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Homochiral Acyl Isocyanates as Diagnostic NMR Probes for the Enantiomeric Purity of Chiral Alcohols

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ايزوسينات الأسيل كمركز كيرالي لتشخيص درجة نقاء الكحولات المتماكبة ضوئيا بواسطة الرنين المغناطيسي

جريجوري روس و أنثوني دونوفان

خلاصـة: لقد تم تطوير واختبار مر كب اسيل وايزوسينات الكبريت في تفاعلاته مع الكحولات الكيرالية. وتمت الدراسة باستخدام جهـاز الرنين المغناطيسي النووي بتمييز الإزاحة الكيميائية التي تسمح المركبات الإيزوسينات النشيطة بإستخدامها لتشخيص نقاوة المركبات المتماكبة ضوئيا.

ABSTRACT: The first reported acyl and sulfonylisocyanates were developed and tested in reactions with chiral alcohols to afford diastereomeric carbamates. NMR analysis of these investigates the chemical shift discrimination that would allow these activated isocyanates to be used as diagnostic probes of enantiomeric purity.

KEYWORDS: N.M.R; Enantiomeric excess; Isocyanates; Camphor derivatives.

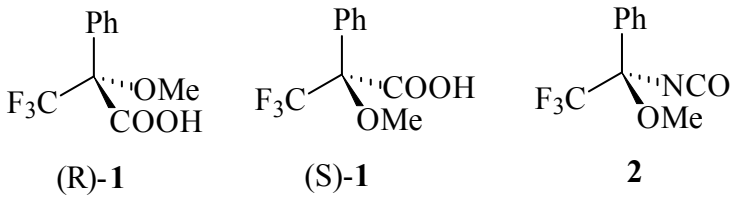
The past two decades have witnessed enormous strides in the art of asymmetric synthesis (Gawley and Aubé, 1996). The level of sophistication today allows for the construction of a vast array of complex chiral molecular structures, many of which possess useful biological properties. In such synthetic endeavors, there exists a continuing need to determine, in a facile manner, the stereochemical integrity of the stereogenic centres within the molecular architecture.

Historical dependence on the measurement of optical rotation requires that the absolute rotation of the product be known. Failing this, confirmation may involve multi-step conversion to some alternative structure whose rotation is known. The relationship between optical purity and the rotation is not necessarily linear and the compounds must be homogeneous and free from optically active impurities. In spite of these disadvantages, optical rotations remain a popular method of determining optical purity due to the relatively low cost of the equipment involved and convenience of operation (Lyle and Lyle, 1983; Parker and Taylor, 1992).

Whilst chiral chromatographic approaches, such as gas chromatography (GC) and high performance liquid chromatography (HPLC), have more recently gained some momentum (Gawley and Aubé, 1996), nuclear magnetic resonance (NMR) based methodologies have now become the mainstream choice because of convenience and general applicability (Yamaguchi, 1983; Parker, 1991; Gawley and Aubé, 1996). Whilst NMR spectroscopy cannot differentiate between enantiomers in an achiral medium since their resonances are isochronous (chemical shift equivalence), diastereomers may be distinguished since certain of their resonances may be anisochronous (chemical shift non-equivalence) (Figure 1). Especially since the availability of high-field NMR instruments, it has been possible to reliably resolve resonances that are separated by only a few hertz (Hz). Thus, to determine the enantiomeric purity of a sample, NMR requires

that the enantiomers first be transformed into diastereomers through the application of some external homochiral auxiliary reagent.

Three types of such reagents are currently in service, chiral lanthanide shift reagents (CSR), chiral solvating agents (CSA) and chiral derivatising agents (CDA) (Parker, 1991). CSR- and CSA-types generally form *in situ* diastereomeric complexes with substrate enantiomers without formal bonding occurring, whilst CDA's require the formation of discrete diastereomers with formal bonds. The successful development of CDA's in recent years has made them the method of choice, with the best known being the widely used Mosher reagents (R)- and (S)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acids) **1** (Dale *et al*, 1968, 1969, 1973).



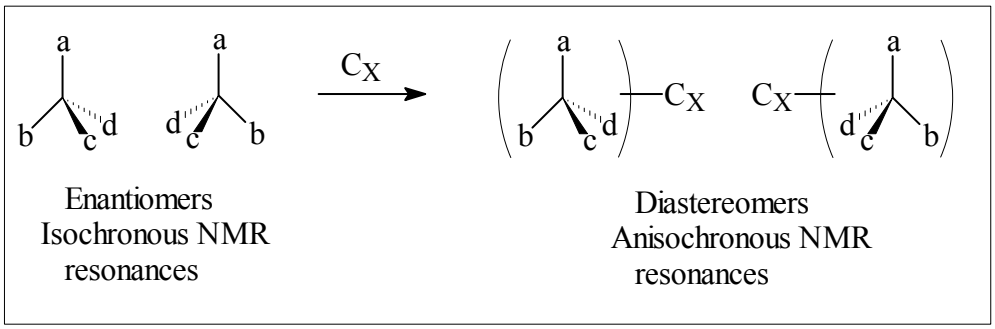


Figure 1. Representation of diastereomer formation by reaction of an external homochiral auxiliary reagent C_X with a mixture of enantiomers.

Acylisocyanate Strategy

In earlier work related to the rapid determination of diastereoselection in aldol-type reactions, we had reported the general utility of trichloroacetyl isocyanate (TAI) as a derivatising agent (Figure 2) (Roos and Watson, 1991; Roos *et al*, 1992, 1994). The special attractions of TAI included: (a) since it was devoid of protons, it could be used in excess; (b) as an acylisocyanate, it was highly reactive toward even hindered alcohols and amines; (c) based on the relative shift of the diastereomeric carbamate *NH* chemical shifts, stereo-substructure assignments were possible.

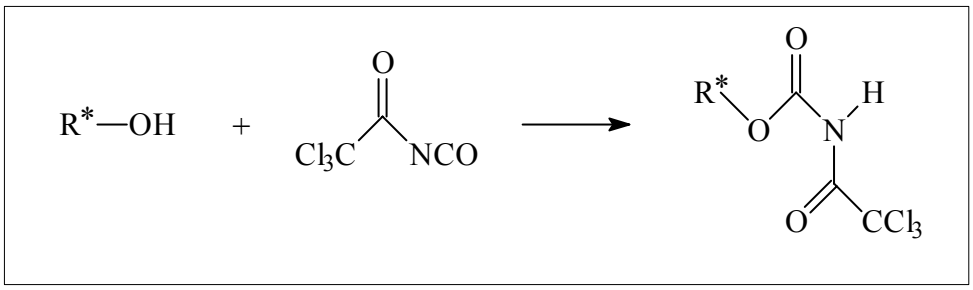
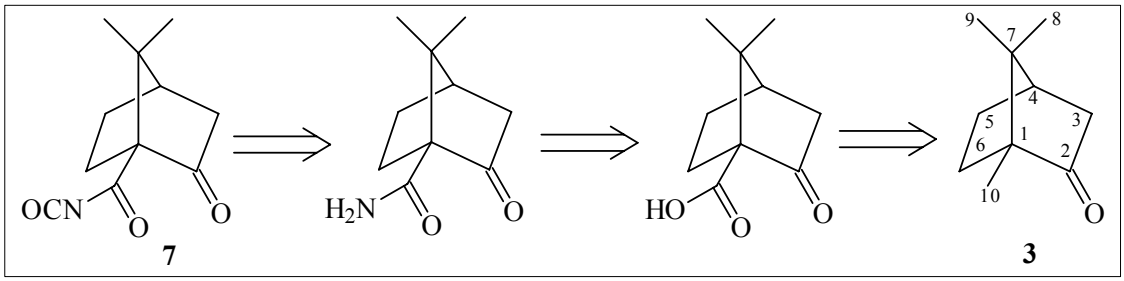


Figure 2. The reaction of alcohol diastereomers R*OH with trichloroacetyl isocyanate to give carbamates.

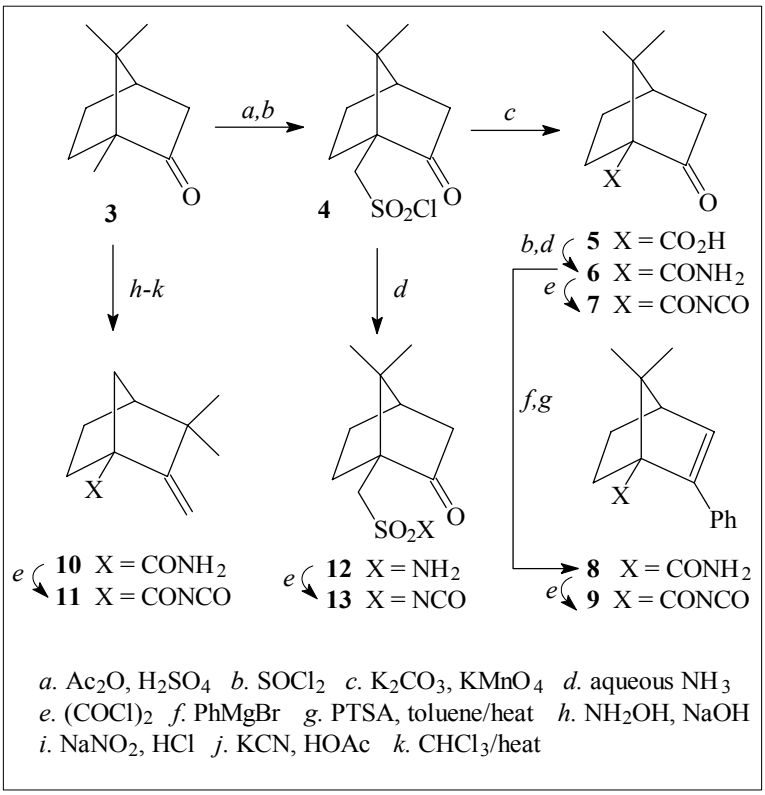
In order to adapt this approach to enantiomeric systems, the creation of a suitable homochiral acyl isocyanate was required. At that stage, no homochiral acylisocyanates at all had been reported in the literature. The closest recorded candidate was the isocyanate **2**, which was related to the *Mosher* system (Schneider *et al*, 1988). The use of **2** as a CDA was however limited by its low reactivity with hindered alcohols, a problem that we knew did not exist with the more reactive acylisocyanate system.

After an extensive literature survey, the naturally occurring (+)-camphor molecule **3** was chosen to provide the skeleton for a suitable acylisocyanate. This choice was based on several factors: (a) The stereogenic centres present are fixed, thus reducing any likelihood of loss of chirality during preparative interconversions; (b) The ^{1}H NMR signals of the camphor moiety would not interfere with the proposed carbamate *NH* shift region (δ 8-10), and other



Scheme 1. Retrosynthetic analysis of acyl isocyanate **7** back to (+)-camphor **3**.

resonances (*eg*. 2xCH_3) might provide additional useful diagnostic information; (c) (+)-Camphor is relatively inexpensive and the product and intermediates were likely to be crystalline solids; (d) (+)-Camphor has played a major role in natural product chemistry, and as such there were numerous documented interconversions (Money, 1985). With these factors in mind, we were able to target the simplest acylisocyanate as compound **7**. The synthetic lineage of **7** was readily envisaged to be as shown in Scheme 1.



Scheme 2. Synthetic routes to camphor-derived acyl isocyanates.

Materials and Methods

Because of the pure synthetic significance of these first reported homochiral acyl isocyanates, we have recently communicated the fundamental routes and formal characterisations of compound **7** and some related derivatives **9, 11, 13** (Donovan and Roos, 1996). The salient features of these preparations are summarised in Scheme 2. The preparation and characterisations details of other new compounds are described under the experimental section.

Acyl isocyanates were then allowed to react with racemic and/or scalemic alcohols to prepare the corresponding diastereomeric carbamates as outlined in Figure 3. The ^{1}H NMR spectra were then recorded and analysed primarily for carbamate NH resonance discrimination. All spectra were recorded using either a Bruker AM-300 or Advance DPX-300 spectrometer (^{1}H, 300 MHz; ^{13}C, 75.5 MHz) or a Bruker AMX-500 spectrometer (^{1}H, 500.13 MHz; ^{13}C, 125.76 MHz). Spectra were run in deuterochloroform ($CDCl_3$) with tetramethylsilane (TMS, δ 0.00) as internal standard at 30°C unless otherwise stated.

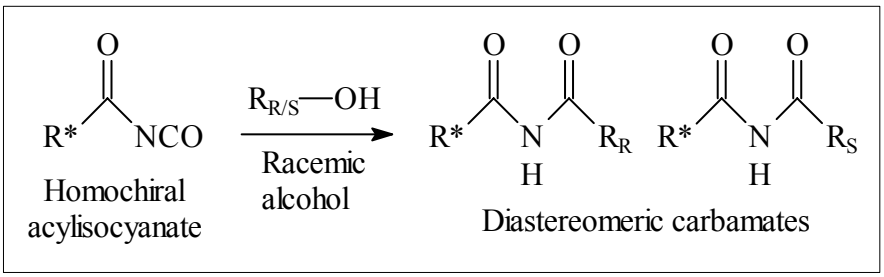
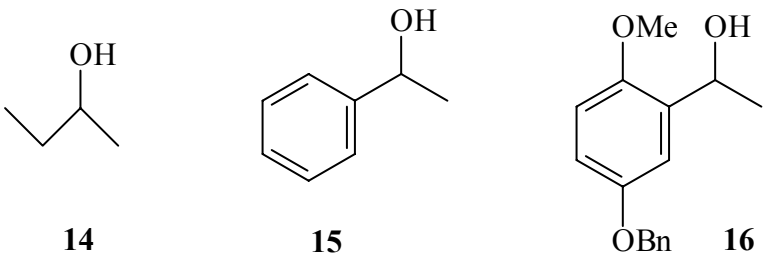


Figure 3. The formation of diastereomeric carbamates from racemic alcohols and homochiral acyl isocyanates.

Results and Discussions

ACTIVATED ISOCYANATE APPLICATION AND ANALYSIS: As per our original strategy, acyl isocyanate **7** was reacted with alcohols **14-16**. In the case of the diastereomeric carbamates derived from 2-butanol **14** (Donovan and Roos, 1996), the ^{1}H NMR spectrum showed that the two *NH* signals were coincident at δ 9.77 ppm. Evidence of the diastereomers was exhibited elsewhere in the spectrum with both the methyl triplet (δ 0.92 and 0.93 ppm) and the methyl doublet (δ 1.27 and 1.28 ppm) of the butyloxy adduct showing duplication. A similar unfortunate result was found with the l-phenylethanol **15** (Donovan and Roos, 1996).

The NH signals were coincident at δ 9.86, but again there was evidence of diastereomer formation in other parts of the spectrum. Ironically in this spectrum it was the *gem*-dimethyl of the camphor moiety (C8 δ 0.99 and 1.04 ppm and C9 δ 1.28 and 1.29 ppm) which exhibited doubling. Finally, reaction of 4-benzyloxy-2-(l-hydroxyethyl)-1-methoxybenzene **16** gave a pair of carbamates in which the two *NH* signals were not coincident and appeared as two distinct singlets at δ 8.94 and 8.95 ppm. However, unfortunately the resolution of these signals was not sufficient for ready determination of optical purity by integration.



14 **15** **16**

In any event, for the acyl isocyanate **7** to be a useful CDA, it would need to be generally effective. The increased steric bulk of alcohol **16** may be the cause of the two distinct NH peaks as opposed to the earlier examples of alcohols **14** and **15** where the peaks were coincident. It was also conceivable that in this type of system that there was strong hydrogen-bonding between the carbamidic *NH* and the carbonyl group of the camphor skeleton. This would result in the formation of a very reasonable 6-membered ring **17** (Figure 4). With the *NH* locked into a set conformation, the effect of the diastereomeric centres could be minimised and the chemical shifts of the *NH* signals very possibly equalised.

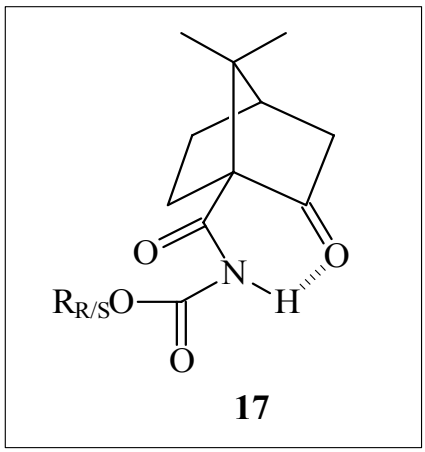


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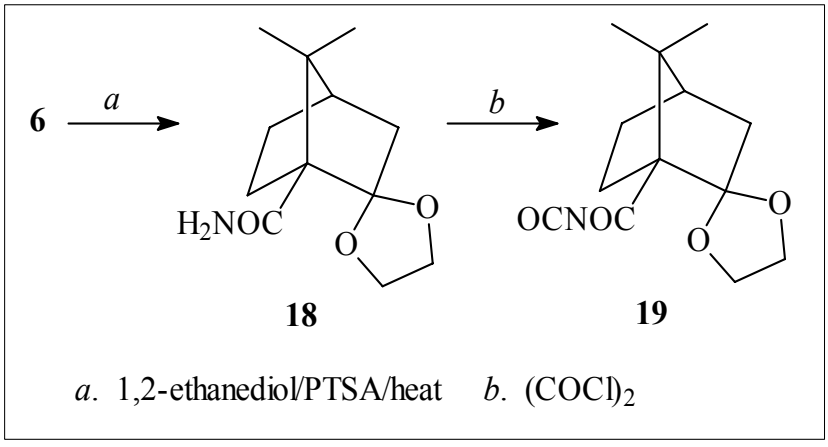
Figure 4. Intramolecular H-bonding in camphor-derived carbamate diastereomers.

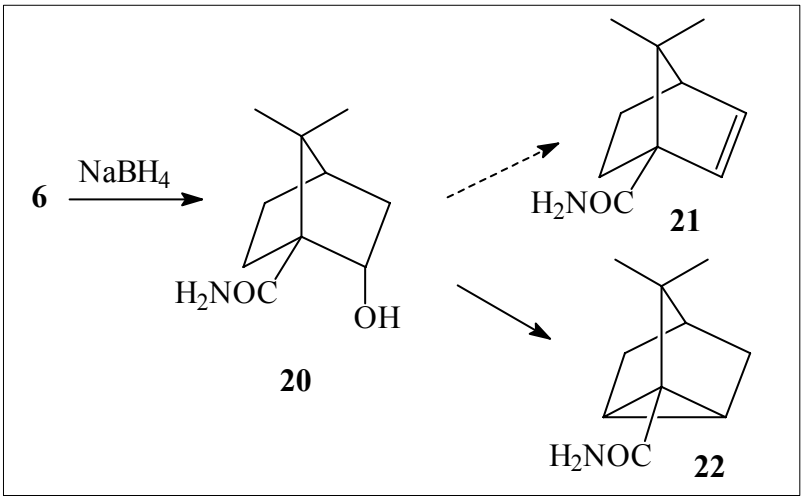
In order to eliminate the above possibility of hydrogen-bonding, it was decided to redesign the acyl isocyanate in a way that effectively removed the potentially problematic carbonyl group. The first option (Scheme 3) involved the ketalisation of the amide **6** to give **18**. Subsequent treatment with oxalyl chloride gave the acyl isocyanate **19** that exhibited the characteristic isocyanate peak at 2237 cm^{-1}. However, numerous repeat treatments of this with racemic 2-butanol **14** failed to yield any detectable carbamate products.



Scheme 3. Synthetic route to acyl isocyanate **19**.

The second strategy to obviate hydrogen-bonding involved the complete removal of the carbonyl oxygen *via* a chemoselective reduction/elimination protocol (Scheme 4). Unfortunately, whilst the reduction of amide **6** proceeded quantitatively to afford the alcohol **20**, all efforts to effect the elimination of water to give alkene **21** proved fruitless. Instead, the only product of note was the previously reported symmetrical tricyclic amide **22** (Connolly and Hill, 1991), which formed irrespective of whether base- or acid-catalysed conditions were employed.

One solution to the carbonyl dilemma was eventually provided by the synthesis of acyl isocyanate **9** in which the presence of an added phenyl group assisted with the final dehydration step. Analysis of the carbamates formed by reaction of **9** with alcohols **14** and **15** was undertaken. The diastereomeric carbamates from alcohol **14** were recovered and fully characterised (Donovan and Roos, 1996). The ^{1}H NMR spectrum of these compounds showed only a single NH peak. This peak, however, appeared at δ 6.86 ppm compared with δ 9.77 ppm for the corresponding diastereomers with acyl isocyanate **7**. This observation of dramatic upfield chemical shift somewhat reinforces the proposal that hydrogen-bonding was occurring in the earlier system. The absence of this intramolecular hydrogen-bonding did not, however, result in two distinct NH peaks as hoped. Once again, doubling was evident in other areas of the spectrum.



Scheme 4. Reductive elimination approach to unsaturated acyl isocyanate **21**.

The reaction between isocyanate **9** and 1-phenylethanol **15** did not proceed to any measurable extent, possibly due to steric hindrance between the two phenyl groups of the alcohol and the acyl isocyanate. The lack of differentiation between the two NH protons, coupled with the absence of reaction between **9** and the benzylic alcohol, led to the termination of this pursuit.

An alternative attractive solution to the carbonyl problem was presented by acyl isocyanate **11**, available via a camphor-fenchone skeletal rearrangement (Passerini, 1925; Kocienski and Kirkup, 1975). Reactions of **11** with both alcohols **14** (Donovan and Roos, 1996) and **15** were carried out and the diastereomeric mixtures analysed. Once again both cases gave carbamate *NH* signals which were coincident (δ 7.50 and 7.53 respectively).

Table 1: Low temperature NMR studies of carbamate **23**.

MHz	**300**			**500**		
SHIFT	**δ1**	**δ2**	**Δδ**	**δ1**	**δ2**	**Δδ**
303 ^{o}K	9.770		0	9.764	9.754	0.010
273 ^{o}K	9.883	9.868	0.015	9.848	9.331	0.017
253 ^{o}K	9.959	9.938	0.021	9.931	9.909	0.022
233 ^{o}K	10.036	10.009	0.027	-	-	-

A similar outcome was achieved with the sulfonyl isocyanate **13**, for which it was reasoned that the replacement of carbonyl by sulfonyl would not retard reactivity. As anticipated, reaction with 2-butanol **14** proceeded well, but unfortunately produced coincident *NH* resonances at δ 8.37. Again it is worthy of note that both activated isocyanates **11** and **13** afforded derivatives which exhibited diastereomer differentiation elsewhere in their NMR spectra.

Table 2: Low temperature NMR studies of carbamate **24**.

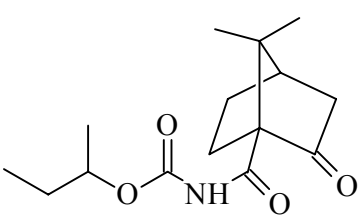
MHz	**300**			**500**		
SHIFT	**δ1**	**δ2**	**Δδ**	**δ1**	**δ2**	**Δδ**
303 °K	7.459		0	7.483		0
273 °K	7.520		0	7.555	7.548	0.007
253 °K	7.568	7.561	0.007	7.609	7.602	0.007
233 °K	7.605	7.598	0.007	7.649	7.643	0.006

To this point, the ^{1}H NMR spectra of all carbamates had been recorded at 300MHz at 30 °C and generally, with the single exception, there was no differentiation between the *NH* signals of the diastereomers present. It was decided to examine the NMR spectra of two of the carbamates, **23** and **24**, at lower temperatures to determine if the desired resolution could be achieved under these conditions. From the results of the low temperature analyses (Tables 1 and 2), it can be seen that by lowering the temperature at which the spectra of these two compounds are recorded, resolution of the low field *NH* signal is observed. The spectra recorded at 500 MHz exhibit this resolution at higher temperatures for both of the compounds, however, as the temperature is lowered further, the 300 MHz and 500 MHz instruments gave comparable results. Compound **23**, in spite of the likely presence of the hydrogen bonding between the *NH* proton and the carbonyl oxygen of the camphor ring system, exhibits the greater differential between the two signals. It was also necessary to verify that the resolution of the *NH* signals observed at low temperature was due to the different chemical shifts of the diastereomeric *NH* protons and not due to some conformational factor. For instance, rotation about either of the carbon nitrogen bonds present in the carbamate system may be prevented at low temperature, thus giving the appearance of two distinct singlets. A further experiment was carried out to clarify this situation. This involved the low temperature study of carbamate **25**, which was derived from the acyl isocyanate **7** and the achiral 2-propanol. The data presented in Table 3 showed no resolution of the NH signal when the NMR spectra are recorded at low temperature, indicating that the effect observed in Tables 1 and 2 is likely to be the result of diastereomer differentiation rather than due to rotational effects.

Table 3: Low temperature NMR studies of carbamate **25**.

MHz	**300**	
SHIFT	**δ1**	**Δδ**
300 °K	9.73	0
273 °K	9.84	0
253 °K	9.93	0

ALTERNATIVE STRATEGIES: It had always been possible that the distance (2 bonds) between the carbamate *NH* and the nearest CDA-derived stereogenic centre might be a factor in determining the degree of diastereomeric resonance discrimination. Reduction of this distance to the 1-bond minimum was clearly impossible to achieve with acyl- or sulfonyl isocyanates – since the acyl or sulfonyl function acted as a natural spacer. Two alternative strategies could readily be envisaged to overcome this.



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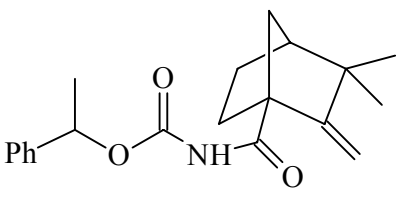

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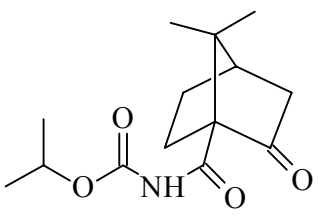

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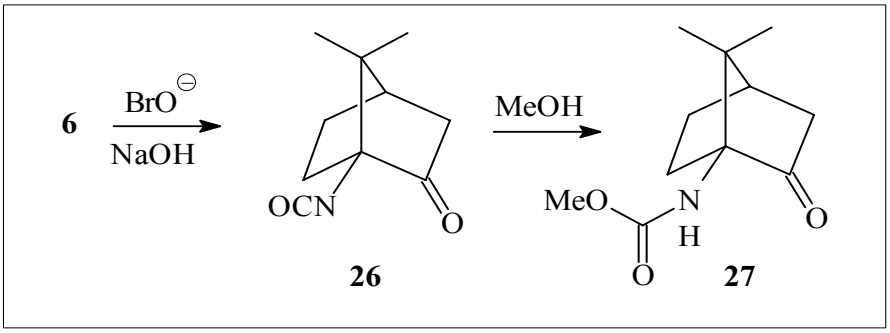
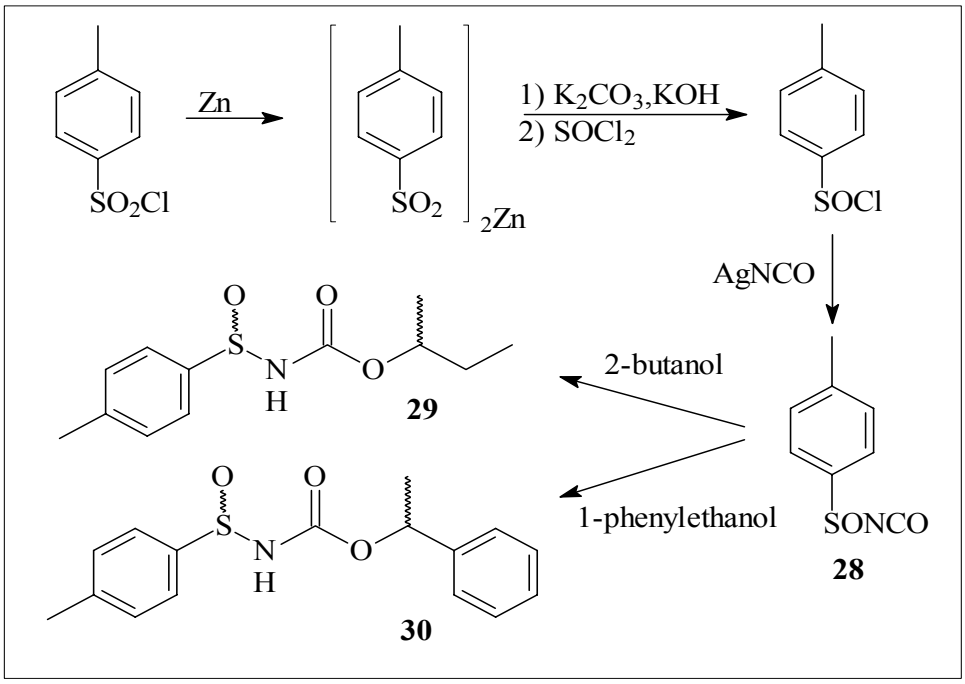
The first of these involved the use of an unactivated isocyanate such as **26**. As mentioned earlier, the related system **2** had displayed a poor reactivity profile. However, in order to exclude the possibility that **26** might prove to be a successful CDA, it was prepared and tested in reaction with methanol (Scheme 5). Removal of methanol *in vacuo* and subsequent chromatography revealed only a trace of material that was characterised by mass spectroscopy as the targeted urethane. Because of the very low yield, even under the extreme conditions of boiling the isocyanate in methanol, it was apparent that the unactivated isocyanate would not be reactive enough for the purposes of reagent development. This line of approach was thus not taken any further.



Scheme 5. Synthetic route to isocyanate **26**.

The second approach was prompted by the ease with which the sulfonyl isocyanate **13** had been prepared. Alternative use of sulfinyl instead of sulfonyl would allow the isocyanate moiety to be part of a stereogenic centre. In addition, the sulfinyl group was envisaged to maintain the isocyanate reactivity profile with alcohols and amines. In order to test this approach, a racemic model was chosen since: (a) this was more readily synthesised; (b) diastereomer differentiation, if present, would still be evident. To this end, 4-toluenesulfinylisocyanate **28** was prepared from commercial toluenesulfonyl chloride *via* reported methods (Scheme 6) (Whitmore and Hamilton, 1941; Kurzer, 1963; Jähnchen and Westphal, 1969).



Scheme 6. Preparation and reaction of 4-toluenesulfinyl isocyanate **28**.

The sulfinyl isocyanate **28** was reacted with both 2-butanol **14** and 1-phenylethanol **15** added to the other (Scheme 6). The two diastereomeric sulfinyl carbamate mixtures were isolated as semisolids *via* column chromatography. The 2-butanol derivative **29** exhibited two signals in the ^{1}H NMR spectrum at δ 7.68 and 7.79, corresponding to the two *NH* protons. An analogous situation was observed for the 1-phenylethanol derivative **30**, with the two *NH* signals occurring at δ 8.35 and 8.40 in the ^{1}H NMR spectrum. Low temperature NMR were again recorded in order to try for further resolution of the *NH* signal pairs (Table 4). From Table 4 it can be seen that the greatest difference in chemical shift for **29** occurs at 303 ^{o}K. An analysis of the spectra, however, reveals that the signals in question become much sharper at the lower temperatures and hence, more amenable to integration. For **30** the data in Table 4 shows that there was marginally greater resolution at lower temperatures, with baseline resolution achieved by 283 ^{o}K. This is possibly due to the more bulky phenyl substituent present in compound **30**. The sulfinyl isocyanate thus exhibited both the required reactivity as well as independent signal resolution (up to a factor of 10 greater than for acyl isocyanates) for the two *NH* protons.

Table 4: Low temperature NMR studies of urethanes **29** and **30**.

SHIFT	δ1	δ2	Δδ
Urethane 29			
263 ^{o}K	8.229	8.196	0.033
273 ^{o}K	8.088	8.057	0.031
282 ^{o}K	7.981	7.952	0.029
303 ^{o}K	7.790	7.680	0.110
Urethane 30			
273 ^{o}K	8.845	8.794	0.051
283 ^{o}K	8.694	8.645	0.049
303 ^{o}K	8.400	8.358	0.042

Conclusion

The study has explored the potential of several novel homochiral activated isocyanates **7, 9, 11, 13** as *in situ* CDA's for diagnostic NMR probes to determine enantiomeric composition. Although none of the examples studied showed themselves as generally applicable reagents at ambient temperature, the results are encouraging enough (especially at reduced temperatures) to warrant further investigation. The work has also led to the observation that sulfinyl isocyanates might prove to be overall better candidates for future development. However, in order to pursue this line further, a suitably flexible synthetic route to homochiral sulfinyl isocyanate will need to be found.

Experimental

GENERAL: Mass spectra were recorded on a Perkin Elmer ITD Ion Trap Detector spectrometer in the electron impact mode at an emission current of 55μA and an electron multiplier voltage of 2000 V. Elemental analyses were carried out by either the Australian National University Analytical Service Unit or by the Canadian Microanalytical Service Ltd. Infrared (IR) spectra were recorded as KBr discs for solids and, as indicated in the text, as thin films between KBr plates for oils, using a Perkin Elmer 1720-X Fourier Transform Spectrometer. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. Optical rotations were recorded at 20 ^{o}C using a Optical Activity PolAAr 2001 polarimeter. Column chromatography refers to columns prepared as slurries of Merck silica gel 60 (70-230 mesh) in the eluent. Pre-adsorption was carried out on Merck silica gel 60 (35-70 mesh). Radial chromatography was performed using Merck silica gel 60 PF_{254}, while thin layer chromatography was carried out on aluminium plates coated with Merck Kieselgel 60 F_{254}. Light petroleum refers to the fraction of boiling point 65-70^{o}C, ether to diethyl ether and bicarbonate solution to

saturated aqueous sodium hydrogen carbonate solution. All solvents were purified by distillation and, if necessary, were dried according to standard methods. The amount of residual water present in the solvents was determined using a Metrohm Karl Fischer Coulometer 684.

1′-(2-Methoxy-5-benzyloxyphenyl)ethyl(1S)-[(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-yl)carbonyl]carbamate from reaction of **7** and **16.**

The amide **6** (150 mg, 0.83 mmol) was dissolved in dry dichloroethane and stirred under an inert nitrogen atmosphere. Oxalyl chloride (3 mol equiv) was added *via* syringe and the reaction mixture heated under reflux overnight. Excess oxalyl chloride was removed *via* azeotropic distillation with dichloroethane and the reactive acyl isocyanate **7** characterised by IR (KBr plate) ν_{NCO} 2244 cm^{-1} The acyl isocyanate was treated with 4-benzyloxy-2-(1-hydroxyethyl)-1-methoxybenzene **16** (216 mg, 0.83 mmol) and heated at reflux temperature overnight to yield the carbamates (231 mg, 60%) as white prisms, mp. 105.5-106.5 ^{o}C. IR ν_{max} 3418 (NH), 3274 (CH Ar), 2929 (CH), 1783, 1715 and 1640 (C=O) and 1590 and 1501 (C=C Ar) cm^{-1}. ^{1}H NMR δ 1.01 (3H, s, C8) one diastereomer, 1.04 (3H, s, C8) other diastereomer, 1.28 (3H, s, C9) one diastereomer, 1.29 (3H, s, C9) other diastereomer, 1.44-1.50 (2H, m, C6 *endo*), 1.53 (6H, d, *J* 6.6 Hz, CH_3), 1.64-1.74 (2H, m, C5 *endo*), 2.03 (2H, d, *J* 18.9 Hz, C3 *endo*), 2.11 (2H, dd, *J* 4.3 and 4.3 Hz, C4), 2.17-2.23 (2H, m, C6 *exo*), 2.45-2.61 (4H, m, C3 *exo* and C5 *exo*), 3.79 (3H, s, OCH_3) one diastereomer, 3.80 (3H, s, OCH_3) other diastereomer, 5.02 (2H, s, CH_2Ph) one diastereomer, 5.03 (2H, s, CH_2Ph) other diastereomer, 6.25 (2H, q, *J* 6.5 Hz, CH), 6.80 (1H, d, *J* 8.9 Hz, C′6) one diastereomer, 6.80 (1H, d, *J* 8.9 Hz, C′6) other diastereomer, 6.84 (1H, dd, *J* 8.9 and 2.9 Hz, C′4) one diastereomer, 6.85 (1H, dd, *J* 8.9 and 2.9 Hz, C′4) other diastereomer, 7.09 (1H, d, *J* 2.9 Hz, C′3) one diastereomer, 7.10 (1H, d, *J* 2.9 Hz, C′3) other diastereomer, 7.31-7.46 (10H, m, Ph), 9.84 (1H, s, NH) one diastereomer and 9.85 (1H, s, NH) other diastereomer. ^{13}C NMR δ 20.3 (C8), 20.7 and 20.8 (C9) , 21.2 ($CH\underline{C}H_3$), 27.7 (C6), 29.2 and 29.3 (C5), 43.3 and 43.3 (C4), 43.6 (C3), 50.7 and 50.7 (C7), 56.2 (OCH_3), 65.4 (C1), 69.0 ($\underline{C}HCH_3$), 70.6 ($\underline{C}H_2Ph$), 111.8, 113.5 and 114.0 (C′3, 4 and 6), 127.6, 127.9 and 128.5 (C′′2-6), 130.9 and 137.2 (C′1 and C′′1), 149.7 (C10), 150.4 and 150.4 (C′2 and 5), 167.7 (C10) and 216.4 (C2). $C_{27}H_{31}NO_6$ (465.22) Calc. C 69.7, H 6.7, N 3.0 Found C 69.9, H 6.4, N 3.0%

(+)-(1S)-7,7-Dimethyl-2-oxobicyclo[2.2.1]heptane-1-carboxamide ethylene ketal **18.**

Amide **6** (500 mg, 2.76 mmol), 1,2-ethanediol (0.406 ml, 8.24 mmol), and p-TSA (150 mg, 0.867 mmol) were added to benzene (30 ml). A Dean-Stark water trap was fitted and the mixture heated at reflux temperature for 48 h. Saturated ammonium bicarbonate solution (30 ml) was added and the product extracted with ethyl acetate (3x15 ml), dried over magnesium sulfate and reduced *in vacuo.* Column chromatography of the crude product with 25% ethyl acetate-light petroleum as the eluent yielded the starting material (170 mg, 34%) and the product **18** (327 mg, 53%) as off-white plates, mp. 122.5-124 ^{o}C. $[\alpha]_D$ 38.5 (c 0.6, $CHCl_3$). IR ν_{max} 3408 (NH), 2950 (CH) and 1668 (C=O) cm^{-1}. ^{1}H NMR δ 1.07 (3H, s, C8), 1.22-1.30 (1H, m, C6 *endo*), 1.28 (3H, s, C9), 1.51 (1H, d, *J* 13.2 Hz, C3 *endo*), 1.78 (1H, dd, *J* 4.7 and 4.5 Hz, C4), 1.78-1.88 (1H, m, C6 *exo*), 2.07-2.27 (3H, m, C3 *exo*, C5 *exo* and C5 *endo*), 3.79-4.03 (4H, m, OCH_2CH_2O), 5.84 (1H, s, NH) and 6.45 (1H, s, NH). ^{13}C NMR δ 21.0 (C8), 21.1 (C9), 26.5 (C6), 26.9 (C5), 45.2 (C4), 45.8 (C3), 50.2 (C7), 61.0 (C1), 63.4 and 64.7 (OCH_2CH_2O), 116.7 (C2) and 174.3 (C10). m/z 226(M^+, 16%), 181(15), 139(99), 113(55) and 99(100). $C_{12}H_{19}NO_3$ (225.14) Calc. C 64.0, H 8.5, N 6.2 Found. C 64.0, H 8.1, N 6.2 %

(-)-(1S)-7,7-Dimethyl-2-hydroxybicyclo[2.2.1]heptane-1-carboxamide **20.**

Sodium borohydride (183 mg, 4.84 mmol) was suspended in 90% ethanol-water (30 ml). Amide **6** (500 mg, 2.76 mmol) in ethanol (5 ml) was added dropwise and the reaction mixture stirred for 18 h at room temperature. HCl (2 ml, 1M) was added and the whole reduced *in vacuo* before extraction with ether. The ethereal layer was washed with water, brine, dried over magnesium sulfate and reduced *in vacuo* to yield the crude product **20**

(476 mg, 94%) which was recrystallised from ether-light petroleum as white needles, mp. 239-241 ^{o}C. $[\alpha]_D$ -11.0 (c 0.3, $CHCl_3$). IR ν_{max} 3397 (NH), 3184 (OH), 2959 (CH) and 1663 (C=O) cm^{-1}. ^{1}H NMR δ 1.05 (3H, s, C8), 1.05-1.15 (1H, m, C6 *endo*), 1.21-1.32 (1H, m, C5 *endo*), 1.25 (3H, s, C9), 1.76-1.96 (4H, m, C3 *endo*, C3 *exo*, C4 and C6 *exo*), 2.08-2.18 (1H, m, C5 *exo*), 3.66 (1H, s, OH), 4.05 (1H dd, *J* 7.6 and 3.5 Hz, C2), 6.12 (1H, s, NH) and 6.67 (1H, s, NH). ^{13}C NMR δ 20.7 (C8), 21.6 (C9), 27.2 (C6), 30.4 (C5), 45.7 (C4), 41.1 (C3), 49.6 (C7), 57.5 (C1), 77.4 (C2) and 177.2 (C10). m/z 184 (M^++1, 100%), 140(89), 122(28), 95(28), 81(73) and 67(43). $C_{10}H_{15}NO_2$ (183.13) Calc. C 65.5, H 9.3, N 7.6 Found C 65.0, H 9.2, N 7.5%

***7,7-Dimethyltricyclo[2.2.1.0^{2,6}]heptane-1-carboxamide* 22.**

Base elimination.

Compound **20** (150 mg, 0.819 mmol) and triethylamine (0.199 ml, 1.44 mmol) were added to THF (10 ml) at 0 ^{o}C; followed by dimethylaminopyridine (17.5 mg, 0.144 mmol) and methanesulfonyl chloride (0.068 ml, 0.862 mmol). The reaction was stirred for 3 h under an atmosphere of nitrogen and then filtered to remove any solids, washed with cold THF and then diluted to 30 ml. Potassium *t*-butoxide (320 mg, 2.87 mmol) was added and the reaction stirred at 0^{o}C for 40 minutes. The mixture was then poured into aqueous citric acid (100 ml, 5%) and extracted into dichloromethane (20 ml). The organic layer was washed with water, bicarbonate solution, brine, dried over magnesium sulfate and reduced *in vacuo* to yield 125 mg of yellow oil. This was purified by column chromatography with 50% ethyl acetate-light petroleum as the eluent to afford the product **22** (114 mg, 84%) as off-white plates, mp. 115-116.5 ^{o}C, lit. (Connolly and Hill, 1991) 117-118 ^{o}C. $[\alpha]_D$ 0 (c 0.5, $CHCl_3$). IR ν_{max} 3471 (NH), 2966 (CH) and 1658 (C=O). ^{1}H NMR δ 1.07 (6H, s, C8 and C9), 1.16 (2H, dd, *J* 10.6 and 1.1 Hz, C3 *endo* and C5 *endo*), 1.49 (1H, dd, *J* 1.4 and 1.4 Hz, C4), 1.76 (2H, dd, *J* 1.1 and 1.1 Hz, C2 and C6), 1.75-1.81 (2H, m, C3 *exo* and C5 *exo*) and 5.70 (2H, s, NH). ^{13}C NMR δ 22.0 (C8 and C9), 24.9 (C2 and C6), 31.17 (C3 and C5), 42.1 (C7), 43.7 (C4), 76.6 (C1) and 175.8 (C10). m/z 166(M^++1, 100%), 165(21), 149(13), 124(54), 105(23), 91(14) and 79(11).

Acid elimination

To a solution of alcohol **20** (400 mg, 0.218 mmol) in dichloroethane (10 ml) was added concentrated sulfuric acid (938 mg, 0.957 mmol). The reaction mixture was stirred for 20 minutes at room temperature, made basic with bicarbonate solution (50 ml) and extracted into dichloromethane. The organic portion was washed with water and brine, dried over magnesium sulfate and reduced *in vacuo*. Column chromatography with 50% ethyl acetate-light petroleum as the eluent afforded the starting material 56 mg (14%) and the product **22** (91 mg, 40%). All spectral and physical data for the product obtained from this synthesis were identical to those recorded for the compound **22** recovered from the base induced elimination above.

***1'-Phenylethyl(1S)-[(3,3-dimethyl-2-methylenebicyclo[2.2.1]hept-1-yl)carbonyl]carbamate* 24.**

The amide **10** (250 mg, 1.39 mmol) was dissolved in dry dichloroethane and stirred under an inert nitrogen atmosphere. Oxalyl chloride (3 mol equiv) was added *via* syringe and the reaction mixture heated under reflux overnight. Excess oxalyl chloride was removed *via* azeotropic distillation with dichloroethane and the reactive acyl isocyanate **11** characterised by IR (KBr plate) ν_{NCO} 2239 cm^{-1} Treatment of **11** with 1-phenylethanol (1 ml) and overnight reflux gave the starting material (84 mg, 34%) and the product **24** as an oil (262 mg, 58%) which was crystallised from light petroleum as an amorphous white solid, mp. 98-100 ^{o}C. IR ν_{max} 3450 (NH), 3199 (CH Ar), 3068 (C=CH_2), 2982 (CH), 1749 and 1700 (C=O) and 1581 and 1511 (C=C Ar). ^{1}H NMR δ 1.11 (3H, s, C8)[a] one diastereomer, 1.11 (3H, s, C9)[a] one diastereomer, 1.12 (6H, s, C8 and C9) other diastereomer, 1.47-1.54 (2H, m, C6 *endo*), 1.55-1.61 (2H, m, C7a), 1.62 (6H, d, *J* 6.6 Hz, CHC$\underline{H}_3$), 1.63-1.67 (2H, m, C5 *endo*), 1.76-1.83 (2H, m, C5 *exo*), 1.96-2.01 (2H, m, C6 *exo*), 2.02-2.04 (2H, m, C4), 2.15 (2H, dddd, *J* 12.0, 4.0, 1.9 and 1.9 Hz, C7b), 4.77 (1H, s,

CH_2) one diastereomer, 4.78 (1H, s, CH_2) other diastereomer, 4.87 (1H, s, CH_2) one diastereomer, 4.89 (1H, s, CH_2) other diastereomer, 5.93 (2H, q, *J* 6.4 Hz, C<u>H</u>CH_3), 7.29-7.42 (10H, m, Ph) and 7.53 (2H, s, NH). ^{13}C NMR δ 21.9 and 21.9 (CH_2<u>C</u>H_3), 24.2 and 24.3 (C5), 25.9 (C9), 29.5 (C8), 30.7 and 30.8 (C6), 41.6 and 41.7 (C7), 43.1 (C3), 47.8 and 47.8 (C4), 62.0 (C1), 74.5 (O<u>C</u>HCH_3), 102.2 and 102.3 (C=<u>C</u>H_2), 126.3 and 126.3 (C′3 and 5), 128.2 (C′4), 128.6 (C′2 and 6), 140.6 (C′1), 150.1 (C=O), 163.1 and 163.2 (C2) and 170.9 (C10). $C_{20}H_{25}NO_3$ (327.42) Calc. C 73.3, H 7.7, N 4.3 Found C 72.7, H 7.6, N 4.2%

***(1S)-1-Isocyanato-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-2-one-* 26.**

Hypobromite, generated *in situ,* by the addition of molecular bromine (380 mg, 2.4 mmol, 2 me) to an aqueous solution of sodium hydroxide (2.5 ml, 6.24 M) was added to amide **6** (217 mg, 1.2 mmol) in dichloromethane (2.5 ml). Tetrapropylammonium bromide (16 mg, 0.06 mmol) was added and the reaction mixture stirred vigorously for 12 min at room temperature. After this time more water (20 ml) and dichloromethane (20 ml) were added and the organic layer separated. The aqueous layer was extracted with dichloromethane and the two organic fractions combined, dried over magnesium sulfate and reduced *in vacuo.* IR (KBr plate) ν_{NCO} 2245.

***Methyl (1S)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptyl-1-carbamate* 27.**

Methanol (15 ml) was added to the crude isocyanate **26** (1.2 mmol) and heated at reflux temperature overnight. Subsequent removal of the methanol and purification by radial chromatography with 10% ethyl acetate-light petroleum as the eluent afforded an oil (7 mg), which consisted of two components (GCMS) in approximately equal amounts. One component was unidentified, the other tentatively assigned as the product **27** on the basis of the mass spectrum. m/z 211(M^+, 3%), 210(39), 169(29), 135(77), 107(83), 91(42), 79(58) and 76(100).

***2′-Butyl-p-toluenesulfinylcarbamate* 29.**

To the sulfinyl isocyanate **28** (5.70 mmol) was added a large excess of 2-butanol (1 ml) and the whole stirred overnight at room temperature. The reaction mixture was filtered and reduced *in vacuo* before chromatography on silica gel with 10-20% ethyl acetate-light petroleum as the gradient eluent yielded the product **29** as a yellow oil (303 mg, 1.18 mmol, 20.8%). IR (KBr plate) ν_{max} 3439 (NH), 3113 (CH Ar), 2872 (CH), 1726 (C=O) 1603 and 1500 (C=C Ar), 1219 (SO), 1095 (ArS) and 853 (SN). ^{1}H NMR δ 0.91 (6H, t, *J* 7.2 Hz, CH_2C<u>H</u>$_3$), 1.25 (3H, d, *J* 6.3 Hz, CHC<u>H</u>$_3$) one diastereomer, 1.26 (3H, d, *J* 6.3 Hz, CHC<u>H</u>$_3$) other diastereomer, 1.50-1.72 (4H, m, CH_2), 2.41 (6H, s, PhCH_3), 4.83 (1H, tq, *J* 6.3 and 6.3 Hz, OCH) one diastereomer, 4.84 (1H, tq, *J* 6.3 and 6.3 Hz, OCH) other diastereomer, 7.31 (4H, d, *J* 8.1 Hz, C3 and 5), 7.56 (4H, d, *J* 8.1 Hz, C2 and 6), 7.68 (1H, s, NH) one diastereomer and 7.79 (1H, s, NH) other diastereomer. ^{13}C NMR δ 9.5 and 9.6 (CH_2<u>C</u>H_3), 19.4 and 19.4 (CH<u>C</u>H_3), 21.4 (PhCH_3), 28.8 (<u>C</u>$H_2$$CH_3$), 75.7 (OCH), 124.8 (C3 and 5), 129.9 (C2 and 6), 140.5 (C4), 142.4 (C1) and 153.8 (C=O).

***1′-Phenylethyl-p-toluenesulfinylcarbamate* 30.**

To the sulfinyl isocyanate **28** (5.70 mmol) was added 1-phenylethanol (0.69 g, 5.70 mmol). The reaction mixture was stirred overnight at room temperature under an atmosphere of nitrogen before filtration, reduction *in vacuo* and chromatography on silica gel using 10-20% ethyl acetate-light petroleum as the gradient eluent yielded the product **30** (0.685 g, 2.25 mmol, 39.5%) as a pale yellow oil. IR (KBr plate) ν_{max} 3434 (NH), 3059 (CH Ar), 2852 (CH), 1732 (C=O) 1645 and 1552 (C=C Ar), 1221 (SO), 1062 (ArS) and 812 (SN). ^{1}H NMR δ 1.52 (3H, d, *J* 6.6 Hz, CHC<u>H</u>$_3$) one diastereomer, 1.53 (3H, d, *J* 6.6 Hz, CHC<u>H</u>$_3$) other diastereomer, 2.33 (6H, s, PhCH_3), 5.84 (1H, t, *J* 6.6 Hz, OCH) one diastereomer, 5.85 (1H, t, *J* 6.6 Hz, OCH) other diastereomer, 7.18-7.33 (14H, m, C3, C5 and C′2-5), 7.50 (2H, d, *J* 8.2 7 Hz, C2 and 6) one diastereomer, 7.52 (2H, d, *J* 8.2 7 Hz, C2 and 6) other diastereomer, 8.35 (1H, s, NH) one diastereomer and 8.40 (1H, s, NH) other diastereomer. ^{13}C NMR δ 21.3 (PhCH_3), 22.2 (CH<u>C</u>H_3), 75.1 (OCH), 124.8 (C3 and

5), 126.0 (C′3 and 5), 127.0 (C′4), 128.5 and 128.5 (C′2 and 6), 129.7 (C2 and 6), 140.2 and 140.2 (C′1), 140.8 and 140.9 (C4), 142.1 and 142.1 (C1) and 153.4 and 153.5 (C=O).

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