between the two diastereotopic methyl groups A and B was achieved by irradiation of H_H which gave 4.6% enhancement of signal for H_B, but did not affect on H_H, whereas, irradiation of H_G and H_Q gave 4.5% and 3.7% enhancement of signal, respectively, for H_A, and 6.2% and 2.1% enhancement of signal, respectively, for H_B. These results prove that H_B is close in space to H_H, and it is closer to H_G than H_A, but H_A is closer in space to H_Q than H_B.

Irradiation of H_A, H_E, H_J, H_M and H_Q almost caused the same enhancement of the signal due to H_N and H_P, in other words, there is no differential enhancements of the diastereotopic protons H_N and H_P. The prochiral protons H_N and H_P are not distinguishable by nOe studies, although irradiation of the neighbor methyl D protons gave 1.6% and 6.3% enhancement of signal for H_N and H_P, respectively.

Fig. 2 illustrates a portion of the 2D-NOESY spectrum for the *N*-propionyl derivative **(13)**. The one-dimension spectrum is reproduced along one axis of the two-dimensional contour plot. Methyl B protons show a cross peak with proton H_H at δ 0.90 and 1.75. That proves methyl B protons are close in space to H_H, but methyl A protons are not close. This result confirms that two diastereotopic methyl groups A and B are distinguishable.

There is a cross peak at δ 1.29 and 1.62 ppm, confirming that H_F is close in space to H_G and proving that discrimination between the diastereotopic protons H_F and H_K was achieved. Proton H_L shows a cross peak with methyl D protons at δ 2.24 and 1.14 ppm. This result proves that H_L is close in space to methyl D protons and confirms that the diastereotopic protons H_L H_J are distinguishable.

There are two cross peaks at δ 1.20 and 1.75 ppm, and 1.62 and 1.29 ppm for H_E with H_H and H_G with H_F, respectively, that proves H_G is close in space to H_F, and H_E is close in position to H_H. These results confirm that the diastereotopic protons H_E and H_G are distinguishable.

The diastereotopic protons H_N and H_P show a cross peak with H_E at δ 2.95 and 1.20 ppm. Proton H_N shows a cross peak with H_M at δ 2.92 and 2.72 ppm, whereas, its geminal diastereotopic proton H_P shows another cross peak with H_M at δ 2.98 and 2.72 ppm. These results prove that discrimi-nation between the diastereotopic protons H_N and H_P was achieved by existence of these two different cross peaks in 2D-NOESY spectrum; *i.e.* the protons are distinguishable.

All of these results determined by 2D-NOESY spectrum confirm all results determined by nOe difference spectra and moreover, confirm that H_N and H_P are distinguishable.

By conclusion, all the signals of the *N*-propionyl derivatives **(12)** and **(13)** were assigned by nOe and 2D-NOESY spectroscopic studies.

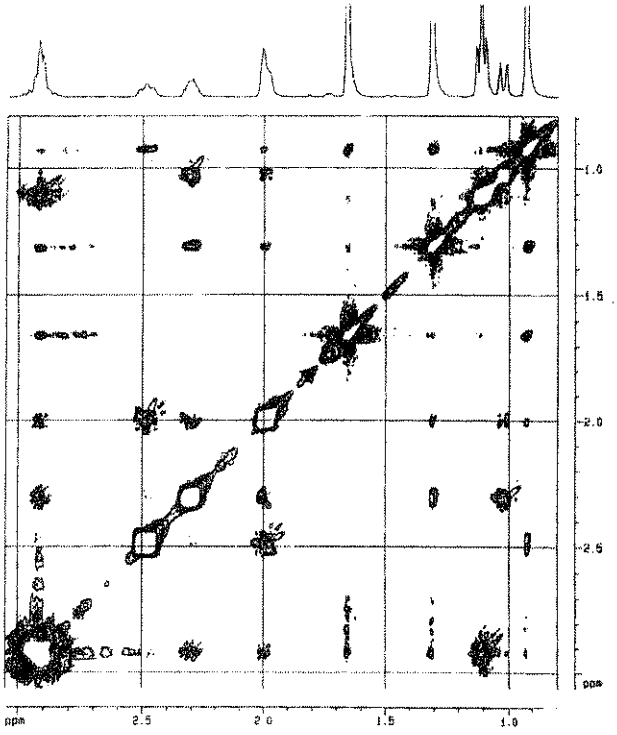


Fig. 1: A portion of the 2D-NOESY 400 MHz NMR spectrum of the *N*-propionyl derivative 12.

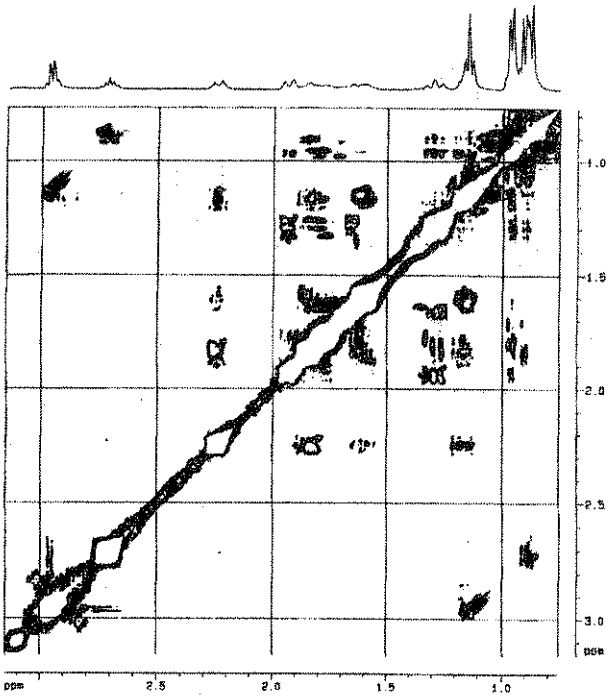


Fig. 2: A portion of the 2D-NOESY 400 MHz NMR spectrum of the *N*-propionyl derivative 13

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