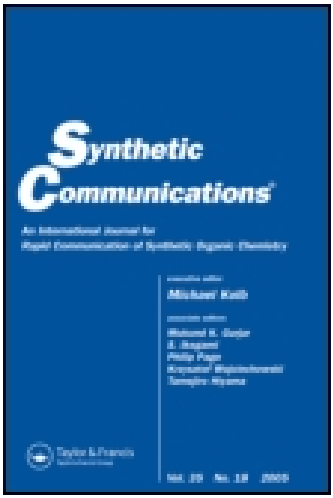

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Homochiral Activated Isocyanates as Chiral Derivatizing Agents

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HOMOCHIRAL ACTIVATED ISOCYANATES AS CHIRAL DERIVATIZING AGENTS

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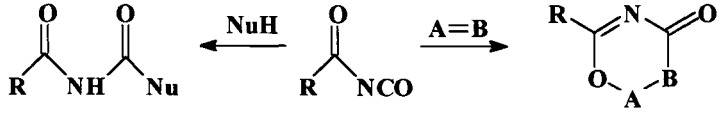
Abstract: The preparation of several homochiral camphor-based isocyanates, activated by either an α-acyl or sulfonyl group, is described. These reactive species present themselves as chiral derivatizing agents (CDA's) with promise.

In connection with an ongoing programme to develop novel CDA's for specific applications, we required access to a range of homochiral α-activated isocyanates. α-Acyl[1] and sulfonyl[2] isocyanates have long been established in the literature as reactive substrates which participate in, amongst others, a variety of nucleophilic additions and dipolar cycloadditions[3] (**Equ.1**). To the best of our knowledge, no analogous homochiral activated isocyanates have been reported.



Equ 1

The most practical route to the activated isocyanates appeared to be treatment of the corresponding amide with oxalyl chloride.[4] The absence of a α-hydrogen in

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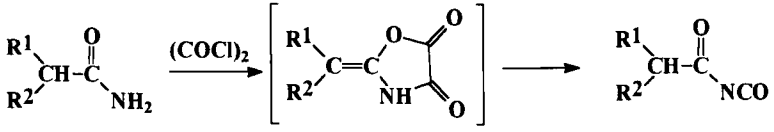
the carboxamide cases became an important consideration in order to avoid any racemisation which might occur via an oxazolidindione intermediate[5] **(Equ. 2)**.

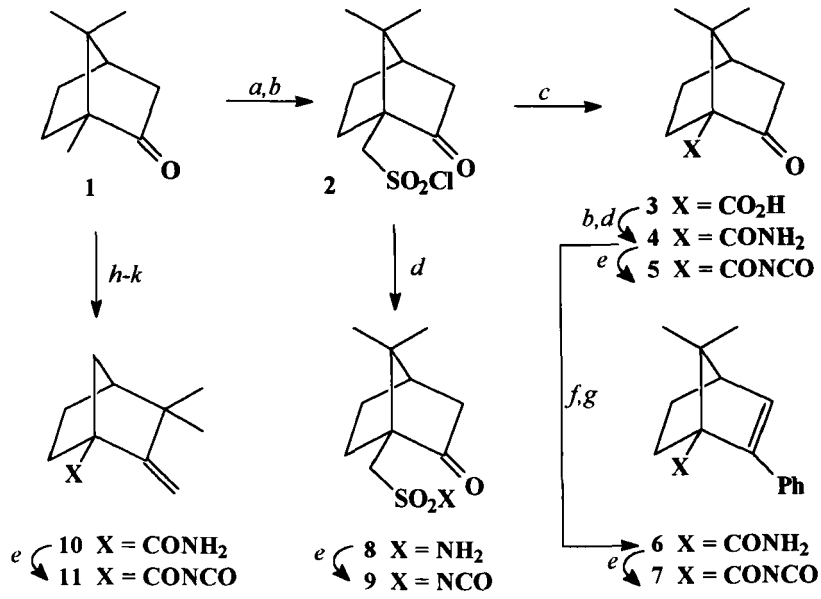


Equ 2

To meet with our requirements of reasonable accessibility, suitable steric demand, and a quaternary chiral centre amenable to manipulation at an adjacent site, we chose the camphor skeleton as the basic chiral adjunct. This skeleton has proven its utility as a CDA in a wide variety of reported applications.[6]

The **SCHEME** below provides a summary of the activated homochiral isocyanates prepared in this fashion. This selection was chosen to allow for the required variations in both structural features as well as isocyanate activation to be met. Thus, (+)-ketopinic acid **3**, prepared from natural (+)-camphor **1** by standard methods,[7] was converted to the carboxamide **4**.[8] This then served as a suitable precursor for the preparation of acyl isocyanates **5** and **7**. By way of alternative isocyanate activation, as well as alteration of the spatial array with respect to the camphor alicyclic, the analogous sulfonyl isocyanate **9** was prepared from the corresponding known sulfonamide **8**.[9] To complete our current programme needs, variation of the adjacent ring ketone as well as the disposition of the *gem*-dimethyl steric environment was sought. The amide **10**, readily available via the documented rearrangement of camphor[10], presented itself as a suitable candidate. This provided the corresponding acyl isocyanate **11**, which is both devoid of the cyclic ketone functionality as well as possessing altered steric requirements at the site of interest.

SCHEME



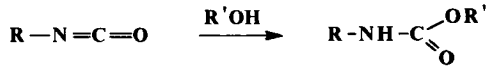
a. Ac_2O, H_2SO_4 *b*. $SOCl_2$ *c*. K_2CO_3, $KMnO_4$ *d*. Aqueous NH_3

e. $(COCl)_2$ *f*. PhMgBr *g*. PTSA, toluene/Δ *h*. NH_2OH, NaOH

i. $NaNO_2$, HCl *j*. KCN, HOAc *k*. $CHCl_3/\Delta$.

In preliminary investigations, the activated homochiral isocyanates **5**, **7**, **9**, and **11** all show high reactivity toward R-XH nucleophiles (X = O, N), as well as generally displaying the desired feature of derivatives with high crystallinity.[11] In fact, due to their high reactivity, the corresponding alcohol addition products were selected as convenient stable derivatives. These, along with the prominent IR stretch for the isocyanate group, allowed for full unambiguous structural characterisations (**Equ. 3** and **TABLE** below). In those cases where a chiral alcohol was employed (carbamates products **13-17**), ^{1}H NMR analysis in particular

has begun to show encouraging trends for their potential use as a probe of enantiomeric composition. These indicators, along with the anticipated ease of hydrolytic removal of the chiral adjunct, makes these isocyanates good potential candidates as practical CDA's. We have recently reported on the utility of trichloroacetyl isocyanate as a convenient NMR diagnostic probe for the determination of diastereomeric ratios as well as the stereosubstructures of diastereomeric alcohols.[12] Our current studies are directed at the potential applications of these novel activated isocyanates in terms of their scope for both diagnostic derivatisation and synthetic purposes (*eg*: resolution).



Equ. 3

TABLE: Reaction of Isocyanates with Alcohols (Equ. 3)

Isocyanate	R'	Product
5	Et	12
5	*sec*-Bu	13
5	Ph(Me)CH	14
7	*sec*-Bu	15
9	*sec*-Bu	16
11	*sec*-Bu	17

Experimental

General. Melting points were obtained using a Reichert melting point apparatus and are uncorrected. Chromatography (TLC, column, and radial chromatotron) was conducted on the appropriate Merck Kieselgel. IR spectra were recorded on a Perkin-Elmer 1720-X FT spectrometer. NMR spectra were recorded on either a Bruker DPX 300 (^{1}H at 300 MHz and ^{13}C at 75.5 MHz) or ARX 500 (^{1}H at 500

MHz and ^{13}C 125.77 MHz) spectrometers in $CDCl_3$ unless otherwise indicated. In the case of diastereomeric mixtures of carbamates **13-17**, separate ^{1}H and ^{13}C signals are reported where appropriate and the integral count adjusted accordingly. (+)-Ketopinic acid **3**[7] [*mp* 227-230°C (lit[7] 226-228); $[\alpha]_D$ 26.4° (c 0.65 in MeOH)] and (+)-camphorsulfonamide **8**[9] [*mp* (ex $CHCl_3$) 131.5-133°C (lit[9] 132°C) $[\alpha]_D$ 22.0° (c 1.0 in MeOH)] were prepared from (+)-camphor by the published procedures.

Ketopinamide (4). Ketopinic acid **3** (1.00 g, 5.49 mmol) was heated at 65° with an excess of thionyl chloride (3.2 ml) under an atmosphere of dry nitrogen for 3 hours. The majority of thionyl chloride was removed *in vacuo*, and then CCl_4 (2 x 10 ml aliquots) was used to remove the last traces by azeotropic distillation. The crude acid chloride was dissolved in CH_2Cl_2 (10 ml) and added dropwise to 20 ml of aqueous ammonia solution (28%). After stirring at room temperature for 4 hours, further CH_2Cl_2 (10 ml) was added, the organic layer separated, washed with water, brine, dried over $MgSO_4$, and reduced *in vacuo* to afford the amide **4** (0.87 g, 87%). This crude product was recrystallised from ether-light petroleum as white spears, *mp*. 192-195°C, (lit.[8] 100°C); $[\alpha]_D$ 116.4° (c 0.75, $CHCl_3$), (lit[8] 101 °); ν_{max} (KBr) 3447, 2970, 1736, 1671; *^{1}H NMR* 0.98 (s, 3H), 1.22 (s, 3H), 1.41 (ddd, *J* 12.6, 9.2 and 3.9 Hz, 1H), 1.61 (ddd, *J* 13.8, 9.2 and 4.6 Hz, 1H), 1.96 (d, *J* 14.7 Hz, 1H), 2.08 (dd, *J* 4.5 and 4.4 Hz, 1H), 2.09-2.17 (m, 1H), 2.48-2.54 (m, 2H), 5.97 (s, 1H), 7.44 (s, 1H); *^{13}C NMR* 20.3, 20.7, 27.6, 28.2, 43.2, 43.6, 50.1, 64.8, 171.7 and 216.6; *MS m/z* 181(M^+, 15), 165(9) and 109(6); *Anal* Calc for $C_{10}H_{15}NO_2$: C, 66.30; H, 8.40; N, 7.70. Found: C, 66.00; H, 8.50; N, 7.90.

1-Carboxamido-2-phenylbicyclo[2.2.1]hep-2-ene (6). Ketopinamide **4** (200 mg, 1.10 mmol) in dry ether (5 ml) was added via a syringe to a cooled (0°C) ether solution of Grignard reagent [prepared from magnesium (116 mg, 4.80 mmol) and bromobenzene (404 mg, 3.85 mmol) in dry ether (10 ml)] and the reaction mixture stirred at this temperature for 5 minutes, then at room temperature for 90 minutes. Ice was added and the reaction extracted with ether (20 ml). The organic layer was dried over sodium sulfate, reduced *in vacuo*, and subjected to radial chromatography (eluant 10% ethyl acetate-light petroleum) to afford starting material (60 mg, 30%) and the intermediate product alcohol (144 mg, 51%) as fine white needles, *mp* 176-178°C; ν_{max} 3418, 2992, 2959, 1738, 1651, 1598, 1493; ^{1}H *NMR* 1.04 (s, 3H), 1.12-1.17 (m, 1H), 1.20-1.25 (m, 1H), 1.25 (s, 3H), 1.80-1.92 (m, 2H), 1.97-2.01 (m, 1H), 2.39-2.52 (m, 2H), 5.97 (s, 1H), 6.50 (s, 1H), 7.22-7.33 (m, 3H), 7.43-7.47 (m, 2H); ^{13}C *NMR* 21.9, 22.3, 26.3, 27.4, 44.8, 46.3, 53.7, 61.6, 84.5, 126.3, 127.2, 128.2, 145.5, and 177.3; *Anal*: Calc. for $C_{16}H_{21}NO_2$ C, 74.1; H, 8.2; N, 5.4 % Found: C, 74.1; H, 8.4; N, 5.2 %

The above product (30 mg, 0.116 mmol) and p-toluene sulfonic acid (5 mg, 0.029 mmol) were heated under reflux in toluene (15 ml) under Dean-Stark conditions for 24 hours. The majority of the toluene was removed and the residue partitioned between water (10 mL) and dichloromethane (10 mL). The organic layer was separated, washed with water, brine, dried over magnesium sulfate, and reduced *in vacuo* to afford the crude product **6** (26.5 mg, 95%). Purification by radial chromatography (eluant 10% ethyl acetate-light petroleum) gave the product as a

viscous oil, $[\alpha]_D$ -222.1° (c 0.1, $CHCl_3$); ν_{max} (film) 3486, 3191, 3055, 2956 1664, 1601, 1492; *^{1}H NMR* 1.01 (s, 3H), 1.12 (s, 3H), 1.47 (ddd, 1H, *J* 12.8, 9.6 and 3.9 Hz), 1.46 (ddd, 1H, *J* 12.7, 9.3 and 3.7 Hz), 2.10-2.19 (m, 1H), 2.56 (dd, 1H, *J* 3.4 and 3.4 Hz), 3.00 (ddd, 1H, *J* 12.4, 8.9 and 3.7 Hz), 5.10 (s, 1H), 5.66 (s, 1H), 6.23 (d, 1H, *J* 3.1 Hz), 7.21-7.24 (m, 2H,), 7.29-7.32 (m, 2H); *^{13}C NMR* 20.2, 20.7, 26.0, 27.3, 53.3, 59.8, 65.7, 125.3, 128.6, 127.2, 134.6, 135.8, 145.2, 174.5; *M.S.* m/z 242 (100%), 241(M^+, 66), 240(67), 197(63), 181(80), 155(71); *H.R.M.S.* $C_{16}H_{19}NO$ requires: 241.1467, found: 241.1466.

1-Carboxamido-3,3-dimethyl-2-methylenebicyclo[2.2.1]heptane (10). This was prepared from (+)-camphor **1** by analogy with the reported method[13] and following later documented observations (data not reported).[10] This afforded the carboxamide **10**[9] in overall 49% yield (4 steps), *mp* (ex acetone) 209-211°C (lit[10] 209-210°C); $[\alpha]_D$ 71.0° (c 0.7 in acetone); *^{1}H NMR* (DMSO-d_6) 1.05 (s, 6H), 1.35-1.45 (m, 2H), 1.45-1.54 (m, 1H), 1.61-1.69 (m, 1H), 1.70-1.82 (m, 1H), 1.84-1.90 (m, 1H), 2.10 (ddd, 1H, *J* 9.8, 3.9 and 1.9 Hz), 4.62 (s, 1H), 4.76 (s, 1H), 6.90 (s, 1H), 6.93 (s, 1H); *^{13}C NMR* (DMSO-d_6) 25.0, 26.6, 30.1, 32.0, 40.4, 41.1, 47.6, 43.1, 61.2, 100.6, 164.9 and 175.3; *M.S.* m/z 180 (m+1, 60%), 179(m^+, 27), 164(55), 138(53), 110(77), 91(100) and 65(53); *Anal*: Calc. for $C_{11}H_{17}NO$ C, 73.7; H, 9.6; N 7.8 % Found: C, 73.9; H, 9.2; N, 7.9 %.

General Method for Isocyanate Preparation The carboxamide or sulfonamide (routinely between 100-200 mg scale) was dissolved in 1,1-dichloroethane (DCE, 5-10ml) and treated with freshly distilled oxalyl chloride [$(COCl)_2$ 1.5-3.0 equiv)] via syringe under dry nitrogen. The mixture was then heated under reflux

(overnight often proved convenient). Any excess $(COCl)_2$ was removed by azeotropic distillation with DCE. The high reactivity of the activated isocyanates mitigated against formal characterisation via combustion analysis. IR spectral analysis of the powerful N=C=O stretch, along with the absence of $-NH_2$ stretches, was taken to indicate complete conversion. The isocyanate products were taken up in fresh DCE and reacted directly with alcohol nucleophiles. The yields of these addition products were taken as the indicators of isocyanate formation and also used for characterisation. The following are representative examples of these adducts.

Carbamates (12, 13, 14) from Acyl Isocyanate (5).

The carboxamide **4** (200 mg, 1.10 mmol) and $[(COCl)_2$ (0.135 ml, 1.56 mmol) gave the isocyanate **5** [ν_{max} cm^{-1} (film) 2244] which was treated with excess EtOH (1 ml). After 1 hour at room temperature, solvent removal gave the product **12** (302 mg, 92%) as colourless cubes, *mp* (ex ether-light petroleum) 64.5-65.5 °C; $[\alpha]_D$ 49.1° (c 0.5, $CHCl_3$); ν_{max} cm^{-1} 3418, 2985, 1779, 1744, 1698; ^1H *NMR* 1.03 (s, 3H), 1.30 (s, 3H), 1.32 (t, 3H, *J* 7.1 Hz), 1.47 (ddd, 1H, *J* 12.4, 9.2 and 4.1 Hz), 1.71 (ddd, 1H, *J* 11.3, 9.3 and 4.3 Hz), 2.04 (d, 1H, *J* 18.9 Hz), 2.12 (dd, 1H, *J* 4.6 and 4.2 Hz), 2.17-2.23 (m, 1H), 2.47-2.62 (m, 2H), 4.25 (q, 2H, *J* 7.1 Hz), 9.28 (s, 1H); ^{13}C *NMR* 14.2, 20.2, 20.7, 27.7, 29.3, 43.3, 43.5, 50.7,.61.9, 65.3, 150.5, 167.7, and 216.4; *M.S.* m/z 254(m+1, 9%), 164(45), 136(54), 95(50),93(61), and 67(100); *Anal*: Calc. for $C_{13}H_{19}NO_4$ C, 61.6; H, 7.6; N, 5.5 % Found: C, 61.6; H, 7.6; N, 5.2 %

In an analogous manner, treatment with excess 2-butanol gave **13** (299 mg, 97%) as white needles (radial chromatography with 5% ethyl acetate-light petroleum), *mp* 44.5-46°C; ν_{max} cm^{-1} 3425, 2973, 1783, 1732, 1632; *^{1}H NMR* 0.92 (t, 3H, *J* 7.5 Hz) one diastereomer, 0.93 (t, 3H, *J* 7.5 Hz) other diastereomer, 1.04 (s, 6H), 1.27 (d, 3H, *J* 6.2 Hz), 1.28 (d, 3H, *J* 6.2 Hz), 1.30 (s, 6H), 1.47 (ddd, 2H, *J* 12.2, 9.1 and 3.8 Hz), 1.70 (m, 6H, C5 endo and CH_2), 2.04 (d, 2H, *J* 18.9 Hz), 2.12 (dd, 2H, *J* 4.7 and 4.2 Hz), 2.15-2.23 (m, 2H,), 2.47-2.63 (m, 4H, C3 exo and C5 exo), 4.87 (qt, 2H, *J* 6.1 and 7.5 Hz), 9.75 (s, 2H); *^{13}C NMR* 9.65, 19.41, 20.3, 20.8, 27.8, 28.7, 29.3, 43.3, 43.6, 50.7, 65.4, 74.3, 150.0, 167.8 and 216.5; *Anal:* Calc. for $C_{15}H_{23}NO_4$ C, 64.0; H, 8.2; N, 5.0% Found: C, 64.1; H, 8.5; N, 4.7%.

In an analogous manner, treatment with excess 1-phenylethanol (1.1 equiv) gave **14** (90 mg, 32%) as white needles (radial chromatography with 5% ethyl acetate-light petroleum), *mp* 129.5-130.5°C; ν_{max} cm^{-1} 3417, 2924, 1772, 1738, 1640, 1575, 1493; *^{1}H NMR* 0.99 (s, 3H) one diastereomer, 1.04 (s, 3H) other diastereomer, 1.28 (s, 3H) one diastereomer, 1.29 (s, 3H) other diastereomer, 1.45 (ddd, 2H, *J* 13.2, 8.5 and 4.0 Hz), 1.61 (d, 6H, *J* 6.6 Hz), 1.54-1.78 (m, 2H), 2.00 (d, 2H, *J* 18.9 Hz), 2.08-2.23 (m, 4H), 2.43-2.62 (m, 4H), 5.92 (q, 2H, *J* 6.6 Hz), 7.28-7.42 (m, 10H), 9.86 (s, 2H); *^{13}C NMR* 20.3, 20.7, 22.0, 27.8, 29.2/29.3, 43.3, 43.5, 50.7/50.8, 65.4, 74.0, 126.3, 128.1, 128.5, 140.8, 149.8, 167.7, and 216.4/216 5; *Anal:* Calc for $C_{19}H_{23}NO_4$ C, 62.3; H, 7.0; N, 4.2% Found: C, 62.2; H, 6.8; N, 4.0%

Carbamate (15) from Acyl Isocyanate (7). The carboxamide **6** (200 mg, 0.83 mmol) and $(COCl)_2$ gave the isocyanate **7** [ν_{max} cm^{-1} (film) 2239] which was treated with excess 2-butanol (1.5 ml) in DCE (10 ml). Gentle reflux, solvent removal, and radial chromatography (eluant 5% ethyl acetate-light petroleum) gave starting amide (16 mg, 8 %) which had either not reacted or resulted from hydrolysis of the isocyanate, along with the product as a slightly unequal mixture of diastereomers (187 mg, 66 %) as white needles, *mp* 83-84.5°C; ν_{max} cm^{-1} 3428, 3243, 3059, 2968, 1754, 1691, 1604, 1505; ^{1}H *NMR* 0.64 (t, 3H *J* 7.4 Hz) minor diastereomer, 0.82 (t, 3H, *J* 7.4 Hz) major diastereomer, 1.02 (s, 6H), 1.06 (d, 3H, *J* 6.3 Hz) major diastereomer, 1.14 (d, 3H, *J* 6.3 Hz) minor diastereomer, 1.16 (s, 6H), 1.32-1.55 (m, 4H), 2.09-2.19 (m, 2H), 2.59 (dd, 2H, *J* 3.4 and 3.3 Hz), 2.65-2.74 (m, 1H), 4.74 (tq, 2H, *J* 6.3 and 4.5 Hz), 6.31 (d, 2H, *J* 3.1 Hz), 6.86 (s, 2H), 7.19-7.34 (m, 10H); ^{13}C *NMR* 9.3, 19.4, 20.1, 20.7, 25.7, 27.1, 28.5, 53.6, 60.7, 67.3, 74.1, 125.1, 127.5, 128.8, 135.0, 135.2, 144.4, 149.8, 169.9 (minor diastereomer), 9.5, 19.2, 20.1, 20.7, 25.7, 27.1, 28.5, 53.6, 60.6, 67.3, 74.2, 125.1, 127.5, 128.8, 134.9, 135.2, 144.4, 149.9 and 169.9 (major diastereomer); *Anal:* Calc for $C_{21}H_{27}NO_3$ C, 73.9; H, 8.0; N, 4.1% Found: C, 74.1; H, 7.7; N, 4.0%

Carbamate (16) from Sulphonyl Isocyanate (9). The sulfonamide **8** (200 mg, 0.87 mmol) and $(COCl)_2$ gave the isocyanate **9** [ν_{max} cm^{-1} (film) 2241] which was treated with excess 2-butanol (1.5 ml) in DCE (10 ml). Gentle reflux, solvent removal, and radial chromatography (eluant 10% ethyl acetate-light petroleum)

gave the product diastereomer mixture as an oil (197 mg, 70%); ν_{max} cm^{-1} 3235, 2967, 1747, 1654, 1343, and 1152; *^{1}H NMR* 0.91 (s, 6H), 0.93 (t, 3H, *J* 7.4 Hz, one diastereomer), 0.94 (t, 3H, *J* 7.4 Hz, other diastereomer), 1.09 (s, 6H), 1.29 (d, 3H, *J* 6.3 Hz, one diastereomer), 1.30 (d, 3H, *J* 6.3 Hz, other diastereomer), 1.46 (ddd, 2H, *J* 12.6, 9.2 and 3.8 Hz), 1.55-1.70 (m, 4H), 1.72-1.87 (m, 2H), 1.95 (d, 2H, *J* 18.6 Hz), 2.00-2.10 (m, 2H), 2.14 (dd, 2H, *J* 4.6 and 4.5 Hz), 2.32-2.47 (m, 4H), 3.29 (d, 1H, *J* 15.1 Hz), 3.30 (d, 1H, *J* 15.1 Hz), 3.91 (d, 1H, *J* 15.1 Hz), 3.93 (1H, d, *J* 15.1 Hz), 4.88 (qt, 2H, *J* 7.4 and 6.3 Hz), 8.37 (s, 2H); *^{13}C NMR* 9.5, 19.3, 19.7, 25.5/25.7, 27.0, 28.6, 42.6, 42.7, 48.4, 50.6, 58.6, 76.1, 151.0, and 214.9

Carbamate (17) from Acyl Isocyanate (11). The carboxamide **10** (250 mg, 1.39 mmol) and $(COCl)_2$ gave the isocyanate **11** [ν_{max} cm^{-1} (film) 2239] which was treated with excess 2-butanol (1.5 ml) in DCE (10 ml). Gentle reflux, solvent removal, and radial chromatography (eluant 20% ethyl acetate-light petroleum) gave starting amide (108 mg, 43%) and the product as a mixture of diastereomers (134 mg, 35%) as white needles, *mp* 69.5-70.5°C (ex light petroleum); ν_{max} cm^{-1} 3434, 3270, 2971, 1768, 1750, and 1517; *^{1}H NMR* 0.93 (t, 3H, *J* 7.4 Hz, one diastereomer), 0.94 (t, 3H, *J* 7.4 Hz, other diastereomer), 1.12 (s, 6H, one diastereomer), 1.12 (s, 6H other diastereomer), 1.28 (d, 6H, *J* 6.3 Hz), 1.47-1.70 (m, 8H), 1.72-1.85 (m, 4H), 1.98-2.03 (m, 4H), 2.11-2.21 (m, 2H), 4.79 (s, 2H), 4.90 (s, 2H), 4.88 (qt, 2H, *J* 7.4 and 6.3 Hz), 7.50 (s, 2H); *^{13}C NMR* 9.6, 19.4, 24.3, 25.9, 28.7, 29.5, 30.8, 41.6/41.7, 43.1, 47.8, 62.0, 74.64/74.7, 102.1, 150.5,

163.2/163.3, and 171.0; *Anal*: Calc. for $C_{16}H_{25}NO_3$ C, 68.8; H, 9.0; N, 5.0 % Found: C, 68.9; H, 9.2; N, 5.2 %

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